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Ultrasound-guided regional anesthesia in children and adults

Aspects on central and peripheral blocks

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Seeing is believing!

Abstract

The universal use of regional anesthesia has previously been hampered by fundamental factors, e.g. excessive failure rates, inability to detect anatomical variations and fear for unintentional tissue damage; all due to the inherent imprecision of previous localization techniques. The introduction of ultrasound guidance (USG) has now made it possible to circumvent previous limitations by allowing real-time visualization of the block procedure. The aim of the current thesis project was to develop and evaluate a new USG nerve block and to investigate some mechanistic issues related to the established pediatric caudal block technique by use of ultrasound (US) imaging.

Infrapatellar nerve (IPN) block: This block has not previously been described as an USG technique. In *Study I* a USG IPN block was performed in 10 adult volunteers using a prospective, observational design and various block characteristics were assessed. The IPN could reliably be visualized by US and the USG IPN block was found to produce an anesthetized area of the anterior aspect of the knee with a median block duration of 30 hours. In *Study II* the clinical usefulness of the USG IPN block was evaluated using a prospective, randomized, double-blind, placebo-controlled design involving 64 patients undergoing outpatient anterior cruciate ligament repair. The primary aim of this study was to evaluate the incidence of a pain score of >3 both at rest and on muscular activity. The addition of an USG IPN block to an established multi-modal analgesic regimen was found to result in a reduced incidence of a pain score of >3 during the latter part of the 24 hour observational period, and was also associated with an increased number of sleep hours.

Caudal blockade: US scanning in young individuals allow for real-time visualization of the spread of LA within the spinal canal, something that previously has been impossible. Using a prospective, age-stratified, observational design the US assessed spread of the local anesthetic (LA) was determined in 47 children receiving a high-volume (1.5 mL kg^{-1}) caudal block in *Study III*. The observed spread was subsequently correlated to patient characteristics. A significant inverse relationship was found between patient characteristics and the maximal cranial level reached by the LA. However, due to unknown reasons the cranial spread assessed by immediate US visualization was found to be in poor agreement with previously published predictive equations. In an attempt to unravel the potential mechanism responsible for this unexpected difference, the pattern of secondary intraspinal spread of LA was observed by US during a 15 minute post-injection period in 16 infants <6 months of age in *Study IV*, which also included measurements of intraspinal pressure and cutaneous testing of the dermatomal block level. The median US-assessed cranial spread was Th10 and Th8 at 0 and 15 min, respectively, and the sensory level at 15 min was Th4. The caudal injection was initially found to compress the terminal part of the dural sac, later followed by a partial re-expansion as epidural pressure was returning towards pre-injection values. An intrasegmental redistribution from the dorsal to the ventral compartment of the epidural space was also observed.

Conclusions: An USG IPN block reliably produces prolonged anesthesia of the anterior aspect of the knee and improves pain relief and sleep after outpatient knee surgery compared to the use of a multi-modal state-of-the-art analgesic regimen alone. US assessment of caudal spread of LA show that the cranial level reached is inversely related to the age, weight and height of the child. Two separate patterns of secondary intraspinal spread of LA can be identified by US: horizontal intrasegmental redistribution and longitudinal cranial spread. A bi-directional movement of cerebrospinal fluid (coined 'the CSF rebound mechanism') does help explain the difference between the initial ultrasound-assessed cranial level and the final level determined by cutaneous testing.

List of publications

**This thesis is based upon the following papers,
referred to by the Roman numerals I-IV.**

- I. **Lundblad M**, Kapral S, Marhofer P, Lönnqvist PA.
Ultrasound-guided infrapatellar nerve block in human volunteers:
description of a novel technique.
Br J Anaesth 2006; **97**: 710-714.
- II. **Lundblad M**, Forssblad M, Eksborg S, Lönnqvist PA.
Ultrasound-guided infrapatellar nerve block for anterior cruciate
ligament repair; a prospective, randomised, double-blind, placebo
controlled clinical trial.
EJA 2011; **28**: 511-518.
- III. **Lundblad M**, Eksborg S, Lönnqvist PA, Marhofer P.
Segmental distribution of high volume caudal anaesthesia in neonates,
infants and toddlers as assessed by ultrasonography.
Pediatric Anesthesia 2011; **21**: 121-127.
- IV. **Lundblad M**, Eksborg S, Lönnqvist PA.
Secondary spread of caudal blockade as assessed by ultrasonography.
Br J Anaesth. 2012; **108**: 675-681.

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List of abbreviations

| | |
|--------|--|
| AAACL | Arthroscopy assisted anterior cruciate ligament repair |
| ACL | Anterior cruciate ligament |
| ASA | American Society of Anesthesiologists |
| AUC | Area-under-the-curve |
| BMI | Body mass index |
| ECG | Electrocardiogram |
| EMLA | Eutectic Mixture of Local Anesthetics |
| G | Gauge |
| GW | Gestational weeks |
| IASP | International Association for the Study of Pain |
| IPN | Infrapatellar nerve |
| IPNB | Infrapatellar nerve block |
| IV | Intravenous |
| L1-5 | Lumbar vertebrae 1-5 |
| LA | Local anesthetic |
| NIBP | Noninvasive blood pressure |
| NRS | Numerical rating scale |
| NS | Nerve stimulator |
| NSG | Nerve stimulator guided |
| PACU | Post anesthesia care unit |
| RA | Regional anesthesia |
| SB | Sham block |
| SN | Saphenous nerve |
| SNB | Saphenous nerve block |
| Th1-12 | Thoracic vertebrae 1-12 |
| US | Ultrasound |
| USG | Ultrasound-guided |
| USNB | Ultrasound-guided nerve block |
| VAS | Visual analogue scale |

1 Introduction

A prerequisite in order to perform surgery is to provide sufficient pain-relief to allow the procedure to be undertaken without undue suffering of the patient. This can be accomplished either by altering the state of consciousness of the patient (general anesthesia) or by rendering the area of the body involved with the surgical procedure anesthetized (regional anesthesia). In ancient times some of the few options available were either the ingestion of alcohol and/or opium to induce a state akin to general anesthesia or by use of external pressure at appropriate anatomical points in order to induce nerve ischemia and thereby reversible numbness of a limb.

The birth of Anesthesiology as a unique specialty, being a relatively recent part of the development of modern medicine, has provided the cornerstone upon which advanced surgery is based. Despite the continuous evolution of anesthesia, there still exists a debate whether general or regional anesthesia should be regarded as the preferred choice for many different types of surgical interventions.

Proponents of regional anesthesia, including the author of this dissertation, argue that regional techniques confer potential advantages when compared to general anesthesia (*please see 2.3: “Benefits of Regional Anesthesia”*). Although many of these advantages still lack a solid evidence base there has been a substantial resurgence of interest for regional anesthesia during recent years. This renewed interest for regional anesthesia is to a large extent inspired by the introduction of ultrasound guidance as well as recently published data indicating that the use of regional anesthesia may beneficially affect various important issues, e.g. the risk for cancer recurrence,¹⁻³ the development of chronic postoperative pain⁴ or even mortality in frail and/or old patients.⁵

Regional anesthesia can be divided into two main categories: central or peripheral nerve blockade. When performing central nerve blocks (e.g. epidural or intrathecal nerve blocks) LA is injected at various locations within the spinal canal, thereby typically producing bilateral anesthesia from a thoracic or lumbar level and caudad. When performing peripheral nerve blocks LA is administered in the immediate proximity of peripheral nerve structures, which can either be located close to the neuro-axis (e.g. paravertebral or interscalene blocks) or quite distally (e.g. ankle block or digital nerve blocks). Peripheral nerve blocks will, thus, result in a much

more localized area of anesthesia, e.g. a uni-lateral part of the torso (paravertebral block), the arm and hand (brachial plexus block) or a finger or toe (digital nerve block). Compared to central nerve blocks, peripheral nerve blocks cause less interference with the autonomic nervous system and are thereby associated with fewer side effects, e.g. hemodynamic instability and urinary retention.

Due to the unique analgesic potential of regional anesthesia, considerable effort has been focused on various methods to extend the excellent pain relief produced by regional anesthesia into the postoperative period. A prolonged duration can for example be achieved by the use of various continuous catheter techniques, by adding adjunct drugs to the LA (e.g. opioids, clonidine and ketamine) or by pharmaceutically modifying the LA preparation (e.g. microsomes and liposomes).

Against the above it should be apparent that regional anesthesia represents an interesting and exciting field for further research. The specific scientific focus of the present academic thesis was, thus, directed towards the use of ultrasound in the context of one peripheral and one central nerve block.

2 Background

2.1 HISTORICAL BACKGROUND OF REGIONAL ANESTHESIA

The first use of local anesthesia in modern medicine is attributed to Karl Koller, who in 1884 used cocaine in the setting of eye surgery. This seminal discovery soon created a huge interest concerning regional anesthesia, a drive that to a large extent was due to the many imperfections of general anesthesia of that time. In 1898 the German August Bier performed the first operation under cocaine spinal anesthesia at the Kiel University Hospital and the use of spinal anesthesia rapidly became established general practice in the early 1900s. Bier did also somewhat later (1908) pioneer the use of intravenous procaine analgesia, the so-called Bier block. Descriptions of peripheral nerve blocks were also soon to follow the initial report by Koller: Halsted is recognized as the first person to perform a brachial plexus block (1885) and in 1911 the first axillary plexus block was described by Hirschel and in the same year Kulenkampff reported the use of the supraclavicular brachial plexus block technique. Even at this time there was an interest to be able to block also small peripheral nerves and Halsted and Hall, thus, described the use of cocaine injections to block the ulnar, musculocutaneous, supratrochlear and infraorbital nerves.

The development and description of the majority of nerve blocks that we use even today was soon accomplished, maybe best exemplified by the well renowned comprehensive textbook by Gaston Labat, *Regional Anesthesia*, first edition published in 1922, and further development of RA was thereafter closely associated with the development of new and better local anesthetics. A major advancement took place already early during the 1900s when the quite toxic and addictive compound cocaine was replaced by procaine and tetracaine. Swedish researchers have also played important roles in the development of new local anesthetics and a large number of the local anesthetics drugs that we use today have been invented and developed in Sweden: lidocaine, prilocaine, mepivacaine and bupivacaine. The discovery of lidocaine by Löfgren & Lundqvist in 1943 even became the foundation on which the ASTRA medical company was originally built.⁶

A reduced interest in and practice of RA gradually took place during the mid-20th century due to the significant improvements of general anesthesia, and a more restrictive attitude to the use of RA also came as a result of the infamous Wooley &

Roe case, which involve serious complications associated with the use of spinal anesthesia.⁷ However, since the 1980s there has been an ever growing interest in the use of regional anesthesia, a trend that recently has been fueled by the development of ultrasound guidance.

2.2 DEVELOPMENT OF PEDIATRIC REGIONAL ANESTHESIA

Regional anesthesia methods were obviously judged as also being beneficial to pediatric patients and spinal anesthesia was used in children already from the early 1900s. In fact, already the very first description of spinal anesthesia by Bier included children (two out of six). The pediatric surgeon Tyrell Gray in London, as early as 1909, published the experience of 300 pediatric surgical cases performed under spinal anesthesia⁸ and a large case series of pediatric spinal anesthesia from the USA was soon to follow.⁹ As in adults the use of spinal anesthesia in children was later reduced as the methods for general anesthesia improved but a renewed interest emerged in the 1980s when it was introduced as a beneficial alternative for surgery in preterm neonates.¹⁰ As with spinal anesthesia a general resurge of interest for pediatric RA emerged during the 1980s, maybe best exemplified by the hallmark review from 1986 by Arthur & McNicol¹¹ and the popularization of pediatric epidural blockade by Ecoffey¹² and Murat.¹³

A further milestone in the history of pediatric RA came in 1933 when Campbell first described the use of caudal anesthesia in the context of pediatric urology.¹⁴ Caudal anesthesia has since become perhaps the most widely spread RA technique in pediatric anesthesia due to its simplicity and clinical usefulness. Furthermore, the dermatomal distribution of a caudal block has also been appreciated as being quite predictable. The first and maybe most disseminated estimation of the cranial extension of caudal blockade by Armitage is based on the injected volume of LA.¹⁵ Subsequently additional predictive equations have been published,¹⁶⁻¹⁸ which form part of the focus of the present thesis.

Since 2004, when Marhofer et al. first described the use of USG for performing infraclavicular brachial plexus blocks in children,¹⁹ pediatric RA has entered into the modern era of USG RA. Ultrasound guidance has been well embraced within the community of pediatric anesthesiologists and since the initial Marhofer publication a vast literature has been published regarding pediatric USG RA, now also including this dissertation project.

The above only represent a brief summary of the history of pediatric RA and, thus, the interested reader is for further information and detail referred to a excellent recent review by Kester Brown.²⁰

2.3 BENEFITS OF REGIONAL ANESTHESIA

Regional anesthesia techniques have the unique property of being able to produce either major modification of afferent sensory input (central nerve blocks)^{21,22} or complete blockade of afferent impulse traffic (peripheral nerve blocks).²³ This exclusive property of RA does not only accomplish excellent intra- and postoperative pain relief but is also associated with a number of other benefits for the patient and the health care system. Many of these benefits are directly linked to the analgesic properties of RA while other advantages may be due to other and still not delineated effects of RA and/or LAs.²⁴

Thus, in addition to producing excellent intra- and postoperative pain relief,²⁵ the use of RA can influence perioperative morbidity and mortality. Adult studies have reported RA to be associated with a number of beneficial effects, e.g. reduced incidence of pneumonia following abdominal or thoracic surgery,^{26,27} modified stress response to surgery,²⁸ improved gastro-intestinal motility,²⁹⁻³¹ and a reduced incidence of postoperative myocardial infarction.³² Recent publications have also reported that the use of various RA techniques may affect the long-term outcome after cancer surgery. In this context a reduced incidence of cancer recurrence has been reported following the use of paravertebral blockade for breast cancer surgery¹ and the use of epidural analgesia has been indicated to improve the outcome after prostate and rectal cancer surgery, respectively.^{2,3} If this beneficial effect of RA with regards to cancer survival ultimately can be supported by large scale prospective randomized trials,³³ it would of course represent a quintessential break-through for the practice of RA.

The use of RA has also been reported to reduce mortality in high-risk surgical patients, as reported by Yeager et al in 1987.⁵ However, the beneficial effect on early postoperative mortality has not been possible to reproduce in more recent studies, a fact that most likely is explained by the very low estimated anesthesia related mortality associated with up-to-date use of anesthetic agents and the current level of intra- and postoperative supervision and monitoring of high-risk patients.³⁴

2.4 BENEFITS OF PEDIATRIC REGIONAL ANESTHESIA

In line with the adult literature a very large number of individual studies and reviews have shown that pediatric RA provides superior analgesia as compared to different systemic analgesic regimens.^{35,36} RA techniques are not only useful in the in-patient setting but can also be successfully used in ambulatory surgery.³⁷ As in adult practice USG is currently put forward as the technique of choice, not only for peripheral nerve blocks^{38,39} but has also been suggested to be of benefit for epidural block placement.^{40,41}

The different aspects of pediatric RA have recently been summarized in a themed

issue of *Pediatric Anesthesia*⁴² and, thus, only a few specific topics will be highlighted below.

Avoidance of general anesthesia

Despite general anesthesia normally being safe and effective in the context of pediatric practice there are at least two instances or reasons for the use of a pure RA technique. First, the use of an awake spinal or caudal technique can be seen as advantageous in ex-premature babies since this approach will avoid the problems associated with endotracheal intubation and may also minimize the risk of postoperative apnea, desaturation and bradycardia.^{43,44} Second, an extensive literature now exists, mainly based on animal experiments, that point to the potential for many anesthetic drugs that are frequently used for general anesthesia to produce apoptosis of cerebral neurons in newborn individuals, which subsequently may lead to negative behavioral and cognitive consequences.^{45,46} The clinical implications of these scientific findings is currently unclear but the use of pure RA techniques as opposed to general anesthesia appear as an attractive alternative to avoid such apoptotic cerebral cell death and is currently investigated in a large-scale multi-center clinical trial.⁴⁷

Attenuation of surgical stress response

Wolf and colleagues have shown that the use of epidural analgesia is associated with a substantial reduction in the surgical stress response as compared to postoperative intravenous morphine analgesia.⁴⁸ Further small scale studies have provided additional evidence in support of RA being capable of beneficially modifying the pediatric surgical stress response. Since reduction of the stress response to surgery has been convincingly proven to reduce morbidity and mortality in the setting of ductus ligation or pediatric cardiac surgery in small babies,^{49,50} it is tempting to postulate that the stress reduction caused by the use of pediatric RA would also be associated with such important benefits. However, as Wolf recently has pointed out, no data are yet available to prove that a modification of the stress response by use of regional anesthesia in the context of pediatric surgery is associated with an improved outcome.⁵¹

Effects on outcome after surgery

As alluded to above very limited data has been published with regards to true outcome parameters and the use of RA in children. A reduced need for postoperative ventilation and, thus, intensive care resources has been associated with the use of thoracic epidural analgesia in the setting of esophageal atresia repair.⁵² Furthermore, the use of epidural blockade in association with traditional open fundoplication for gastro-esophageal reflux surgery, was found to result in a reduction of postoperative complications as well as reduced hospital costs.⁵³ Thus, when compared to opioid-based analgesia, RA appears

to be associated with improved outcome also in children. However, these positive results must be interpreted with a certain caution since both the above mentioned studies are retrospective in nature.

Safety of pediatric regional anesthesia

A key issue with regards to recommending general use of RA in children is of course the safety aspects involved and this topic is nicely summarized in a recent review by Ecoffey.⁵⁴ Luckily a lot of effort have been focused on the safety issues associated with widespread use of pediatric RA. Currently four different large-scale studies, including 10000-30000 patients each, has been published and consistently show an over-all complication rate of 1/1000 and an incidence of 1/10000 for complications that do not resolve within 12 months after the block.⁵⁵⁻⁵⁸ The use of central nerve blocks, especially caudal blockade, has been found to be associated with a slightly higher complication rate as compared to peripheral nerve blocks and, thus, the use of peripheral nerve blocks display an increasing trend.⁵⁷ In summary it can be concluded that the use of pediatric RA is not only efficacious but that complications are few and relatively benign, resulting in an overall acceptable safety profile.

2.5 NERVE BLOCK TECHNIQUES: HISTORICAL DEVELOPMENT

During the evolution of RA the methods to accomplish the deposition of LA in close proximity of the target nerve structures have developed considerably. The most common previously used techniques are listed and summarized below.

Dissection of nerves

Harvey Cushing is credited for coining the name regional anesthesia for his method of blocking a nerve plexus under *direct vision* during general anesthesia in 1902.⁵⁹ Dissection of nerves for perioperative nerve block is no longer in clinical use but is still a valid option in experimental cadaver studies in order to assess the accuracy of other localization techniques.⁶⁰

Anatomical landmarks

Many of the described RA methods rely on using anatomical landmarks. These methods include palpating bones or arteries, and then measure distances to guide the point of needle insertion at a certain angle, direction and depth to be able to inject LA close to the target nerve structures. With the insertion of the needle certain principles can be followed, e.g. feeling for a “pop” or a “click” as the needle tip passes through aponeuroses and fascia, applying pressure on the syringe when passing through muscle and ligament in order to feel the loss of resistance when reaching the appropriate anatomical space where the nerve should be located and also not to inject against a resistance.⁶¹

Nerve Paresthesias

To search for and subsequently elicit paresthesia has been a common and recommended method for localizing nerves and thereby verifying the close proximity between the needle tip and the nerve prior to injection of LA. The expression “*no paresthesia, no analgesia*” was postulated by Daniel Moore in the 1950’s.⁶² Paresthesia is thought to result from mechanical stimulation of the nerve by the needle, resulting in an often unpleasant feeling described as an electric current or shock within the sensory distribution area of the stimulated nerve. Paresthesia can also occur from pressure on the nerve from surrounding tissues.

Nerve stimulator

After first being described in 1912 by von Perthes, nerve stimulator guidance for nerve localization became popular in the 1960’s. To illustrate the enthusiasm with regards to this new and quite revolutionizing technique Greenblatt in 1964 wrote the following: “*This technique has been used in almost all other peripheral motor nerves of the body with equal success. These positive results produce accurate localization, assurance of success, lower doses and volume of local anaesthetic agent, and serve as an excellent method of teaching nerve blocks*”.⁶³ Thus, an electrical current is used to stimulate the nerve, and the resulting depolarization of the nerve membranes subsequently produces a contraction of the effector muscles or, in case of purely sensory nerves, paresthesias in the sensory distribution of the nerve. As the stimulating electrode, in this case the needle, moves closer to the nerve, a lower current is needed to elicit a motor response. Injection of LA in the setting of a peripheral nerve block is performed when an adequate stimulus response is reached with a current of typically 0.2 to 0.5 mA. To further improve the sensitivity of nerve stimulator guidance the stimulation pattern can be refined. By using sequential electrical nerve stimuli (SENS) Urmeý & Gossi have been able to achieve improved sensitivity without compromising specificity of the nerve localizing procedure.⁶⁴

2.6 LIMITATIONS WITH PREVIOUS TECHNIQUES

Anatomical landmarks

To rely solely on anatomical landmarks is associated with obvious limitations due to the wide interpersonal and gender variations in both surface anatomy and the location of nerves in relation to vessels and other important structures. “Blind” blocks that rely purely on anatomical landmarks and fascial “clicks” or “pops”, such as the traditional ilioinguinal-iliohypogastric nerve block, are notoriously imprecise and are therefore associated with the risks of complications (e.g. bowel perforation).⁶⁵

Furthermore, the use of the traditional “blind” ilioinguinal-iliohypogastric nerve block also provides a good example of the limited success rate that can be associated with “blind” regional anesthetic techniques. Thus, the failure rate associated with traditional ilioinguinal-iliohypogastric nerve blocks in children has been reported to be in the 30-40% range.^{66,67} The most likely explanation for this low success rate is that the LA is injected at the wrong anatomical location (see *Figure 1*) in approximately 85% of cases, as reported in a seminal study by Weintraud et al in 2008.⁶⁸

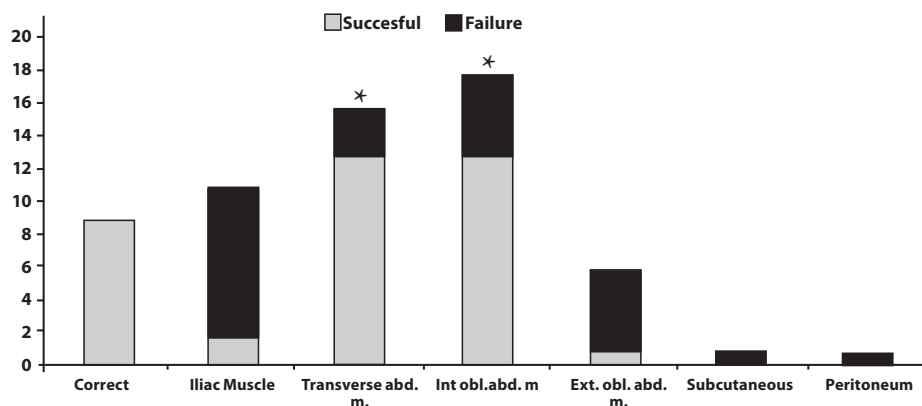


Figure 1. Ratio of successful and failed blocks at different adjacent anatomical structures (* $P < 0.05$ compared with iliac muscle and external oblique abdominal muscle)⁶⁸.

Nerve paresthesias

The use of the nerve paresthesia technique frequently cause considerable patient discomfort and is also associated with an increased risk of neurological sequelae.⁶⁹

It is also important to understand that eliciting paresthesia only indicates that the needle is in the proximity of the nerve but not in direct needle-to-nerve contact. The sensitivity for needle-to-nerve contact with the paresthesia method has been shown to be only 38.2%.⁷⁰

Electrical nerve stimulation

Patient discomfort: As with the paresthesia method electrical nerve stimulation can also produce unpleasant sensations, discomfort and/or overt nerve paresthesia.⁷¹ Furthermore, the motor response caused by electrical nerve stimulation will in conscious patients with limb fractures or joint dislocations result in significantly more pain compared to an USG technique.¹⁹

Needle placement and possible nerve injury: Despite being much more sensitive compared to the paresthesia technique, the motor response to nerve stimulation is still not associated with acceptable sensitivity (74.5%) with regards to confirmation of needle-to-nerve contact.⁷⁰ Another major limitation of the NS technique is that

the absence of a motor response to nerve stimulation does not rule out intraneural needle placement.⁷² Previous guidelines concerning NS has stipulated that a stimulation current of 0.2 mA or less is indicative of intraneural placement of the needle, but stimulation currents between 0.2 and 0.5 mA may still be associated with an intraneural position of the needle tip.⁷³ More recent animal studies have also shown that a motor response can be absent despite intraneural needle placement when using stimulating currents of up to 1.7 mA, and that 12.5 % of intraneurally positioned needles require 0.8-1.8 mA to elicit a specific motor response.⁷⁴ Thus, current data suggest that there are no safe limits when using NS to rule out intraneural needle placement. However, contrary to previous teaching not all intraneural injections will result in injury.⁷⁵

Finally, it is not possible to judge the spread of the LA in relation to the target nerve structures, which represents a substantial disadvantage compared to USG techniques.

2.7 FAILURE RATE OF TRADITIONAL REGIONAL ANESTHESIA TECHNIQUES AND NEED FOR IMPROVEMENT

Despite the reassuringly low risks associated with RA in general and pediatric RA in particular, the most frequent complication of RA both in adults and children is block failure. In the hands of the very seasoned expert success rates above 90 % have occasionally been reported when using traditional techniques, e.g. landmark-based or nerve stimulator-guided approaches.^{76,77} However, even quite skilled clinicians experience failure rates in the range of 10% to 40% when using these previously common techniques and failure rates as high as 75% has occasionally been reported in the literature (*Table 1*).

| | Success rate (range in studies) | References no |
|---------------------------------|------------------------------------|-------------------------|
| Landmark based | ~60% (26-74%) | 67 78 79 |
| Paresthesia or transarterial | ~75% (25-95%) | 76 78 79 80 81 |
| NSG | ~85% (47-97%) | 76 77 78 82 83 84 85 86 |

Table 1. Success rates of traditional RA techniques

Due to the often unpredictable success rate of landmark-based and nerve stimulator guided RA it is hardly surprising that certain anesthesiologists, surgeons and operating room administrators have been skeptical with regards to the use of RA as standard procedure since failed blocks often necessitate block supplementation, administration of additional intravenous analgo-sedation or not infrequently even conversion to general anesthesia.

Since successful RA is associated with unequalled pain relief as well as many other benefits, as outlined above, there is an obvious need to improve success rates to the point that the routine practice of RA for many surgical procedures can become the rule rather than the exception. The most apparent potential for improving the situation would of course be to find new methods that make the performance of the blocks both easier and much more reliable, thereby getting close to the ultimate goal of 100% successful blocks.

2.8 THE DEVELOPMENT OF ULTRASOUND-GUIDED REGIONAL ANESTHESIA

Use of ultrasound in medicine

Ultrasound has been used as a medical diagnostic tool since more than 50 years. Already in 1937 the Dussik brothers attempted to use ultrasound to locate brain tumors. The images produced by a 1.5 MHz transmitter showed areas of decreased wave transmission thought to show the lateral ventricles, though it was later determined that these areas represented variations in bone thickness.⁸⁷ However, after the evolution of better ultrasound transducers, ultrasonography was used for midline encephalography for the detection of epidural hematomas, a method developed by among others Leksell in Sweden.⁸⁷ The first Echocardiogram was developed by the Swedish scientists Edler and Herz in 1953 and in the 1960's M-mode and intracardiac Doppler blood flow recordings were introduced.⁸⁸ In 1969 interventional use of ultrasonography was first described in a paper presented by the obstetrician Kratochwil, at the first World congress on Ultrasound diagnostics in Medicine, Vienna, where he proposed the use of one-dimensional US for percutaneous drainage of amniotic fluid.⁸⁹

Since that time ultrasonographic methods and devices have continuously developed and today many diagnostic and interventional procedures using ultrasound are done outside the radiology and cardiology departments, e.g. intraoperative vascular ultrasound,⁹⁰ ultrasound-guided central venous cannulation,⁹¹ ultrasound evaluation of abdominal pain,⁹² ultrasound-guided trauma examination (FAST),⁹³ endoscopic ultrasound⁹⁴ and cardio-pulmonary ultrasound assessments in the OR and ICU (FATE).⁹⁵⁻⁹⁷

First use of ultrasound in regional anesthesia

In 1978 La Grange and colleagues reported the use of a Doppler flow ultrasound detector to find the subclavian artery and thereby facilitate supraclavicular blockade of the brachial plexus. This is acknowledged as the first study in which an *indirect* sonographic approach was used for regional anesthesia.⁹⁸

Sixteen years later Kapral and colleagues in Vienna published the first report on *direct* or *real-time* ultrasonographic use in regional anesthesia (1994). This seminal study investigated USG supraclavicular plexus blockade of the brachial plexus in adults and was the first to describe the visualization of the spread of the LA in relation to the target nerve structures.⁹⁹ As previously mentioned, Marhofer et al in 2004 introduced ultrasound guidance also in pediatric regional anesthesia¹⁹ and the first review article on USG RA was published in British Journal of Anaesthesia 2005.¹⁰⁰

2.9 ADVANTAGES WITH ULTRASOUND-GUIDED REGIONAL ANESTHESIA

Visualization of target structures

With USG it is possible to identify the target nerve structures and also other relevant anatomical structures e.g. vessels, fascias, pleura, peritoneum and bone. USG also allows anatomical variations to be detected and, thus, the technical approach can be modified to avoid complications and increase the success rate. In a number of various nerve blocks it is not possible to actually see the target nerve structures but the use of USG can still direct the needle tip to the correct anatomical position, will verify that the LA is deposited in the right place and will help avoiding unintentional puncture of important nearby structures.

Monitoring of needle placement and distribution of local anesthetics

Ultrasonography provides the ability to monitor the needle and the needle tip in real-time. The needle and needle tip can either be visualized in its entirety when using an “in-plane” or longitudinal approach or only the needle tip if an “out-of-plane” or transverse technique is applied. Subsequently the injection of LA can be viewed directly and the adequacy of the spread of the administered LA can immediately be determined- the aim being to completely surround the target nerve structures with LA. If the LA spread is found suboptimal or maybe even on the wrong side of a fascia layer, then the needle can be repositioned and further injections can be performed until an optimal distribution of the LA is accomplished.¹⁰¹

Visualization of smaller nerves and blocking sensory nerves

Even very small peripheral nerves and nerve branches are possible to visualize when using appropriate high quality US equipment.¹⁰²⁻¹⁰⁴ Blocking a sensory nerve with NS is quite difficult since this relies on the identification of paresthesias within the sensory distribution of the nerve by the patient and this is obviously not at all possible in deeply sedated or anesthetized patients. With USG it is possible to block sensory nerves with high success rates even if the patient is under general anesthesia, which represents the norm in pediatric anesthesia.

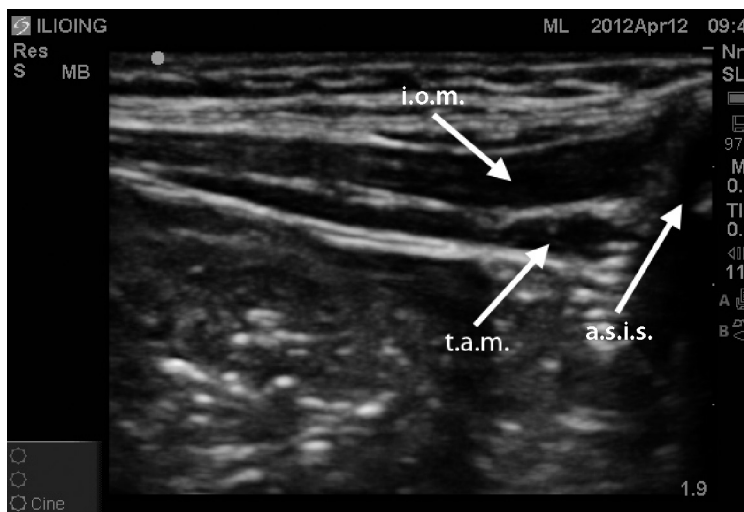


Figure 2. Ultrasound image of the ilioinguinal/iliohypogastric nerve, located in the fascial layer between the transverse abdominis muscle (t.a.m.) and the internal oblique muscle (i.o.m.) in a 10 kg child, a.s.i.s.= anterior superior iliac spine.

Reduction of the total dose and volume of local anesthetics

The use of USG allows for a considerable reduction of the volume of LA needed to accomplish a successful block.^{105,106} This will not only reduce the risk for systemic LA toxicity but will also decrease the risk for unintentional “spillover blocks” of nerves that are located close to the target area (e.g. the phrenic nerve, the stellate ganglion or the recurrent laryngeal nerve when performing an interscalene brachial plexus block). The use of USG may reduce the volume of LA needed for a successful block by as much as 80% compared to using a landmark-based technique.¹⁰⁵

To reduce the amount of LA may not only be possible but also desirable when using USG since pharmacokinetic data indicate faster absorption and higher maximal plasma concentration of LA when ultrasound is used for ilioinguinal-iliohypogastric nerve blocks in children as compared with the traditional landmark based technique

(Figure 3).¹⁰⁷ Such increased absorption may be caused by the appropriate deposition of LA between the fascial layer of the internal oblique and the transverse abdominis muscle (see figure 2), which will increase the area available for absorption, compared to the landmark-based technique that most often results in intramuscular deposition of the LA.⁶⁸

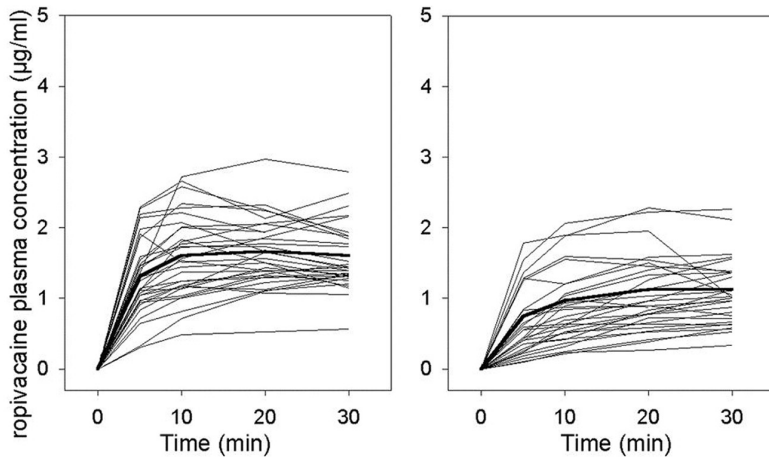


Figure 3. Ropivacaine plasma levels in individual patients (left side: ultrasound- guided technique; right side: landmark- based technique). Thick lines represent the mean values.¹⁰⁷

Faster onset and longer duration

One of the major advantages of USG nerve blocks is that the operator can make sure that the entire nerve structure is surrounded by LA. This should on theoretical grounds substantially reduce the onset time of the block and a large number of publications, both in children and adults, have demonstrated significantly shorter onset times when USG is used.¹⁰⁸⁻¹¹¹ Although data is not as consistent as for the reduction of onset time, a number of studies indicate that the duration of the nerve block is also moderately prolonged by the use of USG.^{108,110-114}

Shorter time to conduct blocks

Due to the advantage of real-time visualization, USG reduces the number of needle passes to reach the target nerve structures, which in turn can shorten the block performance time.^{109,111}

Lower costs

Economic evaluations between different treatment options are often difficult to adequately perform but an ambitious comparison by Liu et al have found USG blocks to be cost- effective when compared to the NS guided technique.¹¹⁵ A reduced onset time and better logistics will allow more adequate use of costly OR time, which in turn results in a positive cost-benefit analysis for the use of USG.^{116,117}

2.10 DOES ULTRASOUND INCREASE SAFETY IN REGIONAL ANESTHESIA?

Even though it is possible to visualize vital structures e.g. the pleura, the peritoneum and various blood vessels when using USG, there is yet insufficient evidence that ultrasound guidance in fact reduce the frequency of more serious complications. Since the incidence of more serious complications in association with peripheral nerve blocks is quite low, very large studies will be necessary to show a reduced incidence of complications when USG is used.¹¹⁸

However, it should be reminded that USG is operator dependent and, thus, USG does not automatically provide a safeguard against complications. Even in experienced hands complications such as blood vessel puncture/intravascular injections, pneumothorax or inadvertent intraneural injections have been reported in the literature.^{111,119-122}

3 Aims

Rationale for the thesis

Regional anesthesia techniques provide excellent surgical and postoperative analgesia but previous techniques are associated with a variety of limitations. The introduction of real-time ultrasonographic guidance has lead to a breakthrough in regional anesthesia and new methods are being developed and their clinical usefulness explored. By use of US it is also possible to gain new knowledge about already established techniques.

Against this background the following aims for the thesis were decided.

Aims

1. To describe a novel ultrasound-guided nerve block technique; the infrapatellar nerve block. (Study I)
2. To investigate the clinical usefulness of the ultrasound-guided infrapatellar nerve block as a complement to current state-of-the-art multimodal analgesia. (Study II)
3. To determine the cranial spread of a high-volume caudal block in children 0-4 years of age, as assessed by ultrasonography. (Study III)
4. To explore the characteristics of secondary spread of high-volume caudal block as assessed by ultrasound and cutaneous testing, and if possible identify a mechanism that can explain secondary longitudinal distribution of LA in the spinal canal. (Study IV)

4 Subjects and methods

4.1 GENERAL

The studies were performed in accordance with the declaration of Helsinki. All studies were approved by the Regional Ethical Review Board of Stockholm, Sweden. Individual or parental consent were obtained in all cases.

4.2 PATIENT/SUBJECT POPULATION AND DEMOGRAPHICS

A total of 140 individual subjects were included in the studies as specified below.

Study I: 10 adult volunteers (7 male and 3 female, age range: 35-60 years, weight range: 54-97 kg). The blocked knee should have been considered fully normal by the volunteer and should have been without previous significant trauma.

Study II: 64 patients ASA 1-2 (32 male and 32 female, age range: 15-53 years, weight range: 47-113 kg) scheduled for elective anterior cruciate ligament repair.

Study III: 50 pediatric patients ASA 1-3 (age range: 0-40 months, weight range: 2.2-14.5 kg) scheduled for elective subumbilical surgical procedures.

Study IV: 16 pediatric patients ASA 1-3 (age range: 0-3.2 months, weight range 2.3- 6.9 kg) scheduled for inguinal hernia repair.

No significant differences with regard to demographic data were detected between the two study groups in the comparative study II. A majority of the pediatric patients were boys (boys: n= 59, girls: n=7) and this dominance relates to the surgical diagnosis- mostly inguinal hernia repair- which is more common in boys.

4.3 ANESTHETIC PROTOCOL

Premedication

Study II: intravenous ketobemidone 2.5-7.5 mg, oral paracetamol 1-2 g and anti-emetic prophylaxis with intravenous droperidol 0.5 mg.

Study III and IV: No pharmacologic premedication was used. A peripheral venous cannula was inserted on the general pediatric ward after prior EMLA cream application.

Anesthetic methods

Study II: General anesthesia was induced by propofol (2-3 mg/kg) and fentanyl (50-100 µg/kg). Following laryngeal mask airway insertion anesthesia was subsequently maintained by sevoflurane-oxygen-air with the patient breathing spontaneously.

Study III and IV: General anesthesia was induced by IV atropine (10 µg/kg) and propofol (2-3 mg/kg), subsequently followed by insertion of a laryngeal mask airway to secure the airway. Anesthesia was thereafter maintained by sevoflurane-oxygen-air. In patients undergoing laparoscopic surgery, airway management was performed by endotracheal intubation facilitated by prior administration of succinylcholine. Anesthesia was thereafter maintained by sevoflurane-oxygen-air at an end-tidal sevoflurane concentration of 2.5-3 % (Study III) and 2.5 % (Study IV).

4.4 ULTRASOUND EQUIPMENT

In **Study I**, nerve structures were visualized with a portable ultrasound machine (Titan, Sonosite, Bothell, WA, USA) with a 38 mm wide 5–10 MHz linear array probe.

In **Study II, III and IV** the ultrasound equipment used for the IPN block and for spinal canal scanning was a portable Sonosite M-Turbo machine (Sonosite, Bothell, WA, USA) with a 38 mm wide 7-13 MHz linear array probe.

4.5 SPECIFIC PROCEDURES AND MEASUREMENTS STUDY I AND II

Ultrasonographic-Guided Infrapatellar Nerve Block Procedure

Detailed descriptions of the USG IPN block procedure are provided in the Methods section of Study I and II and will therefore not be duplicated here. However, two figures are provided below as a brief illustration of the US visualization associated with the block (*Figure 4*). It is important to note that the block procedure differed somewhat between Study I and II, the approach being slightly more distal in Study II than in Study I- a modification made in order to enhance the possibility of achieving a more selective IPN block as well as to avoid the risk of blocking the motor nerve of the vastus medialis muscle. A further difference between Study I and II was that different volumes of LA were used (5 mL vs. 10 mL). The blocks were performed as an out-of-plane technique.

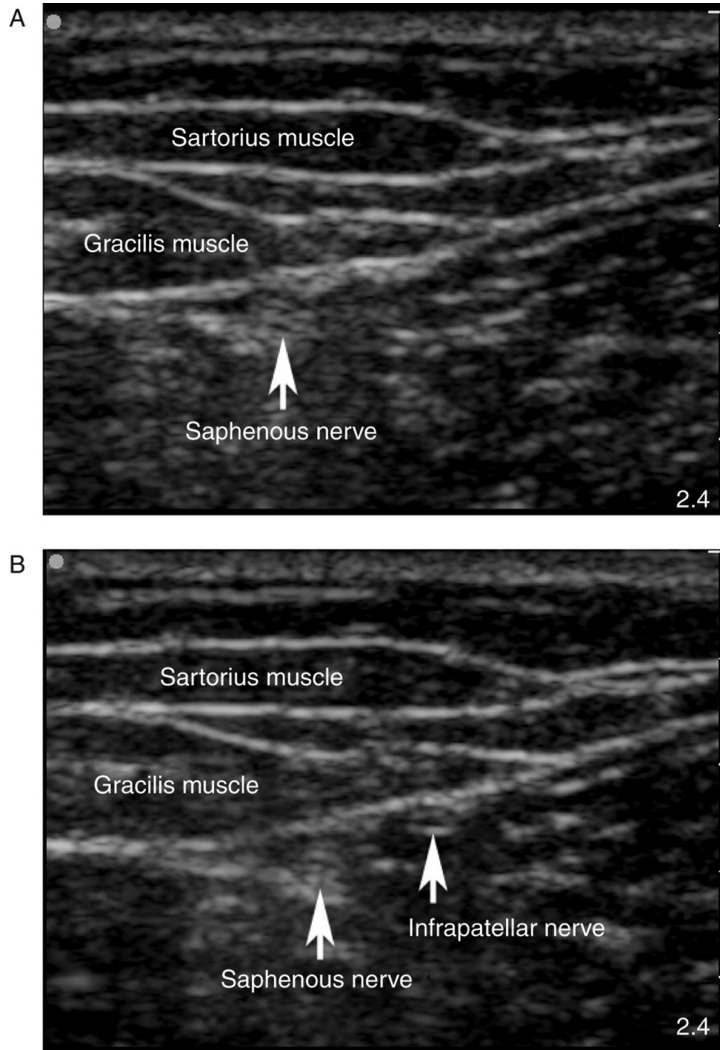


Figure 4. A. Saphenous nerve. B Saphenous and infrapatellar nerve

Ultrasonographic measurements of the IPN

Study I: The skin-nerve distance was measured with the caliper function of the US machine and the ultrasonographic nerve visibility was scored according to a 4 graded scale (0 = not visible, 1 = identified with difficulty, 2 = clearly visible but unable to visualize internal nerve structures and 3 = clearly visible with internal nerve structures) representing a modified Vienna score.¹²³ Based on an US image immediately after the injection of LA, the LA spread around the nerve was scored according to a 3 graded scale (0 = no direct contact between LA and the nerve, 1 = LA only partially in contact with the nerve and 2 = the nerve completely surrounded by the injected LA).

Assessment of Infrapatellar Nerve Block characteristics in Study I

Cutaneous analgesia: cutaneous analgesia was determined by light touch followed by skin pinching. Testing of cutaneous sensation within the innervated area of the IPN was performed immediately after the end of the blocking procedure and then every 3 min until no further extension of the block could be detected compared with the previous assessment. Assessments were continued for a maximum of 30 min and if no effect of the block was noted at this time the block was considered as a failure. The border for pain on skin pinching was marked on the skin and was subsequently measured.

Onset time: The onset time of the block in minutes was defined as the time from the end of the injection of the local anesthetics to the first sensation of changed cutaneous sensation within the innervated area of the IPN.

Maximum area of cutaneous anesthesia: The area of cutaneous anesthesia was determined in a stellate manner using the most cephalad part of the tibial tuberosity as the reference point and was marked on the skin in eight different directions. The assessments were made with the knee flexed at 90 degrees (*Figure 6*).

Time point of maximum extension: The time from the end of the injection to maximum extension of cutaneous anesthesia (min) was defined as the time until two subsequent assessments of the extension of the block generated the same result at which point the time of the last assessment was registered as the time to maximum extension of the block.

Duration: The time between the time point of maximum extension of the block and the return of complete cutaneous sensation was defined as the duration of the block (h).

In study II it was not possible to test the IPN innervated area directly due to postoperative bandaging of the knee and the use of the Cryo Cuff device.

Characteristics of the Saphenous Nerve Block

Study I: In order to detect a possible concomitant block of the SN the skin slightly above and anterior to the medial malleolus was tested in a similar manner to what is described above for the IPN in order to detect involvement also of the SN. The following data were recorded: quality of sensory block (0= no block, 1= slight block of cutaneous sensation, 2 = dense block), time to onset (min) and duration of the block (h).

In **Study II** data on the quality and the duration of the SN block were recorded. The patients were instructed to test the sensitivity to light touch of SN innervated area, and compare the sensation to similar testing performed on the non-operated leg.

The response was then categorized using a 4-graded scale (0 = completely normal cutaneous sensation, 1 = almost normal but different compared to the normal side, 2 = clearly altered cutaneous sensation but still able to feel touch and 3 = profound cutaneous anesthesia). The test was done hourly when awake and the duration until the return of completely normal sensation was noted. The duration of SNB in the study represents a surrogate of the actual duration of the IPNB, since it was not possible to test the area innervated by the IPN directly due to the postoperative bandaging of the knee and the use of the Cryo-Cuff device.

4.6 ASSESSMENT OF POSTOPERATIVE PAIN (STUDY II)

Postoperative pain during the stay in the recovery room (PACU) was assessed by the Visual Analogue Scale (VAS) and for self assessment after discharge from the PACU the Numeric Rating Scale (NRS) was used. Pain scores for knee pain both at rest and on muscular activity (raising the leg from the surface of the bed with the knee extended) were noted immediately on arrival to the PACU and thereafter every 30 minutes during the first 4 postoperative hours. During the PACU stay the patients were given additional analgesia by intravenous ketobemidone 2.5-5.0 mg if visual analogue scores were >3 .^{125,126} After discharge from the PACU the patients were instructed to note their pain both at rest and on muscular activity hourly when awake. The proportion of patients with a pain intensity of >3 (numeric rating scale 0-10) during the latter part of the postoperative observation period was chosen as the primary end-point of the study. Pain scores of 4-6 were considered as moderate pain and >6 as severe pain.¹²⁷

The patients were instructed to note "S" in their protocol when having been asleep. In accordance with the IASP definition of pain (that requires an individual to be in a conscious state to experience pain)¹²⁸ the patients were postulated to have a pain score of zero when they were asleep. In addition to the pain assessments the amount of supplemental analgesics administered in the PACU and following discharge from the PACU was registered. A follow-up phone call was made 24-33 hours postoperatively.

4.7 CAUDAL BLOCK PROCEDURE

Study III and IV: After induction of anesthesia the child was positioned in the left lateral decubitus position. By manual palpation the lumbo-sacral junction was determined and the spinous process of L5 was thereby identified. The lumbar spinal processes were thereafter palpated and counted in a rostral fashion to identify the 12th thoracic spinous process. The 12th rib was subsequently identified by ultra-

sound visualization and followed medially to further verify that the spinous process of Th12 had been correctly identified. The skin overlying the spinous process of Th12 was then marked using a regular skin marking pen.

An initial longitudinal paramedian ultrasonographic investigation was performed to identify the epidural space, the conus medullaris, the cauda equina and the termination of the dural sac. After sterile preparation of the injection site, the sacral cornuae and sacro-coccygeal membrane were identified by palpation. The caudal space was subsequently cannulated using a pediatric 30 mm 25G caudal needle (Epican®, B Braun, Melsungen, Germany) (Study III) or an 24 G intravenous cannula (BD Neoflon™, Becton, Dickinson and Co, NJ, USA) (Study IV). The cannula was then attached to an extension tubing (BD Connecta™, Becton, Dickinson & Co, NJ, USA). An aspiration test was performed to exclude inadvertent intravascular placement, where after the local anesthetic solution was manually injected at a rate of approximately 0.5 ml s^{-1} . A total volume of 1.5 mL kg^{-1} of 0.2 % ropivacaine (Narop®, AstraZeneca, Södertälje, Sweden) was used, representing the upper limit of safe dosage (3 mg kg^{-1}) as described by Bosenberg.¹²⁴

4.8 ULTRASONOGRAPHIC MEASUREMENTS FOLLOWING THE CAUDAL BLOCK

Cranial spread (Study III and IV)

Determination of the most cranial level of LA in the epidural space was performed. During the caudal injection the ultrasound probe was maintained in the previously determined optimum paramedian position in order to visualize the cranial spread of the local anesthetic within the caudal/epidural space. The probe was moved cranially as needed in order to follow the advancement of the front of the LA bulk flow within the epidural space, as evidenced by an anterior displacement of the dorsal dura, resulting in a reduction of the A-P diameter of the dural sac (*Figure 5*). After the injection of 1.5 mL kg^{-1} of LA, the front of the epidural local anesthetic was identified and was positioned in the middle of the ultrasound picture. A skin mark was made corresponding to the middle of the ultrasound probe and the level reached was later determined by counting the spinous processes from the previously indicated Th12 spinous process. If the ultrasonographic front of the LA was “hidden” behind the bone shadow of the vertebral lamina the front was approximated to the middle of the corresponding bone shadow.

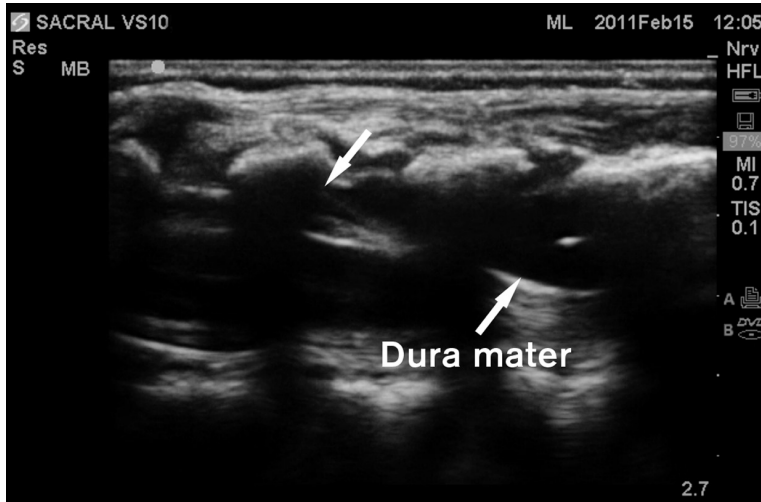


Figure 5. Ultrasound image of the distribution of LA in the epidural space. The LA is seen as an anechogenic area above the dura mater. The left arrow indicates the most cranial limit of spread.

Ultrasonographic evaluation of secondary spread of LA

In *Study IV* measurements of the anatomical relationships within the spinal canal were performed. At the L3-L4 level the distance between the skin and the dorsal dura and also the anterior-posterior (A-P) diameter of the dural sac (the distance between dorsal to ventral dura) were measured using the caliper function of the ultrasound machine immediately before the injection of LA. Directly after assessing the instant cranial spread of the LA, the ultrasound probe was again positioned at the L3-L4 level to measure the compression of the dural sac (distance in mm from skin to dorsal dura and A-P dural sac diameter) at this level. New measurements were performed at the L3-L4 level every 3rd minute during 15 minutes following the injection of local anesthetics.

Due to the contents present in the ventral epidural space it is very difficult to make exact US measurement between the ventral part of the dural sac and the anterior wall of the spinal canal (vertebral bodies and intervertebral discs). Thus, the absence or presence of local anesthetics in the ventral part of the epidural space was categorized as 0 (no fluid layer visible), + (minor layer of fluid layer identified) or ++ (clearly identifiable fluid layer anterior to the dural sac). A millimeter estimate of the ventral redistribution space was generated by subtracting the sum of the measured skin-dorsal dura distance and the dura-dura distance at 3, 6, 9, 12, 15 minutes from the same value measured immediately following injection when both the ventral epidural space and the dura was maximally compressed by the injectate in the dorsal epidural space. This redistribution of LA was considered to represent secondary intra-segmental spread of LA.

Longitudinal secondary spread was evaluated 15 minutes after the caudal block when the spinal epidural space was again scanned in a longitudinal fashion to determine the most cranial level of LA spread visible by ultrasound at this time point

4.9 EPIDURAL PRESSURE RECORDINGS

In *Study IV* the epidural pressure was measured before, during and after the caudal injection. After the caudal space was cannulated using an 24 G intravenous cannula (BD Neoflon™, Becton, Dickinson and Co, NJ, USA), an aspiration test was performed to exclude inadvertent intravascular placement, after which the caudal catheter was connected to the pressure transducer via a three-way stop-cock (BD Connecta™, Becton, Dickinson and Co, NJ, USA) and a baseline epidural pressure was obtained on the anesthesia monitor (Infinity® Delta, Dräger GMBH, Lübeck, Germany). The LA solution with a total volume of 1.5 mL kg⁻¹ was then manually injected at a rate of approximately 0.5 mL s⁻¹. Immediately after the completion of the injection the three-way stop-cock was switched so that the caudal epidural space was directly connected to the pressure transducer and the epidural pressure was thereafter measured continuously. Post-injection epidural pressure values were noted in the study protocol immediately after injection, and 3, 6, 9, 12, and 15 minutes post-injection. Pressure values were only deemed reliable when pulse synchronous pressure variations could be seen on the concomitant pressure trace of the monitor.

4.10 ASSESSMENT OF CUTANEOUS ANALGESIA FOLLOWING THE CAUDAL BLOCK

Study IV: Following the completion of the ultrasound examination sequence to determine the most cranial level of LA spread visible 15 minutes after the caudal block, the child was carefully placed in the supine position and the level of cutaneous analgesia was tested by sequential skin-pinching from the umbilical level in a cranial direction. A skin fold was firmly pinched between the thumb and the index finger for 5 seconds and any positive response (increased heart rate and/or NIBP >15% from baseline or movements of extremities) was noted. The dermatomal level immediately below the level of a positive response was registered as the maximal level reached by the caudal block as assessed by cutaneous testing.

In the case of no response to a skin-pinch immediately inferior to the clavicle, the skin at the lateral side of neck (outside the area of a caudal block) was also tested. A negative response to the testing of the skin on the lateral side of the neck was interpreted as 0.75 MAC sevoflurane producing a too deep level of anesthesia to allow for adequate cutaneous testing of the level of blockade.

4.11 STATISTICAL ANALYSES

Study I: Observational data was presented as mean (SD) and median (range).

Study II: Non-parametric statistical procedures were used in all analyses. Classified data from two independent populations were compared using the Fisher's exact test. The 95% confidence intervals for proportions were calculated as described by Mendenhall.¹²⁹ The Wilcoxon matched-pairs signed-ranks test was used to analyze differences between paired observations. P-values <0.05 were considered as statistically significant. Reported p-values are from two-sided tests.

The randomization was done by computer-generated random numbers and sealed envelopes were used.

Study III: The two main study parameters were maximal cranial segmental spread and the number of patients in each age group where the local anesthetic was identified to have reached the target level of Th12. Associations between two variables was established by the Spearman rank correlation test. Kruskal-Wallis Test (non-parametric ANOVA) and the Mann-Whitney U-test was used for comparison of percentage of blocks reaching the target level Th12 in the three age groups. Based on weight and the resulting number of segments covered by the caudally injected LA a predictive equation was derived.

Study IV: The three main study parameters were maximal cranial segmental spread and distance of skin-dural distance and dural sac diameter. The data in Figure 3 in the original article are expressed by mean values and 95% confidence intervals. The regression lines in Figures 2B and 4 in the original article were calculated by linear regression. Patient characteristics are given as median (range).

5 Results

5.1 EXCLUDED SUBJECTS/PATIENTS

A total of 140 individual subjects and patients were included. One subject in Study I was excluded due to a failed IPN block. Two patients (one in each group SB and IPNB) were excluded in Study II due to intraoperative decisions not to perform an ACL repair. Three patients in Study III were excluded due to study protocol violations ($n = 2$) or inadvertent vascular puncture ($n = 1$). No exclusion of included patients was needed in study IV.

5.2 CHARACTERISTICS OF THE ULTRASOUND-GUIDED INFRAPATELLAR NERVE BLOCK

The characteristics of an ultrasound-guided infrapatellar nerve blockade are shown in Table 2 and the area of maximum cutaneous analgesia is displayed in Figure 6.

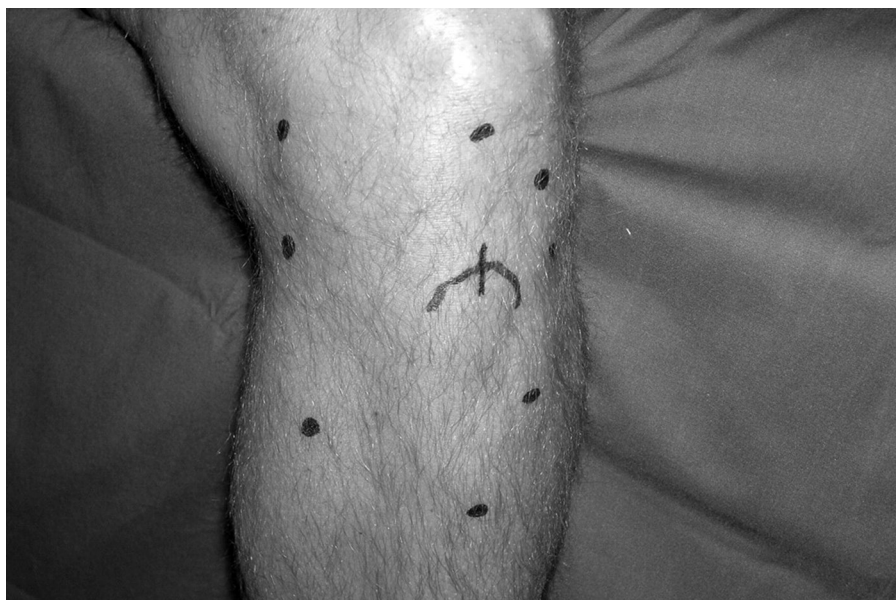


Figure 6. Cutaneous analgesia following infrapatellar nerve block. Circles represent mean values (for numerical values and SD please see Table 1 Study I).

| | Mean (SD) | Median (range) |
|--|-------------|------------------|
| Subject data | | |
| Sex (m/f) | 7/3 | |
| Age (yr) | 44 (6.9) | 42.5 (35–60) |
| Body weight (kg) | 76.7 (17.0) | 79.5 (54–97) |
| Height (cm) | 174.6 (9.7) | 174.5 (160–190) |
| BMI (kg m ⁻²) | 24.9 (3.7) | 24.4 (19.4–30.8) |
| Block characteristics | | |
| Skin-nerve distance | 2.0 (0.6) | 1.9 (1.2–3.2) |
| Medial joint line-puncture distance (cm) | 14.0 (3.1) | 14.0 (8.5–18.0) |
| Nerve visibility (0-3) | 2.7 (0.5) | 3 (2–3) |
| Spread of injectate (0-2) | 1.8 (0.4) | 2 (1–2) |
| Infrapatellar nerve | | |
| Time to onset (min) | 2.2 (1.7) | 1 (1–6) |
| Time to maximal spread (min) | 8.4 (3.6) | 9 (1–12) |
| Duration of block/time to return of full sensibility | 27.5 (19.1) | 30.5 (2.0–58.5) |
| Saphenous nerve | | |
| Degree of saphenous nerve block (0-2) | 1.6 (0.5) | 2 (1–2) |
| Time to onset (min) | 4.4 (5.7) | 2.0 (1–15) |
| Duration of block/time to return of full sensibility (h) | 27.1 (21.3) | 23.5 (2.0–58.5) |

Table 2. Patient and block characteristics (Study I)

5.3 POSTOPERATIVE PAIN (STUDY II)

Pain at rest and on activity- entire 24-h observation period

An overall assessment of the analgesic effect over the entire 24-h observation period was performed using the Fisher exact test. The percent of VAS/NRS assessments with a pain score of >3 (indicating need for supplemental analgesia) was significantly lower in Group IPNB as compared to Group SB at rest (Figure 7A, $p = 0.0207$) but not on activity ($p = 0.2619$). Similarly, the percent of VAS/NRS assessments with a pain score of >6 (indicating severe pain) was significantly lower in Group IPNB as compared to Group SB at rest (Figure 7B, $p = 0.019$) but not on activity ($p = 0.20$).

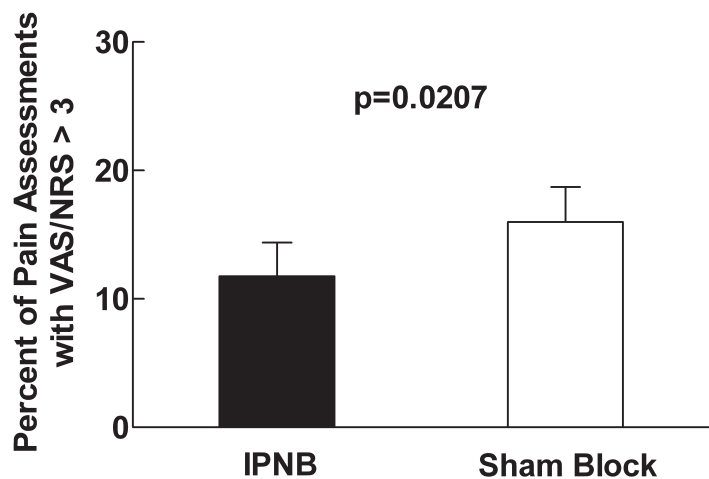


Figure 7A. Percent of pain assessments with a VAS/NRS score of >3 at rest

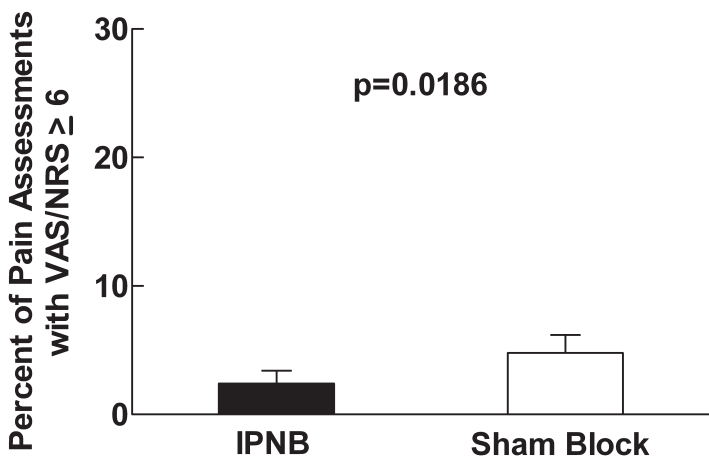


Figure 7B. Percent of pain assessments with a VAS/NRS score of >6 at rest.

Postoperative pain at rest

The percent of patients with a pain score of >3 at rest was significantly lower in Group IPNB compared to Group SB during the postoperative time period 16-24 h ($p = 0.0117$) (Figure 8A). No difference was seen during the early part of the observation period (1-12 h) or during the hours around midnight when the majority of patients in both groups were asleep (13-15 h).

Pain on activity

The percent of patients with a pain score of >3 on activity was significantly lower in Group IPNB compared to Group SB during the postoperative time period 16-24 h ($p = 0.0039$) (Figure 8B). No difference was seen during the recovery room period (0-4 h) or during the time period 5-15 h.

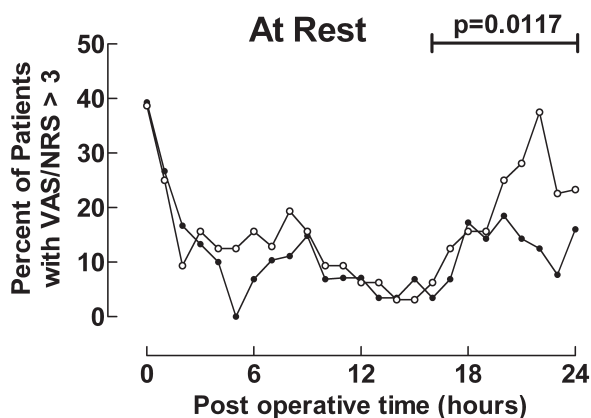


Figure 8A. Percent of patients with VAS >3 at rest during the entire 24-h postoperative observation period. Solid circles=infrapatellar nerve block; open circles=sham block.

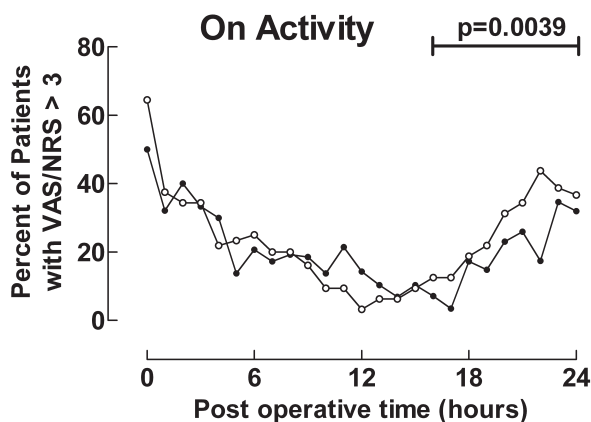


Figure 8B. Percent of patients with VAS >3 on activity during the entire 24-h postoperative observation period. Solid circles= infrapatellar nerve block; open circles= sham block.

Duration of Saphenous Nerve Block

The duration of SNB was significantly longer in group IPNB than in group SB with median values of 23 h (95% CI: 19-24) and 13 h (95% CI: 0-20 h; $p < 0.0117$), respectively.

Sleep

No difference with regards to sleep could be seen between the groups during the 5-12 hour postoperative period. However, during the time period 13-24 h after surgery a significantly higher percentage of patients were asleep in Group IPNB compared to Group SB (Figure 9, $p < 0.0269$).

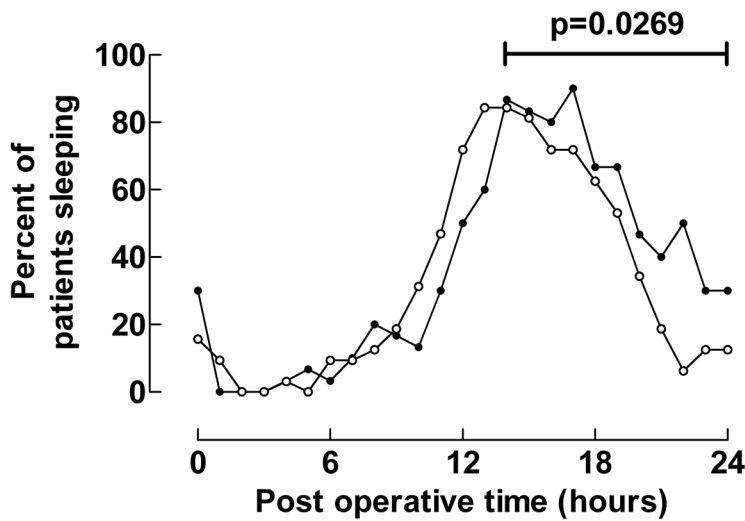


Figure 9. Percent of patients sleeping.

Solid circles= infrapatellar nerve block; open circles= sham block.

5.4 CORRELATION BETWEEN CRANIAL SPREAD OF A CAUDAL BLOCK AND PATIENT CHARACTERISTICS (STUDY III)

An inverse relationship was observed between the different age groups and maximal ultrasonography assessed cranial spread (*Figure 10*).

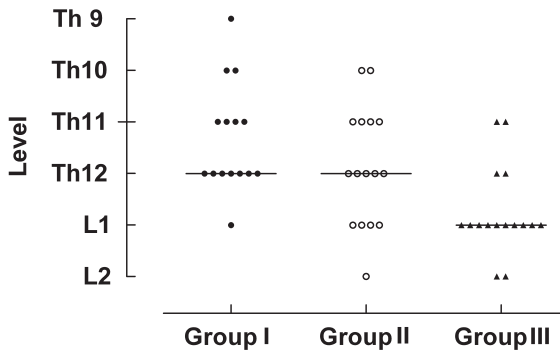


Figure 10.
Maximal cranial level in neonates (group I), infants (group II) and toddlers (group III). The solid bars indicate median values.

An inverse relationship was also observed with regards to individual age ($r_s = -0.5325$; $p = 0.0001$), weight ($r_s = -0.5104$; $p = 0.0002$) and height ($r_s = -0.5326$; $p = 0.0001$) (Please see *Figure 3* in *Study III*).

The percentage of patients where the volume of 1.5 mL kg^{-1} of local anesthetic did reach the target level of Th12 was significantly different in the three age groups (*Figure 11*). In Group I the target of Th12 was reached in 93 % of patients, whereas the corresponding values were 73 % and 25 % of patients in Groups II and III, respectively.

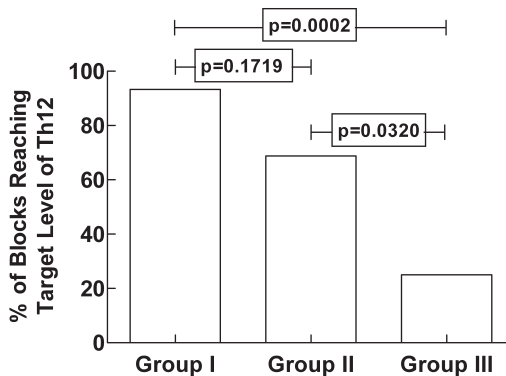


Figure 11.
Percentage of blocks reaching the target level Th12.

The relationship between volume of local anesthetic per covered segment vs. biometric patient data (age, weight and height) is shown in *Figure 12ABC*. Compared to the predictive Takasaki equation, ultrasound assessment overestimated the volume per segment relationship by a factor of approximately 2.5 (median 2.4; range 1.9-3.0) (*Figure 12B*). If compared to the Schulte-Steinberg age-based equation, ultrasound assessment overestimated the volume per segment relationship by a factor of more than three (*Figure 12A*).

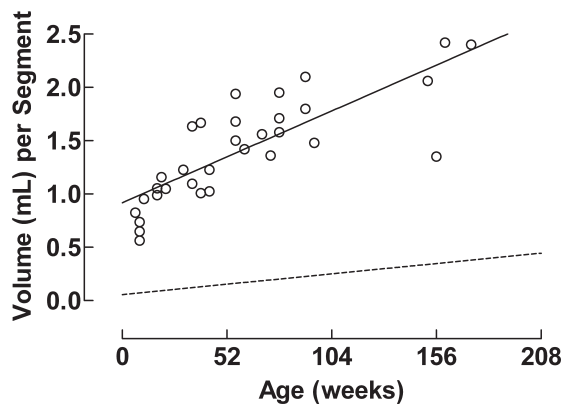


Figure 12A. Volume of local anesthetic per covered segment in relation to age with regression line ($r_s = 0.8371$; $p < 0.0001$). Dotted line represents the Schulte-Steinberg equation.¹⁶

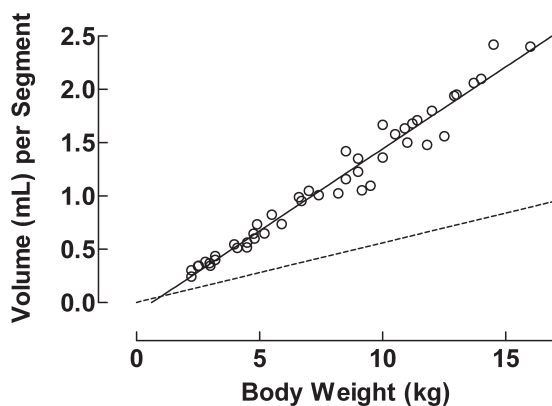


Figure 12B. Volume of local anesthetic per covered segment in relation to weight with regression line ($r_s = 0.9852$; $p < 0.0001$). Dotted line represents the Takasaki equation.¹⁷

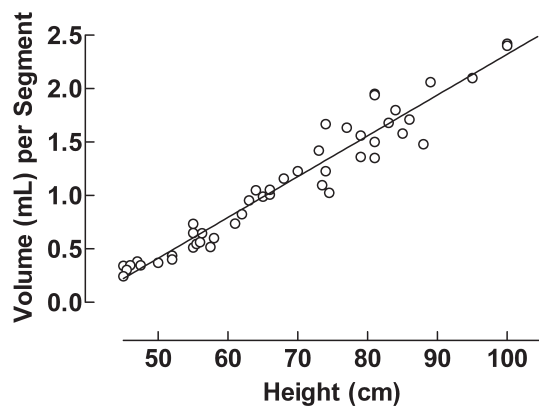


Figure 12C. Volume of local anesthetic per covered segment in relation to height with regression line ($r_s = 0.9662$; $p < 0.0001$).

A predictive equation based on our observed data is given below:

$$\text{Dose (mL/spinal segment)} = 0.1539 \cdot (\text{BW in kg}) - 0.0937.$$

5.5 SECONDARY SPREAD OF CAUDAL BLOCK (STUDY IV)

The median level of cranial spread as assessed by ultrasound directly after the caudal block was Th10 (range Th12 to Th9). 15 minutes after the caudal injection the most cranial level had increased to a median level of Th8 (range Th11 to Th4). In 10 out of 16 patients a cutaneous segmental level of analgesia could be assessed approximately 15 minutes after the caudal block.

The most cranial sensory level determined by cutaneous stimulation was in median Th4 (range Th3 to Th10). Thus, in 6 patients no response to the cutaneous stimulus could be obtained (*Figure 13*).

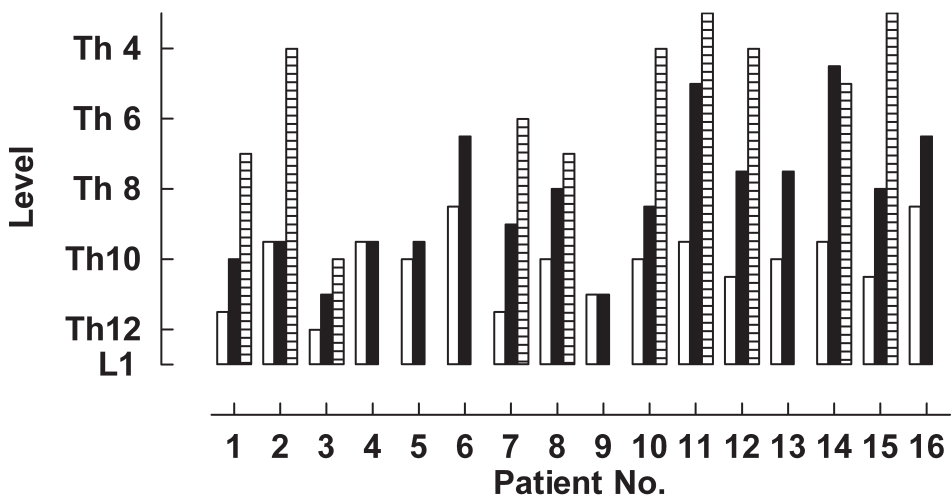


Figure 13. Ultrasound-assessed cranial level of spread immediately after caudal injection (open bars) and after 15 min (filled bars). The striped bars show the level of cutaneous analgesia assessed 15 min after the initial injection of LA.

The increase in ultrasound assessed cranial level between 0 and 15 minutes was 2 segments (median value; range: 0-4.5). The corresponding value was 5.5 segments (median value; range: 2-7.5) when the level of cutaneous analgesia at 15 minutes was compared to the initial level determined by ultrasound immediately after the caudal injection.

The median A-P diameter of the dural sac at the level of L3-L4 was 9.8 mm (range 7.2-11.6 mm) prior to the block, and was seen to be reduced to only 5.6 mm (range 3.0-6.8 mm) immediately after the caudal injection. After 15 minutes a partial re-expansion of the dural sac was observed in all patients (median 6.8 mm; range 5.8-8.5mm) (*Figure 14*).

The skin to dorsal dura distance at the L3-L4 level was 8.6 mm (median; range 6.1-12.5 mm) 13.2 mm (9.1-17.2) and 11.6 mm (7.9-14.6) at baseline, immediately after injection and 15 minutes post-injection, respectively.

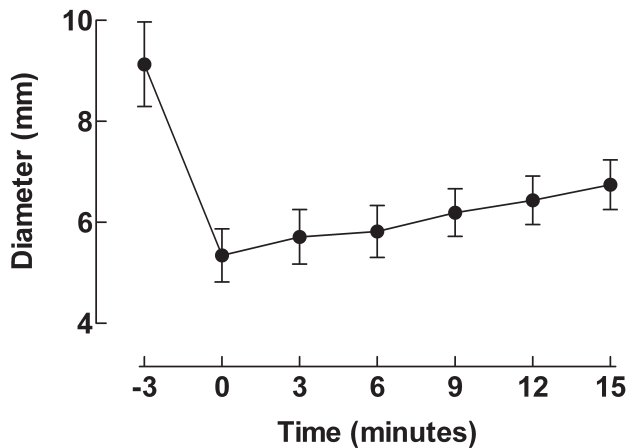


Figure 14. Diameter of the dural sac before caudal injection and during the 15 min observation period. Values are given as mean and 95% confidence intervals.

During the first 3-6 minutes after injection a re-distribution of the local anesthetic to the ventral compartment in front of the dura was observed. The estimated median value of this fluid layer at 15 minutes was 1.1 mm.

5.6 CAUDAL-EPIDURAL PRESSURES
FOLLOWING A CAUDAL BLOCK (STUDY IV)

The caudal-epidural pressures increased immediately following injection and were subsequently seen to gradually decline towards baseline pressures at the end of the 15-min observation period (*Figure15*).

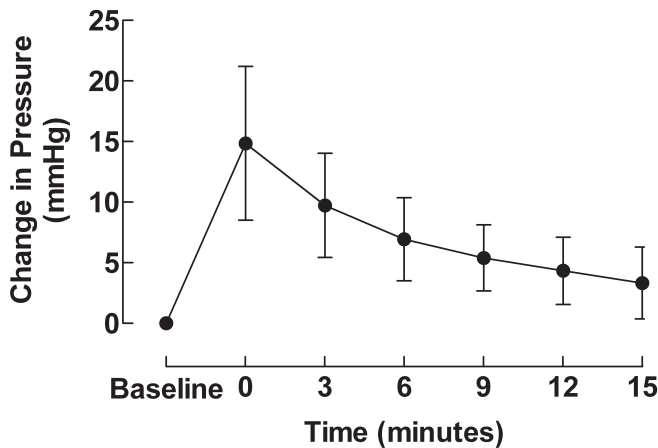


Figure 15. Change in caudal-epidural pressure in relation to baseline (mm Hg). Data are presented as mean and 95% confidence intervals.

6 Discussion

Possibility to block peripheral nerves

The introduction of high quality ultrasound imaging in regional anesthesia has made it possible to visualize and block even very small peripheral nerves and nerve branches, e.g. the third occipital nerve, auricular nerve, medial antebrachial cutaneous nerve,^{102,130,131} something that previously has been impossible when using landmark based or NS guided techniques. Furthermore, USG also simplify the identification of purely sensory nerves, which is quite difficult when using NS guidance.

This recent development has made it possible to reliably block very peripherally located nerves, making regional anesthesia even more regional. Thus, depending on various factors it may prove possible to produce super-selective regional anesthesia, thereby avoiding blockade of unnecessary anatomical structures.

Rationale for developing a super-selective nerve blocking technique for arthroscopic knee surgery

The clinical usefulness of single-injection or continuous femoral blockade for knee surgery is well documented.¹³²⁻¹³⁴ Despite the excellent sensory analgesia associated with this technique the frequent occurrence of motor block of the quadriceps muscle is often problematic and may even result in fall accidents.^{135,136} A current trend to address these limitations is instead to block the saphenous nerve at the mid-thigh level, most frequently by using the trans-sartorial approach.¹³⁷⁻¹⁴⁰ Although avoiding motor block of the major part of the quadriceps muscle a block at this level may still block the motor nerve that innervate the vastus medialis muscle, as evidenced by one of the subjects in Study I.

To be able to accomplish a purely sensory nerve block of the relevant parts of the knee associated with arthroscopic knee surgery a block must be performed distal to the mid-thigh level, which provides the rationale for modifying our approach slightly in Study II.

Factors likely to influence the possibility to achieve super-selectivity

The following features are prerequisites for accomplishing a super-selective nerve block:

- 1) High performance US machine with high frequency linear probes
- 2) Adequate training and experience of the operator.
- 3) Target nerve structure must be superficial.
- 4) Target nerve structure must be anatomically separated from other significant nerve structures.
- 5) The injected volume of LA must not be excessive in order to block only the target nerve, thereby avoiding potential spill-over to adjacent nerve structures.

Although not representing a super-selective nerve blocking approach, a simplified way of achieving ultimate peripheral nerve block in the context of more major knee surgery is the use of the local infiltration analgesia (LIA) technique. This technique was first described by Kerr & Kohan¹⁴¹ and has now become very popular due to excellent postoperative analgesia.¹⁴²⁻¹⁴⁶ Furthermore, in selected patients the use of LIA will make it possible to discharge uni-compartmental knee-replacement patients after only one night's stay in hospital.¹⁴¹ However, this novel technique requires substantial surgical exposure to allow the wide-spread infiltration of LA necessary - a fact that unfortunately makes this technique non-valid in the context of arthroscopic knee surgery.

Ultrasound-guided infra-patellar nerve block and super-selectivity (Study I)

The aim of study I was to develop a super-selective block of the IPN, thereby only producing sensory blockade of the anterior aspect of the knee. How well did we achieve this aim?

With the probe position and puncture site used in study I we were only able to achieve a certain degree of selectivity between the intended IPN block and concomitant spill-over block of the SN, despite the active attempt for injection only close to and around the IPN. However, the duration of the spill-over SN block was of considerably shorter duration compared to the IPN block that displayed a median duration of 30.5 hours. Thus, in regards to the duration of the IPN block we did in fact achieve a certain degree of super-selectivity.

It should also be noted that in one of the volunteers in Study I, no block of the IPN could be detected and the discrete block of the SN noted was very time-limit-

ed. The most probable cause for this failure was that a slightly more proximal probe position was necessary in this patient in order to avoid an extensive rete vasculorum genu. By doing so we most likely mistook the motor branch innervating the vastus medialis muscle for the SN, an observation pointing to the need for a more distal approach in order to possibly produce a super-selective block of the IPN.

Considering the only relative selectivity of the IPN block in Study I it may be interesting to compare the design features of this study against the factors influencing the opportunity to achieve a super-selective nerve block listed above.

First, despite using state-of-the-art equipment for the time of the study a very substantial improvement in ultrasound technology has taken place since 2006. Both the software of recent US machines as well as the development of multi-frequency probes using higher frequency bands, differ considerably from the performance characteristics of the Sonosite Titan with a 5-10 MHz linear probe used in Study I. Thus, more current equipment will most likely provide much enhanced resolution that will make the identification of the relevant nerve structures considerably easier. This should, thus, set the stage for better chances of accomplishing super-selectivity on the basis of better visualization.

Second, performance of USG nerve blocks does require a certain degree of operator skills, both concerning optimization of the US machine settings as well as dexterity in regards to handling the probe and the block needle. To successfully accomplish super-selective distal nerve blocks does for obvious reasons put even bigger demands on the skills of the operator. This fact is of clinical importance and may limit the more wide-spread use of selective IPN blockade.

Third, with the exception of extremely muscular or very obese individuals the SN/IPN in most patients are adequately superficial at the level of the patellar base, representing the modified approach used in Study II, and therefore the opportunity for super-selective nerve blockade appears satisfactory.

Fourth, from an anatomical point of view both the remaining part of the SN and the proximal part of the IPN do run very close together after the branching point, making partial spill-over almost inevitable. With better US equipment it may prove possible to track the IPN even further distally but that may introduce the risk of missing adequate nerve block of some of the more distal IPN branches. Due to these anatomical circumstances a possibly more successful way of achieving super-selectivity would be to use less volume of LA, thereby limiting the risk for SN spill-over.

Finally, as indicated immediately above the issue of LA volume is important when discussing the possibility to achieve a more selective block of the IPN. Since there were no data available with regards to the relationship concerning nerve size

and volume of LA at the time of Study I, we randomly decided to use a volume of 5 mL for performance of the block. From the study results it is apparent that this was an excessive volume since a spill-over SN blockade of a varying degree was observed in all subjects. Since this time two studies have been published that specifically have addressed the nerve size-LA volume relationship. To reliably block the ulnar nerve just distal to the elbow an ED 95 of 0.11 mL mm⁻² was found¹⁴⁷ and with regards to the sciatic nerve a corresponding ED 99 value of 0.10 mL mm⁻² was reported.¹⁴⁸ Considering that the cross-sectional area of the IPN in adults is approximately 4 mm² (own data not shown) then a selective IPN block would only require approximately 0.5 mL of LA, a volume that represents only 10% of the volume used in Study I. Using such a much smaller volume may, thus, increase the chance of producing a selective IPN but how this may affect the duration of the block is unclear.

Against the various issues discussed above it is prudent to reflect on whether it is in fact absolutely necessary or clinically important to achieve a truly super-selective IPN.

By changing the probe position and thereby the level of the LA injection slightly more distal in Study II the risk for unwanted motor block of any part of the quadriceps muscle is minimized or maybe even completely abolished- a fact that must be viewed as beneficial and in line with the concept of super-selectivity. However, this more distal approach did not influence the incidence of concomitant SN blockade since all patients receiving an active block in Study II were found to have a quite prolonged postoperative SN block. This is of course hardly surprising since we opted to use an even large LA volume (10 mL) in Study II- a decision based on the assumption that a larger volume of LA would increase the likelihood of prolonged postoperative analgesia. Furthermore, the unintentional sensory blockade of the distal part of the SN caused by a spill-over effect does not really cause any major problems to the patients and may therefore be judged to be of very limited clinical relevance.

In conclusion, using the nerve block approaches described in Study I and II will result in a preferential/semi-selective block of the IPN, at least with regards to the duration of the IPN block. In our personal opinion it does not appear necessary or clinically useful to strive for an even more super-selective IPN block since this may increase the difficulty in correctly performing the block and may negatively affect the duration of the block if reduced volumes of LA must be used.

Postoperative analgesia following out-patient surgery (Study II)

During the last decades there has been a massive move in health care to perform larger numbers and more complex types of surgery on an out-patient basis and figures from the USA tell that more than 70 percent of all surgical procedures currently

are done on an ambulatory basis.¹⁴⁹ This trend is also evident for children where American figures point to an increase of ambulatory procedures by 50% from 1996 to 2006.¹⁵⁰ However, the problem of postoperative pain is often neglected in the context of ambulatory surgery and an incidence of 30-40% of moderate to severe pain during the first 24-48 hours has been reported following out-patient surgery.¹⁵¹⁻¹⁵⁴ Thus, to be able to provide new more long-acting analgesic options that can address insufficient postoperative analgesia during the 12-36 hour period after surgery is desirable.

In the context of out-patient knee surgery various regimens have been employed in order to improve postoperative analgesia. Building on the positive in-hospital experience with regards to the use of continuous femoral nerve catheters, this technique has also been tried after hospital discharge.¹²⁵ However, as exemplified by case reports the motor block associated with the use of femoral nerve catheters may cause fall accidents at home.^{135,136} Thus, the use of this technique for home care has been questioned.¹⁵⁵ The ambulatory use of intra-articular catheters has also been tried in order to improve post-discharge analgesia but this technique has not been as successful as to be recommended for routine use.¹⁵⁶

Currently the use of a combination of different analgesic treatment options, so-called multi-modal analgesia, has become very popular with regards to out-patient surgery.^{157,158} In the context of ambulatory arthroscopic knee surgery such a multi-modal approach may involve a combination of intra-articular deposition of LA with adjuvant drugs (e.g. ketorolac and morphine), wound infiltrations with long-acting LA at the end of surgery plus a postoperative combination of oral analgesics with different modes of action (e.g. paracetamol, NSAID, codeine, and opioids). This type of multi-modal analgesia often provide excellent early postoperative analgesia but due mainly to the limited duration of the LA the pain situation after hospital discharge may become problematic, with pain scores being in the range of 4 to 8.^{125,159} Despite that multi-modal techniques represent current state-of-the-art for postoperative analgesia following ambulatory arthroscopic surgery there is still a need for improvement following discharge from the out-patient facility.

Although our primary interest was to improve the postoperative pain situation for our teenage patients undergoing anterior cruciate ligament repair the restricted numbers of these procedures at the pediatric hospital precluded any clinical studies to be performed in this age group. Thus, we decided to investigate the clinical usefulness of the USG IPN block in adults having arthroscopically assisted ACL repair performed at the Stockholm Sports Trauma Research Center/ Capio Arthro Clinic-Sophiahemmet.

Use of VAS/NRS scales for pain assessment

The choice to use the VAS scale in the recovery room and the NRS scale following discharge in Study II may deserve further comment. However, since assessment of pain by VAS or NRS both result in adequate data for scientific purposes¹⁶⁰ we decided due to practical reasons to use the VAS during the PACU stay and the more patient friendly numerical scale following discharge from the PACU.

How best to use pain scores in order to scientifically evaluate postoperative analgesia is a quite complex issue. One common approach is to compare the AUC during predetermined time periods but the adequacy of this technique can be discussed and may be considered as a relatively blunt assessment tool when trying to identify more subtle differences between two treatment groups. Thus, we instead decided to use the clinically relevant pain assessment value of >3 as the primary focus of the study, a pain score that both represents a well accepted value that is often used to divide pain in minor or moderate-severe¹²⁷ as well as its use as trigger for administration of supplemental rescue analgesia.^{125,126}

What can be expected from adding new analgesic options to current state-of-the-art multi-modal analgesia?

Figure 16 provides a graph showing the potential for additional postoperative pain-relief by adding new analgesic interventions to previously existing alternatives. Thus, going from zero analgesic treatments (e.g. providing no analgesics or using true placebo) to adding some sort of active analgesic option (0 to A) will have the potential to produce a quite large analgesic effect, as evidenced by a considerable reduction of pain scores. If adding one further analgesic treatment option to treatment A will also have the potential to produce a reasonable effect-size with regards to reduction of postoperative pain (A to B). However, by continuing to add new analgesic treatment option to already existing therapy, the size of the pain reduction will diminish since this relationship is most likely exponential in nature (*Figure 16*).

Due to this exponential relationship it is not reasonable to expect any dramatic improvement in postoperative pain-relief by adding new treatment options to an already quite effective multi-modal regimen since we already are approaching the plateau part of the analgesia curve of Figure 16. Although the effect size may not be as great as adding the first analgesic treatment option, the effect size may still be of benefit for the patient.

In the context of Study II we expected to be on the very flat lower part of the analgesia curve during the first 12 hours after surgery (*Figure 16*; point: “MM incl LA”) and, thus, we did not anticipate being able to show any further benefit from adding

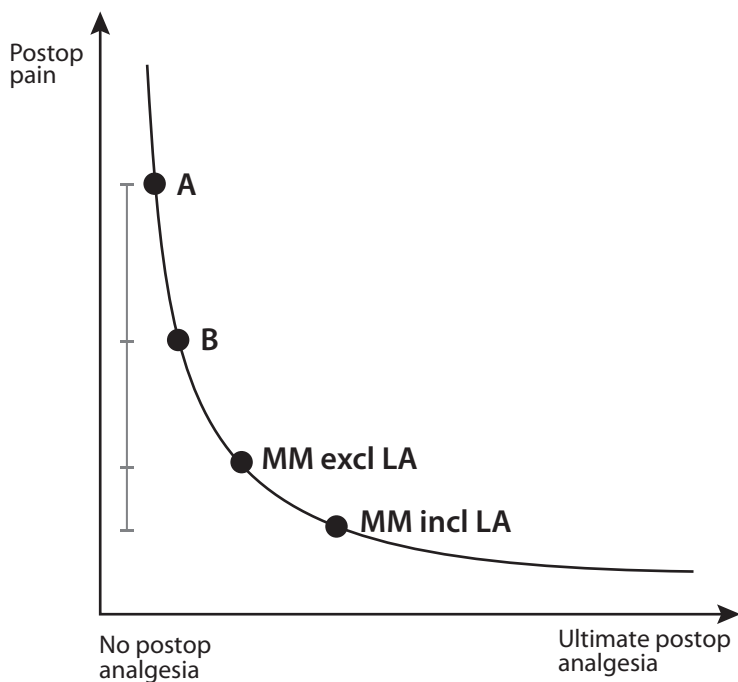


Figure 16. Schematic figure illustrating the potential for achieving postoperative analgesia:
*A= analgesic 1, B= analgesic 2, MM excl LA= Multimodal analgesia without LA,
 MM incl LA= Multimodal analgesia with LA.*

an IPN block to the already established multi-modal analgesic regimen during this time period. However, as the LA component of the multi-modal regimen is starting to wear off, the position on the curve will be shifted upward to the left (*Figure 16; point: “MM excl LA”*), thereby opening up for the opportunity to show added benefit from the addition of a further long-acting analgesic intervention. Thus, since Study I did show that the median duration of a 5 mL levo-bupivacaine 0.5 % IPN block was 30.5 hours we believed that adding this new treatment option to the already existing state-of-the-art multimodal analgesia regimen could potentially be found to produce added benefit to the patients during the latter part of the postoperative period.

Adequate comparison of postoperative analgesia treatment options

To be able to show an anticipated analgesic effect of a new analgesic therapy, researchers often test their new therapy against a modified postoperative analgesic regimen, thereby moving to the left of the curve in Figure 16 and by doing so improve the chance of showing a beneficial effect of the new therapy. In some instances a comparison is made against placebo despite the availability and regular use of established

analgesic options. Despite comparison against true placebo being very questionable from an ethical standpoint, even the American Food and Drug Administration (FDA) until recently demanded placebo controlled trials before granting registration for analgesic drugs! Thus, a large number of positive clinical trials involving various analgesic regimens can be questioned both with regards to efficacy as well as from an ethical perspective.

The Declaration of Helsinki demands that new therapies should be tested against the best currently available treatment option in order not to subject patients randomized to the control group to sub-standard treatment. We strongly believe in the validity of this concept and are therefore proud to have tested the additional usefulness of the new USG IPN block against current state-of-the-art multi-modal analgesia and hope that this will be viewed as a special merit of Study II.

The use of placebo injections in regional anesthesia trials

In Study II the control group was subjected to a placebo injection of saline in order to allow complete blinding as well as exclude any analgesic effect from the injection per se (e.g. localized pressure caused by the injectate on the nerve, potentially resulting in secondary analgesia). Since the placebo injection of saline was not considered to be able to produce any apparent or major side effects or complications we actively decided to use this study design. Reassuringly we did not register any complications during the study that could be related to the injection of either active LA or placebo saline.

However, after the start of Study II we are aware of the discussion regarding the appropriateness of using placebo injections in regional anesthesia trials. Thus, a review published in *Anaesthesia*¹⁶¹ strongly questions the use of placebo injections in the control group and instead suggest other measures to allow for adequate blinding and subsequent efficacy evaluation. According to the Serious Harm and Morbidity categorization system (SHAM scale) put forward by McGuirk et al, study II would be given a score of 2.

Despite the thought-provoking discussion with regards to placebo injections we still are not convinced that the use of placebo injections should be completely abandoned. Since the IPN blocks were performed in awake patients in Study II we still believe that the use of placebo injections was necessary in order to achieve adequate study design and feel that any risks of a saline placebo injection performed at the medial part of the knee are of a minor nature and does not pose any ethical problems.

Ultrasound visualization in the context of caudal-epidural nerve blocks (Study III and IV)

The comparatively superficial position and the relative ease of ultrasound visualization of many peripheral nerves have made the interest for USG peripheral nerve blocks to grow almost exponentially. However, mainly due to the anatomical situation US guidance has not become even remotely as popular in the context of central nerve blocks.

USG epidural blockade in adults

The fact that ultrasound waves are totally reflected by bone structures make it very difficult to get adequate ultrasonographic access to the relevant structures of the spinal canal due to the ossification of the vertebrae combined with the quite narrow anatomical relationships of the spine in adults. Despite real-time US guidance being advocated by Karmakar as an aid when performing epidural blockade in adults,^{162,163} US guidance has not achieved wide-spread use due to the difficulties associated with this technique.

As a consequence of the very limited US window of the intra-spinal contents in adults, it is therefore also very difficult, not to say impossible, to assess the spread of LA within the epidural space.

Despite the limitations outlined above ultrasound examination prior to the performance of a traditional epidural block in adults can generate very useful data.

1. The depth from the skin to the epidural space can be estimated with good accuracy by using the caliper function of the US machine. This can be of great value in many patients, especially in pregnant women and very obese subjects.
2. US scanning can determine the best and most available interspace for epidural puncture.
3. Anatomical abnormalities and foreign materials, e.g. orthopedic rods and plates, can be detected and thereby avoided.

Thus, even if ultrasound assistance is not of any major value as a real-time tool during the active performance of an epidural block or for estimation of LA epidural spread in adults, it should be remembered that pre-block ultrasonographic scanning of the anatomy may still be very helpful in certain adult patient categories.

Ultrasound scanning as part of caudal-epidural blocks in infants and children

Contrary to the situation in adults the vertebrae of neonates and infants are not yet fully mineralized, which allow for complete or almost complete visualization of the intraspinal structures. As children get older the ultrasonographic window available for visualization of the intraspinal structures is gradually reduced from approximately 80% at 5 kg body weight to only 10% at 25 kg body weight.¹⁶⁴

Since US visualization is so much easier in infants and young children an USG epidural block technique has been described by Willschke et al.⁴¹ In this study the use of the USG epidural block technique was associated with fewer episodes of bone contact and a faster performance time as compared to the traditional loss-of-resistance technique. Willschke and colleagues are now so confident about this technique that they regularly use this technique even in premature babies¹⁶⁵ as well as for a novel awake single-injection USG epidural block for pyloromyotomy.¹⁶⁶ Although the latter technique appears exciting caution with regards to general dissemination of this advanced USG technique has been advocated by certain experts.¹⁶⁷ Thus, whether the USG epidural technique eventually will be more widely adopted by pediatric anesthesiologists remains to be seen.

When performing caudal blockade real-time US guidance is not only of benefit for the initial location of the sacral cornuae and the hiatus but is also helpful to verify the correct placement of the injection of LA into the caudal-epidural space. A further interesting and valuable possibility is to tract the injectate of LA and thereby getting a quite accurate estimation on the cranial extension of the injected volume of LA in the spinal canal.^{168,169} Study III & IV were both aimed at further elucidating the problem complex of US assessed cranial spread of caudal blockade in infants and children.

Cranial spread of caudal block (study III)

Influence of age on the US assessed level of cranial spread

Ever since the first report on the use of caudal blockade in children by Campbell in 1933¹⁴ the dosage of LA has been determined entirely on empirical grounds. Furthermore, early dosage guidelines are often based on body size (weight- or height-based equations).¹⁶⁻¹⁸ An example of this is the widely used dosage guideline published by Armitage,¹⁵ which suggests that an equal cranial level would be reached in all age groups if the same volume per kilogram is administered. However, since both the height of each spinal segment and the diameter of the spinal canal will increase with age it is not intuitive that these early dosage recommendations based on body size in fact are accurate.

In Study III a fixed volume of LA per kg body weight (1.5 mL kg⁻¹) was administered to neonates, infants and toddlers and the cranial level of LA spread was assessed by US. As could be expected an inverse relationship between age and the likelihood of reaching the thoracic level could be observed (*Figure 11*). However, when a regression analysis was performed including the entire study population, very similar regression coefficients were found for age, weight and height (r_s -value range: -0.51 to -0.53) (*Figure 3, Study III*)- a finding that is in close agreement with the results reported by Schulte-Steinberg already in 1977.¹⁶ Thus, age does appear to be an important parameter for the cranial extension of caudal blockade in children but the close correlation between age and body size in children less than 6 years of age make the use of age or body size to predict cranial level to be almost interchangeable. However, in the light of the dramatic current increase in the incidence of childhood obesity one may speculate that age will be a better parameter for predicting cranial spread than body weight in this particular sub-group of pediatric patients- a hypothesis that needs to be confirmed in future studies.

Discrepancy between radiographically assessed cranial level of caudal blocks and cranial levels determined by predictive equations

The most intriguing finding of Study III, as well as other studies using radiographic methods to determine cranial spread of caudal blocks in children,¹⁷⁰⁻¹⁷² was the obvious discrepancy between the cranial level determined by the use of US and the cranial level calculated from the predictive equations available.¹⁶⁻¹⁸ A very similar result was also found in our subsequent study that examined the effect of varying LA volumes on US assessed cranial level following caudal block in children within the age range 1 month-6 years.¹⁷³

In summary, the use of previously published predictive equations result in substantially higher cranial block levels as compared to what can be observed by radiographic examination, where the cranial level of the caudal block in the majority of cases never reach more cranial than the thoraco-lumbar junction.

For a more detailed argument behind the possible factors responsible for this obvious discrepancy the reader is referred to the discussion section of Study III. We have become very puzzled by this intriguing disagreement between the two different methods for cranial block level determination and as a result of intellectual reasoning and pilot observations we arrived at the possible explanation outlined in the following sub-section.

The cerebrospinal fluid rebound mechanism as an explanation for secondary spread of caudal block in children (Study IV)

A key element potentially explaining the discrepancy outlined above is the time factor. Radiographic determination of the cranial spread of the caudal injectate is performed immediately at the end of the injection when ultrasound is used and within just a few minutes if an X-ray picture is taken. This differs considerably from cutaneous assessment during light halothane anesthesia that was used in the studies providing the predictive equations. It is not possible from the methods description of these studies to exactly determine when these assessments were performed but it can be approximated to about 15-20 minutes post-injection.¹⁶⁻¹⁸

A very plausible cause for the diverging levels obtained after radiographic determination vs. predictions made from cutaneous testing approximately 15-20 minutes post-injection, is that the radiographic methods only determine the primary spread of the LA, whereas cutaneous testing will also take secondary epidural spread into account. Speculations with regards to the potential mechanisms responsible for secondary spread has been put forward by Thomas et al,¹⁷⁰ but in our opinion none of these suggestions can satisfactorily explain the quite large difference between the cranial level reached immediately after the injection and the level that is finally reached as a result of secondary spread.

When following the caudal injection by US, it can clearly be seen that the initial spread is caused by a bulk-flow of LA, preferentially in the posterior part of the spinal canal. Due to the quite substantial difference between the level reached by primary spread and the level achieved after allowing secondary spread to take place, we have come to believe that some other mechanism must be present to cause a “second wave” of bulk transport of the LA, thereby explaining a large part of the process of secondary spread.

During real-time US scanning of the intraspinal spread of LA during caudal blockade it is readily apparent that the distal part of the dural sac become maximally compressed, thereby forcing CSF cranially. This observation combined with data from the adult literature with regards to how the cranial level of a spinal block can be manipulated by a subsequent epidural injection of saline when performing a combined spinal-epidural technique¹⁷⁴ focused our thought-process on the potential effects of CSF movement on secondary spread of a caudal block. Preliminary data from Bombardieri et al,¹⁷⁵ showing a transient reduction in intracranial blood flow as a result of an epidural injection in adults, gave further support for the potential impact of CSF movement as a mechanism for secondary spread (*Figure 17*).

In Study IV we subsequently tested our hypothesis concerning the “CSF rebound mechanism” by observing the intraspinal process that take place during the initial 15 minute period following the bulk injection of LA into the caudal-epidural space. In line with the hypothesis a partial re-expansion of the distal part of the dural sac could be observed as the intraspinal pressure returned toward baseline values. When approximating the volume shift caused by the secondary rebound of CSF it became evident that this mechanism in fact can cause a “second wave” of LA bulk transport that may corresponds to 15-20 % of the initially injected volume of LA. Thus, a rebound of CSF of this magnitude would, according to the predictive equation reported by Takasaki,¹⁷ result in an increased cranial level of the block of four segments in the studied patient population.

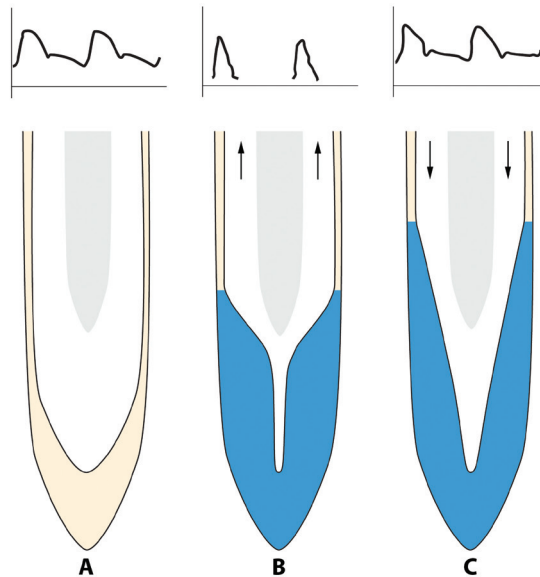


Figure 17. Schematic drawing showing the spinal canal with the spinal cord (grey), dural sac with CSF (white) and the epidural space (yellow): before (A) , immediately after (B) and approximately 15 minutes after (C) a high-volume (1.5 ml kg^{-1}) caudal block . The arrows indicate a rostral movement of CSF caused by the compression of the distal part of the dural sac by the injected LA (blue) (B), followed by re-expansion of the distal part of the dural sac when CSF is moving caudally due to reversal of the relative spinal-to- intracranial pressure gradient, thereby forcing the epidurally located LA to move to a more cranial level (C). The upper panel shows transcranial Doppler measurements (cerebral blood flow velocity), using a transtemporal window in an adult: before (A), immediately on completion of injection (B) and after (C) a relatively rapid lumbar epidural injection (25 ml). Please note the reduced peak velocity as well as the disappearance of diastolic flow immediately after the injection, providing indirect evidence of transiently increased intracranial pressure due to rostral movement of CSF caused by the epidural injection.

The Doppler curves are reproduced by kind permission by AM Bombardieri.

We believe that the observations of Study IV strongly support the fundamental importance of “CSF rebound” for secondary spread of LA following caudal block in children. Further support for this mechanism could be generated by investigating intracranial blood flow during and immediately after the performance of a caudal block in infants. Such studies are necessary in order to verify that a similar transient reduction of intracranial blood flow that can be observed in adults as a result of an epidural volume administration (indicating a transient increase in intracranial pressure) is also present in children. Pilot data from one of our now on-going studies is shown in Figure 18, which quite clearly show a transient reduction in blood flow recorded from the middle cerebral artery, starting to occur after the injection of approximately 50 % of the final volume of 1.5 mL kg^{-1} , returning almost to baseline values after approximately 2 minutes. Thus, we hope that this follow-up study when completed will provide even further verification of the “CSF rebound mechanism” as an important part of secondary spread following caudal blockade in children.

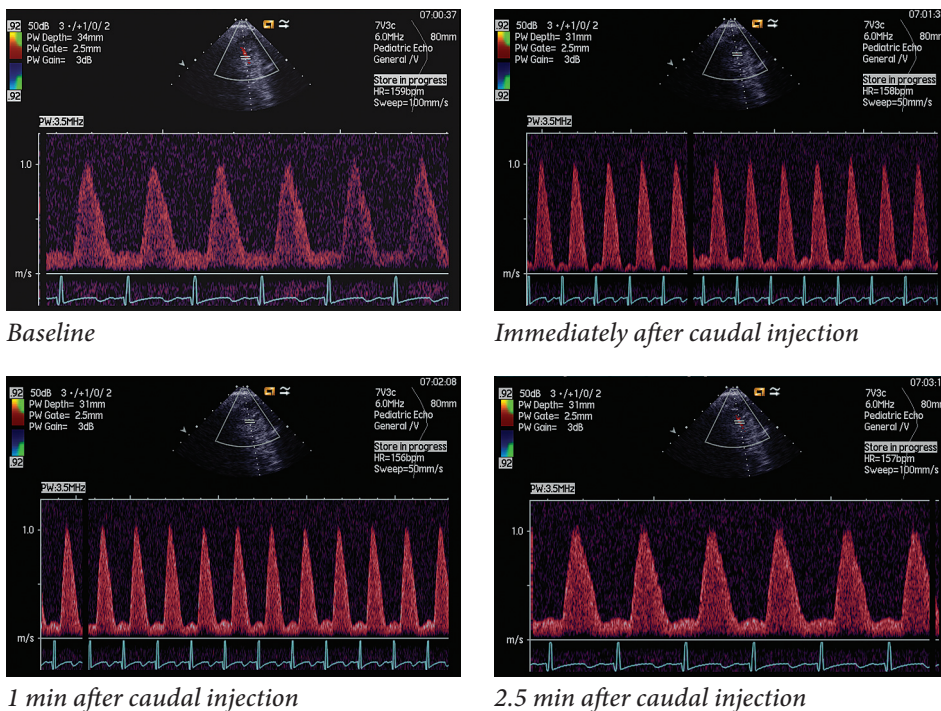


Figure 18. Pilot study; Doppler recordings of cerebral blood flow recorded from the middle cerebral artery in a 5 kg infant.

FUTURE PERSPECTIVES

The introduction of real-time ultrasonographic guidance by Kapral in 1994 has to a very large extent revolutionized the practical performance of RA. In less than 20 years time this new approach to perform RA has already undergone significant technical improvements as well as resulted in numerous scientific publications that have helped providing the necessary initial evidence-base for this technique. Against that background it is not very bold or controversial to predict that the near future will continue to provide new and even more refined ultrasonographic technology, which will make RA even more accurate and easy to perform. Furthermore, clinical research will hopefully provide large-scale prospective randomized trials that will allow us to determine which USG nerve block techniques that are associated with the greatest clinical advantages, both with regards to patient benefits as well as concerning the best use of limited health care resources.

Finally- it is now more than one hundred years since Koller first discovered regional anesthesia and during this time it has experienced both periods of extensive use as well as times of disuse. However, the introduction of ultrasound guidance combined with new technical and pharmacologic developments will most likely strengthen the place for regional anesthesia in every-day clinical care and will thereby continue to provide substantial benefit to our patients.

7 Conclusions

From the studies of which this thesis consists the following conclusions are drawn.

1. Study I

- The infrapatellar nerve can be successfully identified and subsequently blocked using ultrasound guidance.
- A single injection IPN block has a fast onset time and duration in excess of 24 hours. The resulting area of analgesia is in agreement with the requirements of arthroscopic knee surgery.
- The ultrasound-guided infrapatellar block technique is not completely super-selective due to the close anatomical relationship between the infrapatellar nerve and the saphenous nerve, thus, a varying degree of concomitant saphenous nerve block is virtually inevitable.

2. Study II

- The use of an ultrasound-guided block of the infrapatellar nerve as an adjunct to multimodal analgesia is associated with improved pain relief and an increased number of sleep hours after arthroscopy assisted anterior cruciate ligament repair.

3. Study III

- After a caudal injection of 1.5 mL kg^{-1} in children 0-4 years old, the maximum cranial spread of local anesthetics in the epidural space as assessed with ultrasonography was found to range from L2 to Th9.
- An inverse relationship between age, weight and height and the number of segments covered by local anesthetics was found.
- The cranial spread of LA within the spinal canal as assessed by immediate ultrasound visualization was found to be in poor agreement with previously published predictive equations based on patient characteristics and actual cutaneous dermatomal testing.

4. Study IV

- Two separate patterns of secondary spread of a high volume caudal injection in infants could be observed; horizontal intrasegmental redistribution and longitudinal cranial spread.
- The magnitude of secondary longitudinal cranial spread at 15 minutes post-injection was 2 segments (median) when assessed by ultrasound and 5.5 segments (median) when assessed by cutaneous testing.
- The observed bi-directional movement of cerebrospinal fluid in association with a high volume caudal block, coined “the CSF rebound mechanism”, represents one factor causing secondary longitudinal cranial spread.

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