Diagnostic Segmental Nerve Root Blocks in Patients with Chronic Radiating Low Back Pain: Bringing Light to the Darkness?

André P. Wolff, M.D.

Diagnostic Segmental Nerve Root Blocks in Patients with Chronic Radiating Low Back Pain: Bringing Light to the Darkness?

een wetenschappelijke proeve op het gebied van de medische wetenschappen

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Table of Content

Chapter 1

GENERAL INTRODUCTION

Chronic pain is a common problem leading to a high individual and societal burden. A cross sectional survey amongst adults revealed that chronic pain was present in 17% of males and 20% of females [1], whilst self reported chronic pain was present in some 46% of the general population [2]. Low back pain (LBP) constitutes a major part of all chronic pain problems. Its incidence with and without radiation to the lower limbs is 11,6 and 28,0 per 1000 patients referred to the general physician per year, respectively [3]. In the Netherlands year prevalences of up to 40% of the total adult population are reported. Of all patients having acute LBP, about 10% develop chronic back problems [4-6]. No specific diagnosis, such as a herniated disc or spinal stenosis, is found in more than 90% of all cases of low back pain. Diagnosis and treatment in this patient population are laborious and problematic. Once patients have chronic low back complaints they rarely recover, and 32% are unable to work at all [3].

Chronic (low back) pain: a complex problem

Since the mid 20th century there has been increasing attention to the idea that chronic pain is multifactorially determined. Thus a multidisciplinary approach has been advocated to improve treatment outcome. At present, the bio-psycho-social approach [7] is considered the basis for the treatment of chronic low pain, which should be considered as a disease of itself [8]. In most pain centers, at least 3 different disciplines representing psychologists, neurologists, surgeons, anesthesiologists, physical therapists and rehabilitation physicians are involved in the treatment of chronic pain. Multiple factors such as psychological, social, behavioral, cultural, physical and economical factors are assessed to diagnose and treat chronic pain patients, whose problems are often complex. Recently, increasingly biological factors contributing to the complexity of the pain problem have been identified, such as pain and time induced functional changes of the central and peripheral nervous system, i.e., neuroplasticity [9], neuronal networks [10], and involvement of the (neuro-)immune system and inflammatory processes [11]. New diagnostic techniques like neurofunctional imaging [12], quantitative sensory testing [13] (QST) and sophisticated spinal endoscopic procedures [14,15] are helping us to develop further insights into the complex problem of pain and specifically into the problem of LBP and its chronification.

Most LBP patients are treated by general practioners, usually according to the guidelines of their professional societies [16,17]. In most patients with non-specific back complaints, the problems will disappear spontaneously [18] and therefore initial additional investigation by general practitioners is discouraged. Thus LBP patients are most commonly treated conservatively using education, physical therapy, and oral medication. Patients with a more chronic or recurrent course of LBP are referred to medical specialists such as neurologists, orthopedic surgeons or rehabilitation medicine physicians. In severe cases chronic patients are referred to multidisciplinary pain clinics for further assessment. If the diagnosis in patients with chronic low back pain radiating to the leg (CLBP-r) is not clear despite extensive physical, neurological, orthopedic and radiological examination, "precision diagnosis", such as diagnostic facet blocks, sacroiliac joint blocks, diagnostic disc injections and segmental nerve root blocks (SNRBs) has been advocated [19].

Segmental Nerve Root Blocks

Segmental Nerve Root Blocks (SNRBs), also known as nerve root sheath infiltration or periradicular nerve root injection, have been employed since the early thirties of the last century. They are typically done for diagnostic purposes in patients with radicular pain to determine the pain conducting spinal segment prior to surgery [20-25], to identify the putative symptomatic level for diagnostic reasons in patients with pain presenting as radicular but not fully concordant with the radiological diagnosis [26-28], and to select patients for a radio-frequency procedure of a dorsal root ganglion [29-31] (RF-DRG). Furthermore, SNRBs with local anaesthetics have been followed by or combined with corticosteroid agents [32,33] for diagnostic and therapeutic reasons.

However, SNRBs are not mentioned as an additional diagnostic step in the guidelines on lumbosacral radicular syndrome for general practitioners [16]. As already mentioned, further diagnostic assessment is in fact discouraged in case of non-specific low back complaints [17,34]. Non-specific or aspecific LBP is an accumulation of complaints after specific diagnoses such as a herniated disc, spinal stenosis, infection or tumour have been excluded or if indications for their presence cannot be found. Nevertheless, other diagnostic entities as underlying cause of pain in CLBP-r patients [19] have been suggested, such as syndromes related to the lumbosacral facet joints, lumbar discs and sacroiliac joints. Imaging techniques commonly do not bring about a diagnostic classification in these patients, either, and therefore "precision diagnosis" is frequently suggested to further establish a diagnosis [19,26,31]. For this reason, when CLBP radiates to the leg according to a dermatomal pattern in the context of non-concordance of radiological diagnosis and pain presentation, SNRBs are commonly advocated.

Problems with SNRBs

There are many uncertainties with respect to the diagnostic value of SNRBs. One of the fundamental problems in CLBP-r patients is that pain reduction after SNRB may not inform us about cause and source of the pain, in contrast to a specific radicular pain syndrome where surgery and subsequent pain relief can confirm SNRB-aided diagnosis retrospectively. Thus, one of the main questions in this context is how one should interpret pain reduction with SNRB in CLBP-r patients with an uncertain underlying diagnosis. The justification for the use of SNRBs is based upon the axiom that pain reduction after blocking a particular spinal segmental nerve root indicates that this nerve root plays an essential role in the pain-conducting pathway. This is surprising, since SNRB outcome in CLBP-r patients lacks a gold standard upon which to base such a supposition [35].

Gold standard

A gold standard is a conclusive test or type of information that distinguishes patients having a disease or not. The ideal gold standard diagnoses the problem with 100% accuracy. A diagnostic test is considered reliable if it has a high sensitivity (ratio indicating the persons positive for the test related to persons who really do have the disease) and a high specificity (ratio indicating the persons negative for the test related to those who do not have the disease). The gold standard for validating SNRB effect in patients with specific radicular

pain, e.g. a herniated disc with nerve root compression diagnosed by history, clinical examination and MRI, is an accurate and specific anatomical and functional diagnosis followed by abolition of the patient's pain after surgical repair of the previously diagnosed prolapsed disc with relief of nerve compression in that patient. If an anatomical diagnostic gold standard is not available, which is the case in CLBP-r patients who have no clear diagnosis, at least a functional diagnostic gold standard, i.e. an objectively quantifiable disorder of pain system function should be present. In the case of SNRB, the underlying rationale would be that functional block of the disordered segment of the pain system results in reduction – or abolition – of pain symptoms. If SNRBs were a sensitive and specific diagnostic test, all SNRB-positive patients should together form a homogeneous population with respect to anatomical or functional diagnosis. CLBP-r patients, however, do not seem to form such a homogeneous population and we thus lack a gold standard upon which to base interpretation SNRB effects to compare with.

Further, if SNRB are applied to a heterogeneous population, its effects should at least be reproducible, i.e. consistent, leaving only the outcome variable. The outcome should distinguish patients with spinal segment related radiating pain in a reliable fashion from patients without segmental related radiating pain. This means that in case of applying SNRBs, the blocking effect on the segmental nerve roots should be consistent and predictable. To assess consistency of effects, SNRB induced changes in sensory and motor function should be measured. If these blocking effects indeed are reliably and predictably consistent, SNRB can be considered a useful diagnostic tool in CLBP-r patients.

Diagnostic value of SNRBs

Hildebrand (36) postulated that the diagnostic value of nerve blocks rests on 3 premises. Firstly, causal pathology is located at an exact and defined peripheral location. Secondly, injection of a local anaesthetic will abolish only the sensory function of the target neuronal location. Thirdly, pain relief subsequent to a local anaesthetic injection is attributable solely to the nerve block. The first premise raises problems in CLBP-r patients because the exact causal pathology is often not known and a diagnostic gold standard to compare with is absent. With respect to the second premise, the sensory selectivity of the SNRB is questioned [37]. The last premise may be tested by repeating the SNRB and by comparing the effects with blocks at neighbouring levels. Thus SNRBs, in reality, do not fulfill Hildebrand's criteria either. In patients, no relevant data are available on the relationship between volume, dosage of local anaesthetics and their effects. Despite all these uncertainties, i.e., we neither know what we are blocking nor do we understand the variability with respect to patients and blocking technique, SNRBs are assumed to produce predictive information regarding sensory and motor function within the segmental innervation territory, i.e., the corresponding dermatome and myotome respectively. Up to now no studies have appeared to describe these effects systematically in CLBP-r patients.

Lumbosacral Segmental Nerve Root Block Technique

To locate the target spinal nerve, a needle is inserted under CT or fluoroscopy

guidance towards the intended nerve root or its DRG. Correct anatomical position is assumed when the tip of the electrode is in the dorsocranial quadrant of the intervertebral foramen lateral to the medial half of the adjacent pedicles. Correct functional position of the needle is achieved by redirection of the needle and is assumed when, with the proper stimulation criteria, electrical or mechanical nerve stimulation elicits paraesthesias in the corresponding dermatome. Recently, the use of nerve stimulation after SNRB as well has been suggested in order to match patterns of pain and elicited paraesthesias[38]. Next, a small volume of contrast dye (0.5-1.0 ml) is injected to confirm needle tip position. Finally, a small volume of local anaesthetic is applied locally, which should reduce the radiating pain. There is no consensus in the literature as to what amount of pain reduction should be considered significant with SNRB. Pain reductions between 30% and 100% are commonly used. Also, hypoaesthesia or anaesthesia in the related dermatome is expected to develop as result of partial or even complete block of the afferent pathways. SNRBs should be selective at the same time. In order to act on sensory pathways as much as possible, the local anaesthetic needs to be restricted to the target spinal sensory nerve root or DRG by limiting injection to the intervertebral foramen. Both the position of the tip of the electrode and the use of a small amount of local anaesthetic are assumed to prevent (or reduce) blockade of motor fibers in the anterior root and of adjacent spinal nerve roots via extraforaminal spread. This combination of conditions is important because SNRB induced paresis/paralysis may attenuate pain provocation by hindering adequate use of the affected leg by the patient. If the tip of the electrode is positioned more laterally in the intervertebral foramen or outside the foramen, paresis/paralysis may develop as consequence of a motor axon conduction block in the mixed spinal nerve. However, we do know from our own experience that many patients report reduction of muscle strength in their leg on the painful side, despite SNRBs being applied intraforaminally. This, again, suggests that much of the data on SNRB is based upon assumptions and that the relationship between SNRB effects on pain and motor function needs further elucidation.

Background to this thesis

At the beginning of the studies presented in this thesis, we realized that it is actually not known if a SNRB is a consistent entity, despite it having been used for many years. Indeed, the reliability and selectivity of SNRBs[37,39] continues to be debated. Furthermore, the specificity of SNRBs even in sciatica is questioned[40]. To determine any sensitivity and specificity a gold standard is needed. For SNRBs in specific radicular pain syndromes in which a cause can be objectively and reliably identified, findings at surgery may be considered as gold standard, in which MRI and CT can be supportive but not conclusive. Unfortunately, as already discussed, such a gold standard is lacking for non-specific radiating pain, in which no direct cause can be reliably and objectively identified. This is often the case in the CLBP-r patient population that is referred to pain specialists for further diagnosis. Tests such as EMG, CT or MRI only have a weak relationship with pain, and surgery, by which a more specific diagnosis could be made, is generally not indicated. Recent techniques to visualize putative symptomatic nerve roots, such as spinal endoscopy, might prove to be of help in this regard.

Aims of this thesis

A simple description limited to the effect of SNRBs on the patients' pain does not bring us further in understanding the value of these blocks. Thus, we need to focus on the accompanying objectifiable and quantifiable clinical and physiological effects of SNRBs. Therefore, we started by systematically mapping and documenting the paraesthesias elicited by electrostimulation, and the hypoaesthesia and changes in muscle force induced by SNRB. Further, we studied the variability and consistency of these effects in relationship to pain and pain reduction and assessed their mutual relationships to better comprehend the diagnostic role of SNRBs in CLBP-r patients without an unequivocal anatomical and functional diagnosis. Various other issues regarding technical and pharmacological aspects may also be relevant for the assessment of the variability and consistency of SNRB effects.

We were not able to study all of these aspects, but we did document the epidural spread of the injected agent as one factor that is quite simple to assess in clinical practice. Improved insight into the value of SNRBs should bring us further in understanding underlying pain mechanisms, which is essential to raise efficacy of pain treatment in CLBP-r patients.

Thus, the key points with respect to SNRBs in CLBP-r patients are:

- CLBP-r patients, forming together a large population, lack an equivocal anatomical and functional diagnosis.
- SNRBs are used with the aim of improving diagnosis in these patients.
- In CLBP-r patients there is no anatomical and no functional gold standard with which to compare SNRB diagnosis.
- Thus: is the SNRB a defined tool to diagnose segmental pain in CLBP-r patients?

Subsequently, we can summarize the main questions addressed by this thesis:

1) What is the present basis for the application of SNRBs in CLBP-r patients? (chapter 2)
2) Are SNRB effects expressed in a dermatome-related fashion? (chapter 3)
3) Do SNRBs exert consistent effects on sensory function? (chapter 4)
4) Do SNRBs exert consistent effects on motor function? (chapter 5)
5) Is there any role for SNRBs as a diagnostic tool in CLBP-r patients? (chapter 6)

In **chapter 2** a survey of the present knowledge regarding the background of SNRBs and its diagnostic value in CLBP-r patients without overt neurological deficits is given.

In **chapter 3** we describe an observational prospective double blind study on the variability and interpretation of SNRB effects on sensory function. Pinprick is used to assess post block dermatomal related hypoaesthesia after lumbosacral SNRBs in CLBP-r patients without overt neurological deficits. Sites with maximum experienced pain, pre-block elicited paraesthesias, and local anaesthetic induced hypoaesthesia are compared between standard and extended dermatomes, which display the overlap with neighbouring dermatomes.

In **chapter 4** we present a case series of CLBP-r patients undergoing L4 SNRBs with lidocaine and ropivacaine in a prospective randomised crossover fashion. We describe

changes in pre- and post block extent and location of hypoesthesia that occurred related to the blocks.

Chapter 5 conveys a prospective randomised crossover study concerning the SNRB effects of lidocaine and ropivacaine in CLBP-r patients on pain and muscle force. We compare pain reduction with changes in maximum voluntary myotomal muscle force to assess mutual interactions.

In **chapter 6** we describe a prospective observational study performed to evaluate the spread of fluoroscopy controlled contrast dye that was added to the local anaesthetic agent injected with lumbosacral SNRB. Fluoroscopy is commonly used in pain practices to guide invasive diagnosis. Inadvertent spread of the injected agents into the epidural space and to adjacent nerve roots may influence the reliability and selectivity of diagnostic SNRBs.

In **chapter 7**, finally, we discuss the study findings and present recommendations for future studies.

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Chapter 2

DIAGNOSIS IN PATIENTS WITH CHRONIC RADIATING LOW BACK PAIN WITHOUT OVERT FOCAL NEUROLOGICAL DEFICITS: WHAT IS THE VALUE OF SEGMENTAL NERVE ROOT BLOCKS?

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Summary

The purpose of this paper is to discuss the value of spinal segmental nerve root blocks in establishing diagnosis in chronic low back pain patients with pain radiating to the leg without overt focal neurological deficits. These patients represent a large population. Establishing diagnosis is often problematic and the effectiveness of presently available therapies is low. Indication, character of radiating pain, pain diagnosis, factors influencing segmental nerve blocks, reliability of segmental nerve root blocks in diagnosing pain, recently performed studies on the reproducibility of segmental nerve block effects and considerations with respect to 'segmental pain' will be discussed herein.

Introduction

Segmental Nerve Root Blocks (SNRBs) are applied for diagnostic purposes in patients with radiating pain to determinate the pain-conducting segmental spinal level [1-7]. SNRBs have been applied in patients with chronic lower back pain radiating to the leg (CLBP-r) to select those eligible for a radiofrequency procedure of the dorsal root ganglion [7,8] (RF-DRG). A positive SNRB can further be used to establish the indication for spinal segmental nerve injection therapy [9-14]. Huston and Slipman [14] and Gajraj [15] have reported that SNRBs are valuable in the assessment of sciatica, but warn of the mainly retrospective nature and procedural limitations of the studies describing the predictive value. High sensitivity and specificity are attributed to SNRBs when used to predict surgical outcomes in patients with specific radicular syndromes. These patients suffer from nerve compression with secondary neurological deficits as result of a lumbar herniated disc or spinal stenosis [3-6,14,16-19] . Hogan, in contrast, postulates that no role has been demonstrated for SNRBs in evaluating patients for neuroablative procedures [20].

Radiating pain

CLBP-r patients may exhibit pain following a spinal segmental pattern or a non-segmental pattern, whereby a segmental pattern is defined as being concordant to the innervation area of a spinal (segmental) nerve. Non-segmental radiating pain may be referred, caused by local sources in the posture and motor apparatus of the back [21], but may also be related to structures outside the back. Furthermore, radiating pain can be related to a neuropathy of a peripheral nerve.

When pain is felt in one neuraxial segment we distinguish between pain with a specified, diagnosable, cause and pain in which no certain cause can be established. When a patho-anatomic cause, related to a spinal segmental nerve, nerve root or dorsal root ganglion is ascertained, and pain follows the innervation area of a spinal nerve (i.e., dermatome, myotome or sclerotome), it is defined as radicular pain. When radicular pain is accompanied by sensory changes in the corresponding dermatome, by decrease in motor function in the corresponding myotome, by positive spinal nerve stress tests and decreased tendonreflexes corresponding to the symptomatic level, it is defined as *radiculopathy*.

We should be aware that a substantial part of CLBP-r pain patients does not conform to the diagnostic criteria for radiculopathy. In many of these patients obvious causal pathology related to the spinal nerve suspected to be involved cannot be demonstrated with the **presently** available diagnostic tools. Nevertheless, patients may experience pain that follows a segmental or a segment-like pattern. To differentiate between radicular pain and radiculopathy, we propose to define this type of radiating pain, in which a specified cause cannot (yet?) be found, as *segmental* pain. A classification with respect to different types of pain radiating into the leg is displayed in table 1.

Pain diagnosis

Radiological examinations, such as plain radiography, myelography, discography, CT and MRI have a low specificity with respect to establishing the pain cause or source of the pain. For example, a herniated disc may be the cause, but the compressed and excitated dorsal root ganglion is the source [7,22-25]. Potential pain generating conditions, such as a herniated disc, spinal stenosis and epidural fibrosis can be present in symptom free patients, and *vice versa*. Thus, the quest for a patho-anatomic cause for CLBP-r remains a challenge. In this search, spinal endoscopy is a promising diagnostic and potential therapeutic tool, which can be performed in addition to (and in the future perhaps as replacement of) presently available radiological and clinical neurological examinations. This technique has received more attention recently and is of interest, due to its ability to aid in diagnosing pathology in the epidural space that cannot, or cannot yet be demonstrated in another fashion, such as MRI or CT. Using spinal endoscopy, abnormalities such as spinal nerve inflammation, can be visualized that may compromise or threaten radicular nerves [26-29].

Neuro-inflammatory and neuro-immunological processes in the spinal cord, spinal nerve root, dorsal root ganglion or spinal nerve [30-33] may explain the presence of radicular pain that cannot at present be diagnosed by radiological examination. These processes, as well the presence of chronic pain itself, may result in altered nervous system function (i.e., *neuroplasticity*). Such neuroplastic mechanisms [34-37] can lead to pain that persists after an initial nociceptive triggering process or event, which may not be present or detectable any more later on. The interpretation of this type of pain can be difficult because other pain sources that can generate radiating pain as well may be present concurrently: e.g., spondylolisthesis, disorders of facet joints, intervertebral disc(s), sacroiliac joint or tendomyogenic structures. Olmarker [30] demonstrated that the intervertebral disc is a potential source of biochemical substances that may directly and indirectly lead to excitation of dorsal root ganglion cells (PLA2 and TNF-α). This complex picture is further complicated if pain originates from regions outside the back, the peripheral nervous system or the central nervous system. Finally, multisegmental innervation of the spine and dermatomal overlap [38,39], presence of neuronal networks in the spine [21,40], and influence of psychogenic and behaviour-related factors can all coalesce to make the clinical diagnosis of CLBP-r extremely difficult. Thus, pain originating from the spine or related structures will be referred multisegmentally as a result of its multisegmental innervation [21,40]. This pain is defined as *pseudo-radicular* pain and is generally felt in parts of more than one dermatome. It can mimic segmental radiating pain, despite having no actual segmental origin (table 1).

Table 1 **Radiating pain**

	Pain distribution in neuraxis segment	Neurological deficits	Patho-anatomical substrate
Segmental			
Radiculopathy	+	+	+
Radicular pain	+	-	+
Segmental pain	+	-	-
Non-segmental			
Referred pain	-	-	+ (or ?)

In case of nerve root compression, the presence of radiating pain with a dermatomal pattern in the leg (i.e., radicular pain) seems to be one of the most significant diagnostic features. The sensitivity of this diagnostic symptom is reported as lying between 90% and 99% [41,42]. However, not one single physical test or examination appears to have an equally high sensitivity and specificity for radiculopathy [43]. In summary, the diagnostic accuracy of history taking and physical examination still remains unclear in the diagnosis of low back pain with radiation to the leg.

Factors influencing segmental nerve root blocks

The diagnostic use of SNRBs is based on the assumption that SNRBs can identify segmental pain and its spinal level by using significant pain reduction as an end-point. However, so far there is no gold standard against which the SNRB result can be measured. Therefore, there is a strong need to develop measures to confirm the effectiveness of SNRBs. Changes in sensory and motor function could be a useful tool to clinically document the reliability of SNRBs. Despite the fact that SNRBs have been used for many years in back pain diagnostics, only few studies systematically have described the clinical effects of SNRBs. In table 2 we present methods, which could be helpful in testing spinal segmental nerve function in humans. Table 3 shows the most commonly applied tests for quantifying alterations in spinal nerve function.

Table 2 **Techniques used to test human spinal nerve function**

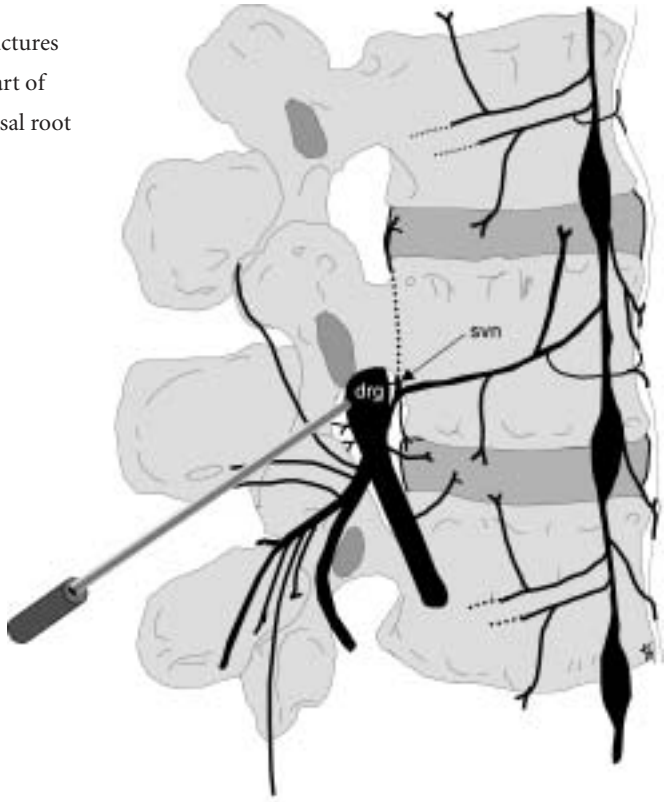
Nerve stimulation	mechanical
	electrical
Nerve block	conduction block with local anaesthetic agent

Table 3 **Most commonly used tests to quantify alterations in nerve function**

Function	Examination	
Sensory/Pain	QST (Quantitative Sensory Testing)	electrical; gradual, continuous mechanical; gradual, continuous Von Frey hairs; graded, discontinuous temperature; graded, discontinuous
	pinprick (semi quantitative mapping)	
	brush (semi quantitative mapping)	
	intramuscular injection with hypertonic NaCl	
Motor	muscle force in myotome	
	spinal reflexes	
	EMG	
Sympathetic	skin infrared thermography	
	skin impedance (galvanic reflexes)	
	skin temperature	

Furthermore, the technique used to identify the spinal nerve root, the dorsal root ganglion or the spinal nerve must be reliable and reproducible. The needle should be introduced and inserted to the upper, dorsal part of the intervertebral foramen (just intra- or extraforaminally) and should be documented radiologically. Use of imaging guidance via fluoroscopy or CT is strongly recommended. The spinal nerve, spinal nerve root or dorsal root ganglion may be mechanically or electrically stimulated via the tip of the needle, evoking paraesthesias in the corresponding dermatome and provoking muscle contractions in the corresponding myotome. A low volume of radio contrast dye (0,2-0,5 ml) should also be injected to visualize its spread around the target neural structure. In this way the target neural structure is made visible and it allows assessment of unwanted spread of the injected solution. The spread should be limited to the target structure. It is important that neural structures lying at spinal segmental levels above or below the target level should be unaffected. To prevent unintended non-targeted spread of the injected agent to adjacent neural tissues, a low volume should be injected extradurally (sometimes this is described as peridurally), either in- or outside the intervertebral foramen.

Figure 1 Representation of spinal nervous structures and needle placement in the upper part of the intervertebral foramen. DRG, dorsal root ganglion; svn, sinu-vertebral nerve.



Theoretically, anaesthetizing the mixed spinal nerve extraforaminally should block afferent signals coming from peripheral sites distal to the injection and thus prevent centripetal conduction (figure 1). In an intraforaminal block chances are higher to block the so-called sinu-vertebral nerves as well. These nerves conduct afferent signals from the spine itself, e.g. from neighboring intervertebral discs, anterior and posterior ligaments of the spine, and ventral dura [21,40]. Although the dorsal ramus, originating just outside the intervertebral foramen, may remain out of reach of an intraforaminal block, it should be noted that the sensory fibers from the dorsal nerve pass through the dorsal root ganglion, and, consequently, are blocked as well. This nerve branch innervates local muscles in the back and the neighboring facet joints. Furthermore, it has been reported that pain generated proximal to the nerve block may be relieved by a conduction block performed distal to the exciting locus. In this way, pain related to proximal spinal nerve root excitation and experienced in the leg and the back [44,45] is affected by a distant block.

The concept of "controlled blocks" for zygapophysial joint blocks [46] to increase reliability and improve interpretation may also be applied for SNRBs: blocks are performed on two different occasions, with a short and a long acting local anaesthetic agent in equipotent dosage. The duration of pain reduction should correspond with the duration of action of the local anaesthetic agent used. It may be expected that not only duration of pain reduction, but also duration of other concomitant changes, e.g. in sensory and motor function, should be concordant to the duration of effect of the local anaesthetic agent used. However, in our experience, this is not always the case. To further increase reliability, we should also take into account the presence of multisegmental innervation [21,40]. Thus we would suggest that SNRBs should be performed at least at 2 or 3 spinal levels. These double controlled blocks with long and short acting local anaesthetics have been advocated as gold

standard [46], however, in view of the discussion above with regard to single SNRBs, this is hardly likely. Even controlled blocks do not distinguish between source and cause of the pain.

When the local anaesthetic reaches the target neural structures, it has to diffuse into these structures before it can exhibit its blocking property. Local effects may be affected by factors such as the physical and chemical properties of the local anaesthetic agent. Furthermore, size and position of the dorsal root ganglia may vary in relation to the intervertebral foramen [47-53]. There is a large variation in anatomic positions of dorsal root ganglia. Three positions are possible: outside the foramen, inside its aperture, and actually within the spinal canal (figure 2). In this context, the use of radio contrast dye and electrostimulation may be helpful to raise insight into the variability of the dorsal root ganglia topography. Furthermore, spinal nerve roots and ganglia have an internal topographic organization regarding nervous and non-nervous cells [49] So far, it is unknown if there is a relationship between electrostimulation and the intraganglionic topographic organization. Therefore, the effects of the local anaesthetic within the innervation area of a spinal nerve can be expected to vary, dependent upon its penetration into in the dorsal root ganglion and spinal nerve.

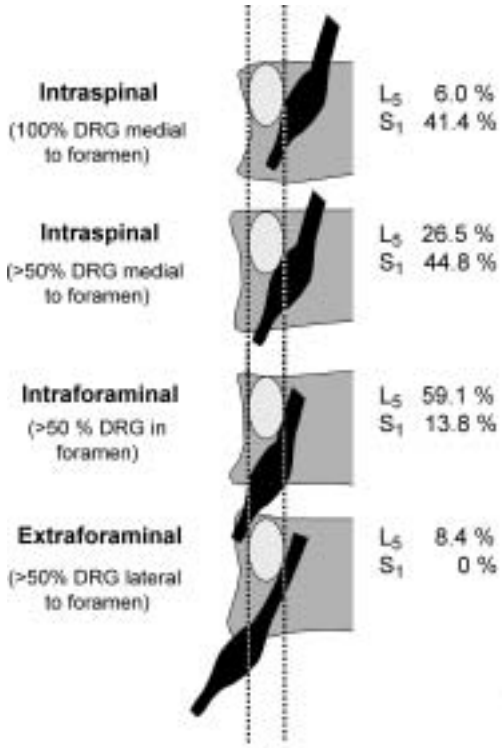


Figure 2 Variation in anatomic positions of the dorsal root ganglia (redrawn and adapted from Hasue et al 1989) with regard to the intervertebral foramen. At the left the location of the dorsal root ganglion (DRG) with respect to the interverebral foramen is depicted. The percentages on the right side represent the incidence of the indicated position at spinal level L5 or S1.

Reliability of segmental nerve root blocks

Pain patterns, pain reduction and concomitant changes in sensation and muscle force by SNRB, should be clearly associated with the blocked spinal segmental nerve. To date, no data are available with respect to the reproducibility of sensory effects, pain reduction, and motor effects by SNRB. The same holds true for elicited paraesthesias.

SNRBs should be sensitive and specific. North et al [45] reported a high sensitivity, but a low specificity for SNRBs in the context of sciatica patients. In these patients blocks,

performed at spinal level L5 and S1, were compared with sciatic nerve blocks, consecutive blocks of the medial branch of the dorsal ramus (i.e., supplying the facet joints) and subcutaneous injections with local anaesthetics. Surprisingly, they found that the two blocks performed far from the affected spinal nerves also resulted in significant pain reduction in a substantial number of patients compared to SNRBs of the affected spinal nerve. Subcutaneous injections did not lead to pain reduction. The authors argued that negative blocks may have some predictive value, but that isolated, positive, i.e. pain reducing, blocks are to be considered non-specific. All included patients had positive diagnostic imaging findings of ongoing nerve root compression or a positive history of root compression, which had been identified surgically.

In CLBP-r patients, who have no detectable and specific underlying diagnosis for their radicular pain, it is impossible to generate data on sensitivity and specificity with respect to SNRBs. However, an alternative or better tool than SNRB to identify segmental pain is not available at this moment.

The lack of a diagnostic gold standard in patients with chronic, non-specifiable, radiating pain emphasizes the need to develop other methods to monitor the quality and reliability of SNRBs, by systematically documenting sensory and motor function [39,54,55]. Such methods could include: 1) paraesthesias elicited by electrostimulation, 2) changes in sensory function, and changes in muscle force. Findings resulting from monitoring these signs should correspond to the blocked spinal level. The method should be consistent and reproducible. Until recently, no studies had been performed to answer these questions. However, with respect to the large population of CLBP-r patients without overt focal neurological deficits and with respect to the frequent need for diagnosis and treatment of these patients, this is extremely relevant.

Studies on the consistency of SNRB effects

Interesting findings of a series of studies to the relationship between segmental pain in the leg, pain reduction, and changes in sensory and motor function after SNRBs in CRLB-r patients without overt focal neurological deficits [39,54,55] will be discussed here.

The first finding is that the incidence, location and extent of skin areas with hypoaesthesia for pin prick after SNRB are very variable. These results can be seen in a so-called density map of hypoaesthetic effects for pinprick after SNRB (chapter 3). The extent of the total skin area where hypoaesthesia is found in this series appears to be extremely large. Of notice is the fact that in some patients no hypoaesthesia develops at all, although all nerve blocks were technically adequate. It seems that patterns of pain radiation and hypoaesthesia, which mostly exceed the boundaries of the standard dermatomes can be better understood if overlap by neighboring dermatomes is taken into account in the representation of dermatomes (chapter 3). The resulting "adapted" dermatomes are then seen to be twice as large as in standard dermatomal maps. Using the map with "adapted" dermatomes, sensory clinical SNRB effects occur more often within the dermatomal boundaries. In contrast, the variability of paraesthesias elicited by electrostimulation is much lower, being mainly

experienced in the central part of the standard dermatome. The reproducibility of paraesthesias elicited with electrostimulation via the tip of the needle appears to be high: 80% of experienced paraesthesias are found to be present within the boundaries of the corresponding standard dermatomes and in 98% paraesthesias are found within the boundaries of the corresponding, "adapted", dermatome. Nevertheless, the relation with pain remains poor: when pain is experienced in a specific "adapted" dermatome, only in one third of the cases concurrent pain reduction, paraesthesias and hypoaesthesia are present in this dermatome.

When the sensory function is tested with pinprick before SNRB in CLBP-r patients without overt focal neurological deficits, it is found that in the majority of the cases a variable pre block hypoaesthesia is present [54] (chapter 4). This alteration in sensory function may change in time and location. Although a large variability in extent of post block hypoaesthesia is found, the changes with block are non-significant compared to pre block situation. The presence of the pre block alterations in sensory function may be the result of neuroplastic effects due to the chronicity of pain in these patients.

When the SNRB effects on motor function are examined [55] (chapter 5), it appears that average muscle force within the corresponding myotome **decreases** with block. However, the muscle force in the corresponding myotome **increases** if pain is reduced by the nerve block. This finding can be interpreted as follows: in patients with chronic pain in the leg, pain has an inhibitory effect on the muscle force [56] (so-called diffuse noxious inhibitory control or DNIC, a phenomenon also attributed to neuroplasticity). After pain reduction, inhibition is ceased, which normalizes muscle force.

These observational studies demonstrate that long lasting back pain with segmental radiation to the leg, even when specific causes have not been found, induces neuroplastic changes in both the sensory and motor system. It is possible that the large variability in sensory effects with SNRB is also related to these neuroplastic changes. However, the role of multisegmental innervation should not be forgotten in this context. It should be emphasized that the segmental changes related to sensory and motor function are poorly reproducible in CLBP-r patients. Only the elicitation of paraesthesias with electrostimulation is reliably reproducible in a dermatomal fashion. At present this combination of clinical signs present after SNRBs is not useful to assess the quality of SNRBs.

Does segmental pain exist?

As discussed above, attempts to select only those patients that have segmental pain, from the large population of CLBP-r patients, have remained futile. Even assessing the effectiveness of SNRB by measuring subsequent successful treatment outcome as endpoint did not resolve the problem. The diagnostic value of SNRBs as selection tool for successive segmental invasive pain treatment could also not be confirmed in a recent study by Geurts et al. [8] In a prospective, randomized and placebo controlled study they demonstrated that radiofrequency treatment of lumbosacral dorsal root ganglia in patients with radicular pain, selected with SNRBs, were not effective. However, one should add that in that study controlled, double blocks have not been used for patient selection. Besides the lack of

treatment effectiveness itself, this could also be attributed to SNRB-bound properties, e.g., low selectivity of SNRBs or absence of applying double controlled SNRBs, or to wrong concepts or hypotheses with respect to the phenomenon of segmental pain. Thus, "segmental pain" as clinical concept lacks experimental evidence for its existence when no specific cause can be demonstrated. It appears that, with respect to underlying mechanisms in chronic radiating pain, we will have to find other conceptual frameworks. A possible alternative framework would involve the afore-mentioned mechanism of neuroplasticity. With the presently available diagnostic tools we cannot clearly demonstrate, or exclude, processes such as (neuro-) inflammation or persistent neuroplasticity. It should be noted that neuroplasticity can be segmental, e.g. sensitisation of dorsal root ganglion neurones and glial cells [35]. However, the lack of consistent segmental effects of SNRB makes it unlikely that it will aid in the diagnosis of this type of problem, either.

In future, studies of pain related neuroplastic changes in sensorimotor systems may provide us with more insights in underlying pain mechanisms. It is of eminent importance that we obtain a better understanding of the mechanism involved in the development of pain, of the processes facilitating the chronification of pain, and of its impact on systems involved. If segmental effects are related to pain, then diagnosis and treatment should take into account that the nerve cells involved are connected both to peripheral (sensory and motor function) and central neural structures higher in the neuraxis. Increasing numbers of studies performed in the last few years have demonstrated that pain, chronicity, neuroplasticity, cerebral functions, emotions, cognitions and behaviour are all strongly related to each other. Longer lasting back pain with non-specifiable "segmental" pain should be viewed as being a part of a more extended and complex system that demonstrates functional plasticity. It would seem that our conceptual frameworks with respect to the concept of "segmental" pain and with regard to diagnostic "segmental" nerve blocks as main tool, have to be reconsidered. Further studies should demonstrate if this assumption is correct or not.

We have to keep in mind that the diagnosis '"segmental pain" is a constantly evoking concept. Our diagnoses are dependent on our diagnostic tools, and these diagnostic tools should provide us with a better insight in underlying mechanisms. Therefore, an important future goal in the context of CLBP-r patients would be to develop more sophisticated diagnostic techniques that enable us to better identify pain-induced neuroplastic changes in the nervous system.

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Chapter 3

DIAGNOSTIC LUMBOSACRAL SEGMENTAL NERVE ROOT BLOCKS WITH LOCAL ANAESTHETICS: A PROSPECTIVE DOUBLE-BLIND STUDY ON THE VARIABILITY AND INTERPRETATION OF SEGMENTAL EFFECTS

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Summary

Introduction. Selective spinal nerve infiltration blocks are used in patients with chronic low back pain radiating into the leg. Generally, a segmental nerve block is considered successful if the pain is reduced substantially. Hypoaesthesia and elicited paraesthesias coinciding with the presumed segmental level are used as controls. The interpretation depends on a standard dermatomal map. However, it is not clear if this interpretation is reliable enough, because standard dermatomal maps do not show the overlap of neighboring dermatomes. The goal of the present study is to establish if dissimilarities exist between areas of hypoaesthesia, spontaneous pain reported by the patient, pain reduction by local anaesthetics and paraesthesias elicited by sensory electrostimulation. A secondary goal is to determine to what extent the interpretation is improved when the overlaps of neighboring dermatomes are taken into account.

Methods. Patients suffering from chronic low back pain with radiating into the leg underwent lumbosacral segmental nerve root blocks at subsequent levels on separate days. Lidocaine (2%, 0.5 mL) mixed with radiopaque fluid (0.25 mL) was injected after verifying the target location using sensory and motor electrostimulation. Sensory changes (pinprick method), paraesthesias (reported by the patient), and pain reduction (Numeric Rating Scale) were reported. Hypoaesthesia and paraesthesias were registered in a standard dermatomal map and in an adapted map in which included overlap of neighboring dermatomes. The relationships between spinal level of injection, extent of hypoaesthesia, location of paraesthesias, and corresponding dermatome were assessed quantitatively. Comparison of the results between both dermatomal maps was done by paired t-tests.

Results. After inclusion, data were processed for 40 segmental nerve blocks (L2-S1) performed in 29 patients. Pain reduction was achieved in 43%. Hypoaesthetic areas showed a large variability in size and location, also in comparison to paraesthesias. Mean hypoaesthetic area amounted 2.7 ± 1.4 (± SD: range, 0 to 6; standard map) and 3.6 ± 1.8 (0 to 6; adapted map; $P < .001$) dermatomes. In these cases, hypoaesthesia in the corresponding dermatome was found in 80% (standard map) and 88% of the cases (adapted map, not significant). Paraesthesias occurring in the corresponding dermatome were found in 80% (standard map) compared with 98% (adapted map, $P < .001$). In 85% (standard map) and 88% (adapted map), spontaneous pain was present in the dermatome corresponding to the level of local anaesthetic injection. In 55% (standard map) versus 75% (adapted map, $P < .005$), a combination of spontaneous pain, hypoaesthesia, and paraesthesias was found in the corresponding dermatome.

Conclusions. Hypoaesthetic areas determined after lumbosacral segmental nerve blocks show a large variability in size and location compared to elicited paraesthesias. Confirmation of an adequately performed segmental nerve block, determined by coexistence of hypoaesthesia, elicited paraesthesias and pain in the presumed dermatome, is more reliable when the overlap of neighboring dermatomes is taken into account.

Introduction

Selective segmental nerve blocks are applied for diagnostic purposes in patients with chronic pain to differentiate the segmental level of pain [1-5]. If the pain lasts more than 6 months without improvement despite conservative treatment, and if a selective segmental block has led to temporary pain relief, there may be an indication for invasive symptomatic pain treatment [1]. To assess the quality of a diagnostic segmental block, the presence and extent of temporary motor deficit, dermatomal hypoaesthesia, and elicited paraesthesias are useful criteria.

Location and size of hypoaesthetic regions and intensity of paraesthesias are generally evaluated by using a standard dermatomal map. In the past, different attempts have been made to develop a human dermatomal map. Maps were designed based on the location of skin eruptions in herpes zoster [6], innervation territories of peripheral branches of lumbosacral and brachial plexuses by meticulous anatomical dissection of 1 human [7], and by experimental animal work on monkeys [8]. Sherrington [8] determined dermatomal areas by using the isolation method and checking the areas of remaining sensibility. Sherrington used the "remaining sensibility method" or "isolation method" in monkeys, by cutting a continuous number of dorsal roots and leaving intact the most middle root. In this way, he created for nearly all spinal nerves areas with intact sensibility surrounded by areas in which sensibility was absent. Thus, he proved an overlap in sensory nerve supply by consecutive nerve roots and showed that most cutaneous loci were innervated by 2 or 3 dorsal roots. Larger dermatomal areas were found with considerable overlap between neighboring dermatomes. Keegan and Garrett [9] used local anaesthesia of the dorsal root ganglia in healthy subjects. Hansen and Schliack [10] made use of the above-mentioned studies and synthesized the data with personal clinical observations into a renewed human dermatomal map. Their map was again modified by Buckhöj (an artist) and is currently used in many pain clinics and anaesthesia practices. The maps of the dermatomes in humans worked out by different methods are not concordant in all respects, but the main patterns are identical [11].

Diagnostic segmental blocks performed at the same level do not always produce equal dermal extension of sensory changes [12] and may provide false-positive results [13]. North et al. [13] compared the temporary pain-relieving effects of lumbosacral nerve root blocks, sciatic nerve blocks, medial branch posterior primary ramus blocks, and subcutaneous injections in patients with sciatica and diagnosed root entrapment. The first 3 blocks produced temporary relief in the majority of patients despite the fact that they were distal to the entrapped nerve. The study hypothesis was confirmed that false-positive results are common and specificity is low. Much of the exact mechanism of diagnostic segmental nerve blocks still needs to be elucidated.

In the present study the extension of sensory changes after single segmental lumbosacral nerve blocks was assessed by the pinprick method and fitted in a standard dermatomal map (Buckhöj; Astra-Zeneca, Södertälje, Sweden; Figs 1A and 2A) frequently used in investigations in local and regional anaesthesia. Sherrington [8] and Foerster [14] showed that neighboring dermatomes overlap to a large extent. This means that the full extent of

each dermatome is larger than depicted in the vast majority of complete dermatomal maps. Foerster[14] defined the total extent of a dermatome as "one dermatome to which both half neighboring dermatomes were added". However, in Foerster's dermatomal map, not all dermatomes are presented as a continuum from proximal to the periphery. Therefore, Keegan and Garrett[9] proposed a dermatomal chart representing dermatomes extending without interruption from the dorsal midline to their termination. However, Keegan and Garrett's chart represents only the core of the dermatomes, described as "areas of primary hyposensitivity". As a result, we modified the frequently used standard map of Buckhöj by adding to the original dermatome both halves of the 2 neighboring dermatomes. Thus, larger dermatomes were obtained (adapted map; see Figs 1B and 2B). The findings were quantitatively fitted in both maps and compared with each other.

Although spinal segmental test blocks are performed to obtain more insight into pain patterns, the questions in this study were limited to the following issues: (1) How often does a single segmental nerve block lead to hypoaesthesia in the corresponding dermatome? (2) How often does electrical nerve stimulation of a single segmental nerve elicit paraesthesias in the corresponding dermatome? (3) How often do areas of spontaneous pain, hypoaesthesia, and elicited paraesthesia coincide within the corresponding dermatome? The results will be compared between the standard and adapted dermatomal map.

Patients and Methods

Patients suffering from unilateral chronic low back pain radiating to the leg, in which noninvasive therapy was excluded, were referred for symptomatic invasive pain treatment. All patients were examined extensively, including by computed tomography (CT), magnetic resonance imaging (MRI), and electromyograph (EMG), and diagnosed as "radicular syndrome without neurological deficit" by a neurologist or an orthopedic surgeon. Patients were recruited in accordance with the rules of the Declaration of Helsinki and the study was approved by the Hospital Ethics Committee. Written informed consent was obtained from each patient. All patiënts were over 18 years of age.

Exclusion criteria were the following: availability of noninvasive therapy, known hypersensitivity to amino-amide-type local anaesthestics or iodide, presence of coagulopathy, or mental disorders. In the study period, 38 consecutive patients with radiating pain in the lower limbs were considered for diagnostic lumbosacral segmental nerve blocks. After obtaining written, informed consent, 29 patients were enrolled the study. They were scheduled for 3 test blocks with local anaesthetics - 1 block at the segmental nerve corresponding with the most painful dermatome, and the remaining 2 at the super- and subjacent levels. Finally, during the study period, 29 patients underwent 42 diagnostic segmental nerve blocks at lumbosacral levels according to the experimental protocol.

The blocks were performed by three anesthesiologists specialized in invasive pain treatment. A research fellow, unfamiliar with the exact level of the executed block, performed assessment of the blocks.

Technique

The patient was positioned prone. Fluoroscopy was executed in an antero-posterior and lateral direction. Under fluoroscopic guidance, the insertion site of the needle was marked on the skin by a skin marker. After subcutaneous injection with 1 mL of lidocaine 1.5%, a 10-cm isolated needle was inserted into the intervertebral foramen (23-gauge, Top-XE, Top Corp, Tokyo, Japan).

To confirm the position of the needle, an electrical current generated by a radio frequency pulse and lesion generator system (model RFG-3B; Radionics, Burlington, MA, USA) was applied, stimulating the segmental nerve. Paraesthesias were evoked by stimulation with a frequency of 50 Hz and muscular contractions by stimulating at 2 Hz. The paraesthesias elicited in the patient were registered by the anesthesiologist in an empty dermatomal map. The anesthesiologist recorded the locations of these sensations as expressed by the patient as well as the presence of muscular contractions manifest during electrical stimulation. Thereafter, 0.3 mL contrast medium (Omnipaque Nycomed Ireland, LTD, Cork, Ireland) was injected through the needle to visualize the segmental nerve. Radiographs were taken for documentation. Then a mixture of 0.5 mL lidocaine 2% (Astra Pain Control AB, Södertälje Sweden) and 0.25 mL of contrast dye was injected. In case of epidural or abnormal spread the data were excluded from further analysis. The "blind" investigator examined the patients twice: 30 min before and between 15 to 30 minutes after the injection. Sensory tests were performed in the affected limb from distal to proximal in annular shapes at 10-cm distances by pinprick (hypo, 825044A, 27-gauge, MPL Technologies Inc, Franklinpark, IL, USA). The other limb was used as a reference.

The areas with sensory changes were fitted in the standard and the adapted dermatomal map (figure 1 and 2).

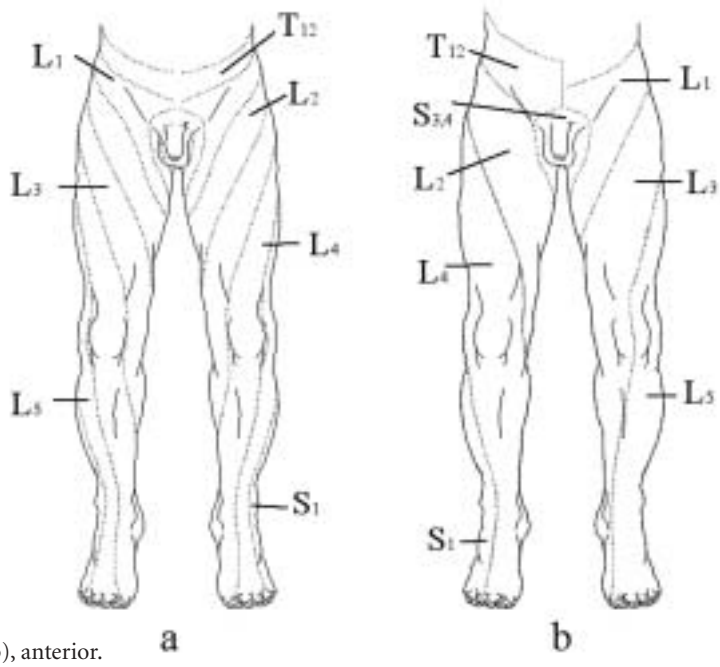

Figure 1 Standard dermatomal map (a) vs adapted dermatomal map (b), anterior.

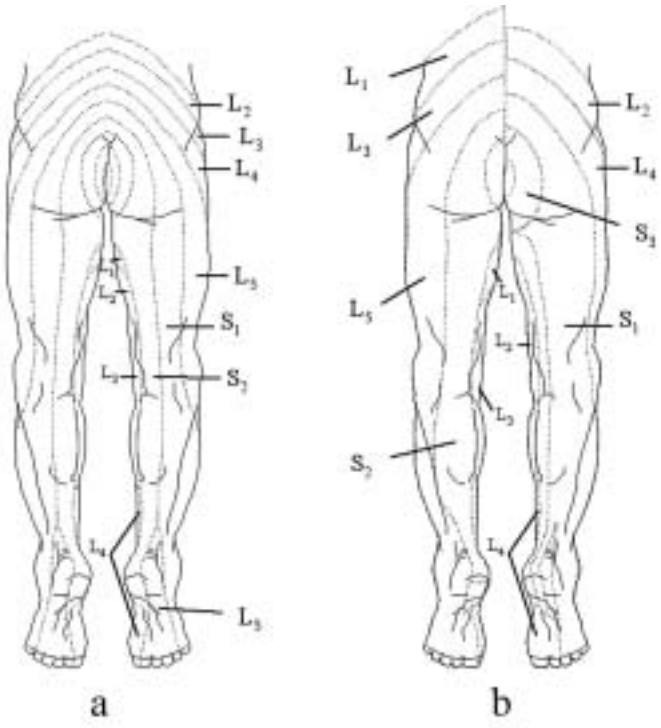

Figure 2 Standard dermatomal map (a) vs adapted dermatomal map (b), posterior.

The dermatomal map was provided with a grid with a resolution of 1 mm^2 to quantify the surface of the hypoaesthetic areas. Hypoaesthetic areas were marked. The number of marked squares per dermatome, as well as the total number of marked squares were counted. Thus, the relative sizes of hypoaesthetic areas within affected dermatomes in comparison to the total hypoaesthetic areas were calculated. This was done for both standard and adapted maps. With the standard map, each affected locus in a hypoaesthestic area lies in only 1 dermatome. These dermatomes are only neighboring. Using the adapted map, each affected locus is, by definition, lying in more than 1 dermatome because the larger dermatomes on the adapted map do overlap. Therefore, the mean hypoaesthetic area will be larger using the adapted map. For example, when a small coin-sized area is affected at the lateral side of the knee with a total surface of "X", it can only be counted once in dermatome L5 in the standard map. In the adapted map, the affected area is found within dermatome L5, but also in L4 (see Figs 1 or 3). When we calculate the total surface of the hypoaesthetic area using the standard map we only can count "X", but using the adapted map in this case we can count "2X". To determine which areas were hypoaesthetic in the majority of patients, intensity maps were produced from superimposed data of all cases.

The following data were processed: the dermatome(s) in which the patient experienced the pain, the pain score before and after the segmental nerve block (on a 10-point Numeric Rating Scale (NRS), 0 = no pain, 10 = unbearable pain), the spinal level of the blocked nerve, the voltages at which paraesthesias and muscle contractions were perceived during electrical stimulation (mean ± SD), and the dermal projection of paraesthesias. A decrease of at least 2 points on the NRS was considered as clinically significant.

To compare the effects related to the level of spinal nerve infiltration, hypoaesthesia, and paraesthesias between standard and the adapted dermatomal maps, the paired t-test was used with a confidence interval of 95%.

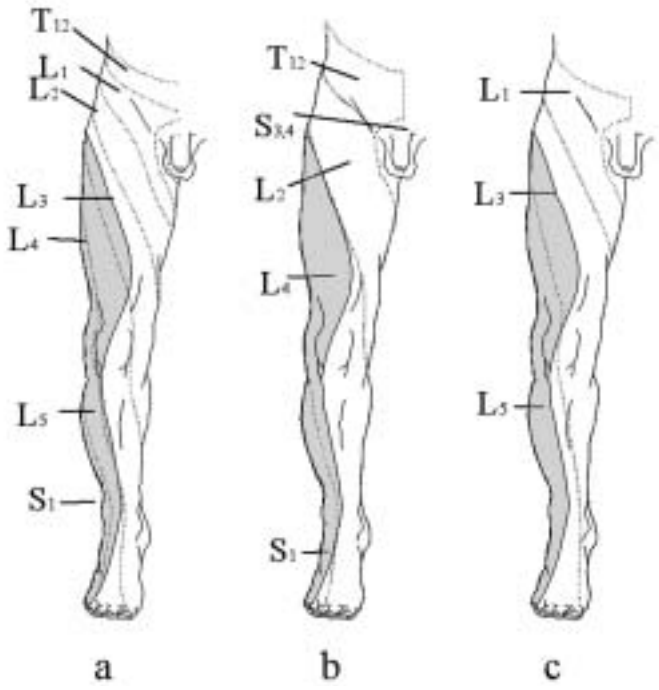

Figure 3 Hypoaesthetic area, developed in a case after a segmental nerve block of S1, projected on a standard (a) and on a adapted dermatomal maps (b,c).

Results

Forty-two segmental nerve blocks were performed in 29 patients. Data of 2 block procedures were excluded from further analysis because of epidural spread. An L2 nerve block was performed in 6 cases, an L3 in 1, an L4 in 8, an L5 in 14, and an S1 in 11 cases. In all cases, the number of the vertebrae from C1 to the treated level was normal. For demographic data, see Table 1.

Table 1 **Demographic data in patients with pain in the lower limbs undergoing segmental nerve blocks.**

	number
patients	29
sex: f/m	12/17
age (sd, spread)	49.3 (11.0, 29-77)
blocks	40

In figure 3, a hypoaesthetic area, developed in a case after a segmental nerve block of L4, is presented in a standard map (3A) and in adapted dermatomal maps (3B and 3C). Superimposition of hypoaesthetic areas per level of segmental nerve block shows a large overlap in all cases, as shown for levels L5 and S1 in intensity maps (Figs. 4 and 5). Hypoaesthesia locations with the highest intensity are found at the anterior thigh (L2, 30%), at the anterolateral side of the knee (L4, 40%), at the lateral caudal half of the lower leg and lateral ankle (L5, 80%) and at the dorsolateral thigh, lateral ankle, and lateral side of the foot (S1, 60%).

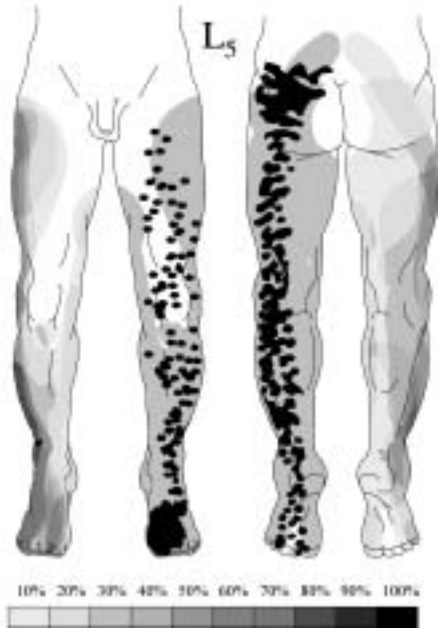

Figure 4 Intensity map of L5 areas of hypoaesthesia (grey tones in right legs) and paraesthesias (black dots in left legs; grey area represents total area of hypoaesthesia) in 15 patients. Areas of hypoaesthesia and paraesthesia of all patients have been superimposed. The grey tones correspond with the intensity scale that describes the percentage of patients in which the areas overlapped each other.The darkest areas represent sites that were found hypoaesthetic in the largest number of patients. For paraesthesia it is depicted as more black dots at a certain spot.

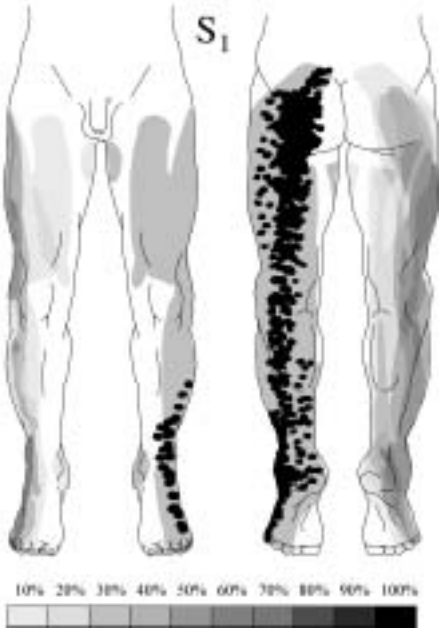

Figure 5 Intensity map of S1 areas of hypoaesthesia (grey tones in right legs) and paraesthesias (black dots in left legs; grey area represents total area of hypoaesthesia) in 11 patients. Areas of hypoaesthesia and paraesthesia of all patients have been superimposed. The grey tones correspond with the intensity scale that describes the percentage of patients in which the areas overlapped each other.The darkest areas represent sites that were found hypoaesthetic in the largest number of patients. For paraesthesia it is depicted as more black dots at a certain spot.

Elicited paraesthesias are found in the anterior side of the upper leg, knee and upper part of the lower leg (L4), over the buttock along the dorsal side of the thigh and lateral side of the lower leg to the great toe (L5, Fig. 4), and from the buttock over the dorsal side of upper and lower leg to the lateral side of the foot to the fifth digit (S1, Fig. 5).

Comparisons were made between the presence of spontaneous pain, hypoaesthesia, paraesthesia and pain reduction in corresponding dermatomes in standard and adapted dermatomal maps (Fig. 6). In all but one (i.e. frequency of hypoaesthetic area) the frequency of signs and symptoms located in the corresponding dermatome is significantly higher in the adapted dermatomal map.

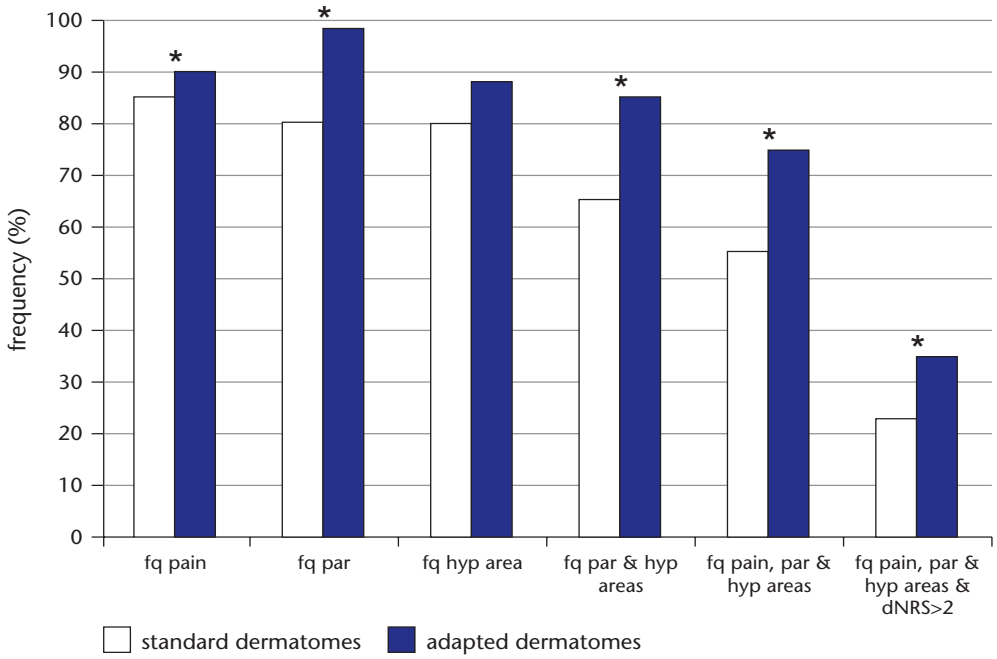

Figure 6 Relationships between frequency of presence of spontaneous pain, elicited paraesthesias (par), hypoaesthesia (hyp), decrease in pain (dNRS) in corresponding dermatomes of standard (blank) vs adapted (dashed) dermatomal maps in 40 cases undergoing lumbosacral segmental nerve blocks. * $p<0.05$.

After single segmental nerve blocks, hypoaesthesia was found in 34 cases (85%), but was not detected in 6 cases (15%). The hypoaesthetic surface areas as recorded on the dermatomal maps (both standard and adapted) varied from 0 to 1,244 mm^2 (mean ± SD, 537 ± 357 mm^2; Fig. 7). In 40 cases, areas of hypoaesthesia were recorded within the boundaries of a total of 106 (standard map) and 145 dermatomes (adapted map). Hypoaesthetic areas extended over 2.7 ± 1.4 dermatomes (mean ± SD; range, 0 to 6; standard map) and 3.6 ± 1.8 dermatomes (mean ± SD; range 0 to 6; adapted map; $P < 0.001$, paired t-test).

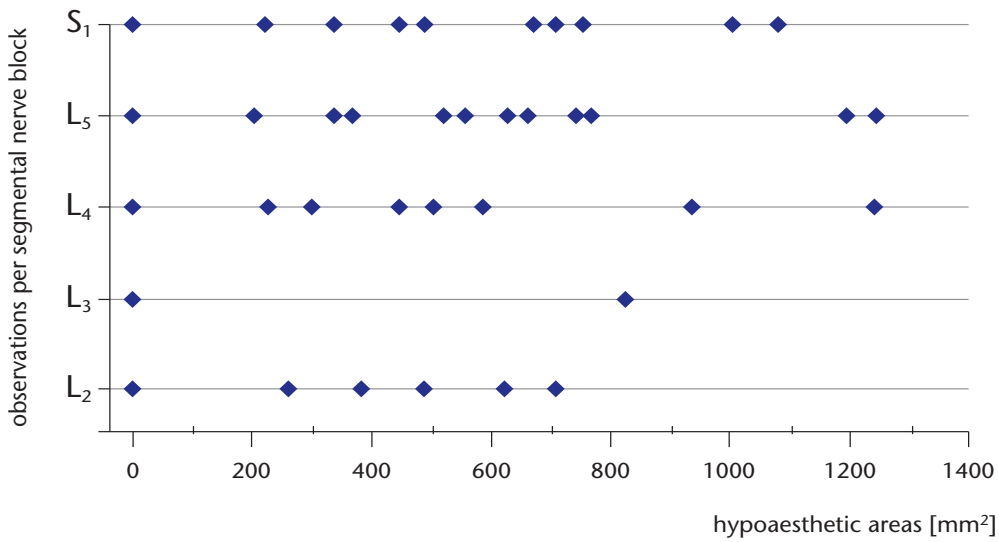

Figure 7 The hypoaesthetic surface areas per segmental nerve block (L2 6 cases, L3 1 case, L4 8 cases, L5 14 cases and S1 11 cases) as recorded on the dermatomal maps, both standard and adapted, depicted in mm^2. In 6 cases no hypoaesthesia occurred: L2 1 case, L4 1 case, L5 3 cases, S1 1 case.

Hypoaesthesia occurred in the corresponding dermatome in 32 cases (standard map) and 35 cases (adapted map; not significant (NS), paired t-test). The mean hypoaesthetic surface area in the corresponding dermatome (as percentage of the mean total hypoaesthetic area) was 26% (standard map) versus 52% (adapted map; $P < 0.01$, paired t-test). Using the standard map, at least 50% of the total hypoaesthetic area was found within the corresponding dermatome in only 6 cases (15%), but in 23 cases (58%; $P < 0.001$, paired t-test) for the adapted map.

The mean measured voltage necessary to elicit paraesthesias was 0.8 ± 0.6 V, range 0.1 to 2.0 V. Muscle contractions were elicited at a mean voltage of 1.4 ± 1.1 V, range, 0.15 to 4.0 V. After electrical stimulation, in 32 cases (80%, standard map) versus 39 cases (98%, adapted map; $P < .01$, paired t-test) paraesthesias were experienced in dermatomes corresponding to the level of the segmental nerve block. In the remainder of cases, paraesthesias were perceived in dermatomes not corresponding to the level of the stimulated segmental nerve. Areas with paraesthesias were generally of limited size and showed a more bandlike pattern in comparison with hypoaesthetic areas. In 26 cases (65%, standard map) versus 34 cases (85%, adapted map; $P < 0.005$, paired t-test) hypoaesthesia and paraesthesias were recorded in the corresponding dermatome.

In most cases, spontaneous pain was located in an area exceeding the boundaries of at least 2 dermatomes with a mean of 2.4 ± 1.3 dermatomes (mean $\pm$ SD, range 1 to 6; total 93; standard map) versus 3.4 ± 1 dermatomes (mean $\pm$ SD, range, 2 to 6; total 131; adapted map; $P < 0.001$, paired t-test). Using the standard dermatomal map, pain was present in only 1 dermatome in 11 cases. Using the adapted map, in 5 cases pain was present in just 2 dermatomes. In 34 and 35 cases, pain was present in the dermatome corresponding to the treated spinal nerve. In 17 cases (43%, both maps) pain was reduced significantly, of which in 14 (standard map) and 15 cases (adapted map) the level of segmental nerve block corresponded with the dermatomal area. In 3 and 2 cases the segmental nerve block was performed at a spinal level not represented in the painful area. In 55% (standard map) versus 75% (adapted map, $P < 0.005$) the combination of spontaneous pain, hypoaesthesia, and paraesthesias was found in the corresponding dermatome.

Discussion

The mean hypoaesthetic surface area in the corresponding dermatome with the standard maps was half (26%) of the mean area found using the adapted dermatomal map (52%; $P < 0.01$, paired t-test). This is a direct consequence of the characteristics of the maps: each locus on the standard map is always represented twice on the adapted map. It is, nevertheless, remarkable that on both maps the dermatome representing the greatest part of hypoaesthesia generally is not the dermatome corresponding to the blocked segmental nerve. This was only found in 11 (standard map) and 12 (adapted map) of the 40 test blocks.

In most cases using the standard and adapted dermatomal maps, hypoaesthesia after single segmental nerve block was found in at least 2 dermatomes (range 1 to 6). The mean area of hypoaesthesia interpreted in the standard map differed statistically significance from

the adapted map areas (2.7 ± 1.4 dermatomes, standard v 3.6 ± 1.8 dermatomes, adapted map; $P < 0.001$, paired t-test). In 6 cases, no hypoaesthesia was found. Therefore, single segmental nerve blocks, as applied in the present study, seem to have a limited selectivity with regard to sensory changes. In the cases where no hypoaesthesia was found, the pinprick method might have been too insensitive to detect hypoaesthesia, or hypoaesthesia did not develop at all, or the effect was concealed by overlap by neighboring dermatomes.

The finding of hypoaesthetic areas exceeding 1 dermatome might be surprising, but it is actually a normal representation of the extensive receptive fields of 1 segmental nerve. In this way, the peripheral nerve branches of 1 segmental nerve intermingle with similar branches of the sub- and suprajacent segmental nerves, as already described by Bolk [7]. Sherrington [8,15] also described an overlap in skin innervation and showed that most cutaneous loci were supplied by 2 or 3 consecutive posterior roots. This was corroborated in dogs by Fletcher and Kitchell [16]. Foerster [14] confirmed overlap in human dermatomes using 3 different methods: Sherrington's "remaining sensibility method"; the Strickers and Bayliss method [14], dermatomal vasodilatation by faradic stimulation of the distal part of a divided posterior nerve root; and finally his own "constructive method"- when a series of contiguous roots is divided, the superior border of the resulting anaesthesia represents the inferior border of the dermatome corresponding with the next higher intact root, while the inferior border of the anaesthetic area represents the superior border of the next lower dermatome. Finally, overlap of innervation was shown in various animals by several other investigators [17-23].

The extent of hypoaesthesia over more than 3 dermatomes may be related to undetected epidural or distal spread of local anaesthetics during injection, although this was controlled visually. Epidural spread was only seen in 2 cases that were excluded. A second explanation might be the way in which the adapted map was constructed. We assumed an overlap by 2 halves of neighboring dermatomes. However, a more extensive overlap might exist, as, for example, suggested by Fletcher and Kitchell [16].

Other factors may also contribute to inaccuracies in the findings with respect to hypoaesthesia. The conversion from skin to map may lead to a shift. The pinprick method is rather insensitive in assessing the extent of the vital sensory changes. It cannot discriminate between subtle differences with respect to lower and higher tactile thresholds [16]. More precise outcomes can possibly be obtained when applying a modified Von Frey-hair test: e.g., Semmes-Weinstein [24,25].

Nitta et al. [12] studied spinal nerve blocks by applying lidocaine to the spinal nerves L4, L5 and S1 and tested the sensory system by using the writing brush method. They found distinctive regions including the medial side of the lower leg (L4), the posterior side of the great toe (L5), and the fifth digit of the foot (S1). In 43%, 44% and 92% (L4-S1), respectively, Nitta et al. [12] found bandlike zones from the posterior midline of the trunk to the periphery formed by regions of sensory impairment. Their findings are in agreement with the theory of Keegan and Garrett [9] with respect to the bandlike dermatomes. In the present study, the same regions were found included in the hypoaesthetic areas. However, the highest frequency of hypoaesthesia were found in the lateral thigh and anterolateral side of the

knee (L4), at the lateral caudal half of the lower leg and lateral ankle (L5), and at the dorsolateral thigh, lateral ankle, and lateral side of the foot. (S1). Only the latter is in agreement with the findings of Nitta et al.[12] Furthermore, we discerned bandlike hypoaesthetic zones in many individual cases, but after superimposition of all total hypoaesthetic areas we found quite extensive regions, as depicted in the intensity maps. However, regions with higher intensities tend to form bandlike zones as well. Nitta et al.[12] present bandlike zones but do not give any description of superimposition of the total hypoaesthetic areas. Furthermore, they used lidocaine at a volume and concentration twice as high as that used in our study and did not describe any control of spread of their study drug after injection.

In contrast, superimposed areas with paraesthesias were generally of limited size and showed a more bandlike pattern in comparison to hypoaesthetic areas. The discrepancy between the occurrence of paraesthesias and hypoaesthesia in the corresponding dermatome can possibly be explained by the more local effect of electrostimulation on the neural tissue. The effect of the injected local anaesthetic also depends on many pharmacokinetic and pharmacodynamic factors. Although the methodology differs, our findings of regions with paraesthesias seem to fit with those of Nitta et al.[12] for L4, L5 and S1. Also, the locations representing the highest density of superimposed paraesthesias correlate quite well for L5 and S1, with the highest incidence of hypoaesthesia for L5 and S1 in the study Nitta et al. Only paraesthesias after neurostimulation at L4 remain more anterior in the lower leg in our patients.

The frequency of hypoaesthesia and paraesthesias in the corresponding dermatomes (Fig 6) was equal for the standard map (80%). For the adapted map these figures tend to be somewhat better: 98% (paraesthesias) versus 88% (hypoaesthesia; $P = 0.1$, paired t-test). Comparison between both maps for frequency of paraesthesias in the corresponding dermatome shows a significantly higher score for the adapted map (98% v 80%; $P < 0.01$, paired t-test), stressing the significance of including neighboring dermatomes in dermatomal maps.

Whereas this study was primarily directed toward the interpretation of the sensory effects caused by segmental nerve blocks, some remarks can be made with respect to pain. Using the adapted map, pain was present in 1 dermatome (mean ± SD: 2.4 ± 1.3) in only 11 cases, while using the adapted map pain was always present in at least 2 dermatomes (mean ± SD: 3.4 ± 1.0). The extensive areas representing pain in most cases, and the multisegmental innervation pattern (each dermal locus is supplied from 3 adjacent spinal levels), reemphasize the need to perform diagnostic segmental nerve blocks at more than 1 level to obtain insight into the effects on pain. However, after blocking 40 single segmental nerves, in 6 cases no sensory changes could be demonstrated at all. In 2 of these cases, a significant decrease in pain was experienced: in one, the segmental nerve, block was performed at a level represented in the pain area, and in the other case the block was performed at an adjacent level. In both cases there was no difference between the standard and the adapted map. In the 4 remaining cases pain did not diminish, while the block was performed at a spinal level corresponding with the painful area. These phenomena underline the complexity of pain transmission.

Although all patients had been diagnosed as "radicular syndrome without neurological deficit", this does not mean that all patients should have a pathophysiological process comprising the segmental nerve. Other sources of pain might be considered [1,13]. However, the mechanism and interpretation of the effects of diagnostic lumbosacral segmental nerve blocks was the primary issue of the present study, and not pain or pain reduction. Questions remaining are the influence, type, and concentration of local anaesthetic drug, the minimal volume needed, and consequences on extension, duration, and quality of block of mixing a local anaesthetic agent with radio-opaque fluid. Also, the position of the tip of the needle is critical for the spread of the study solution. Particularly, the position of the tip of the needle relative to the foramen is of paramount importance obtaining a selective spinal nerve (and ganglion) block [1]. Placing the needle tip too medially can result in epidural spread. A refinement of the projection procedure in computing the area of hypoaesthesia from skin to paper needs further study. Furthermore, we are aware of the rather small number of cases included in this study.

Nevertheless, the results contribute to a further elucidation of the mechanism and role of the segmental nerve blocks. With respect to the use of dermatomal maps, the frequency of hypoaesthesia and paraesthesias in the corresponding dermatome are significantly higher in the adapted map compared with the standard map. As stated earlier [11] dermatomes should not be considered as static, but need to be regarded as neurophysiological entities. In our opinion, a dermatomal map in which neighboring dermatomes are included is more concordant with this principle, as shown by the significant higher scores of combined presence of spontaneous pain, hypoaesthesia, and paraesthesias in corresponding dermatomes.

Conclusion

After segmental nerve block, a large variability in size and location of hypoaesthetic areas is found that is much more variable than considered until now; hypoaesthesia shows also more variability compared with elicited paraesthesias. This seems to be in accord with the overlapping innervation pattern of dermatomes and reemphasizes the fact that dermatomes are more extensive than depicted in standard dermatomal maps. Confirmation of an adequately performed segmental nerve block, as determined by coexistence of hypoaesthesia, elicited paraesthesias, and pain in the presumed dermatome, is more reliable when the overlap of neighboring dermatomes is taken into account.

Further studies are necessary to enhance the technique of the segmental nerve block, to find the optimal mixture of drugs used in the spinal nerve block, and to elucidate the clinical significance of the adapted map.

Acknowledgement

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Chapter 4

DO DIAGNOSTIC SEGMENTAL NERVE ROOT BLOCKS IN CHRONIC LOW BACK PATIENTS WITH RADIATION TO THE LEG LACK DISTINCT SENSORY EFFECTS? A PRELIMINARY STUDY

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Summary

Introduction. The present preliminary study documents the effects of a Selective Nerve Root Block (SNRB) with short or long acting local anaesthetic compared to baseline measurements in patients with chronic low back pain radiating to the leg with maximum pain in one dermatome (L4).

Methods. Ten consecutive patients underwent 20 controlled SNRBs at L4 with ropivacaine 0.25% and lidocaine 1% in a prospective, randomized, double blind, crossover fashion. Baseline measurements included sensory function (assessed by pinprick on both unaffected and painful leg) and pain (Verbal Numeric Rating Scale; VNRS, 0-10). A change in size of areas with altered sensory function above 10% and a VNRS change of ≥ 2 points were considered clinically significant. P values < 0.05 were considered statistically significant.

Results. Asymptomatic hypoaesthesia, variable in extent and non-dermatomal in distribution, was present in 7 patients at baseline. It appeared to be more extensive and distal with longer duration of preexisting pain. SNRB produced no consistent changes in extent and distribution of hypoaesthetic areas. Change in VNRS did not correlate with the extent of pre- or post block hypoaesthesia. No differences in effects were found between lidocaine and ropivacaine.

Conclusions. Pre block assessment of sensory function is essential to assess the net effect of SNRBs. In this small study group, SNRBs failed to demonstrate uniform or distinct effects on sensory function.

Introduction

In many patients suffering from chronic low back pain radiating to the leg (CLBP-r), diagnosing the underlying cause is problematic, since no clear patho-anatomic process can be identified. Segmental nerve root blocks (SNRBs) have been suggested as a means to identify the "symptomatic" spinal nerve segment, and are typically used for diagnosis and prediction of the outcome of surgical or invasive pain treatment [1-9]. In earlier studies we measured the effects of SNRB on sensory [10] and motor function [11] and found a large variability in effects. However, insight into the net effect was not obtained since no baseline measurements were made. In view of the altered sensory processing (neuroplasticity) described in a variety of chronic pain conditions [12-15], such alterations may also be expected to be present in CLBP-r patients. Clearly, if sensory function is already altered pre SNRB, this will influence interpretation of SNRB outcomes. To date, however, neither extent nor distribution of pre-existent sensory changes, nor how they are affected by SNRB [16] has been formally studied.

The present preliminary study documents the alterations in sensory function present prior to the SNRB, and the effects of subsequent SNRBs on sensory processing. We used the pinprick method, a non-quantifying sensory test, but suitable for mapping.

Patients and methods

Patients were consecutively recruited from referrals to our pain clinic for symptomatic invasive pain treatment. All patients had been examined extensively by (experienced) neurologists and/or orthopaedic surgeons, including CT, MRI and EMG and were diagnosed as having chronic low back pain unilaterally radiating beyond the knee. According to our standard hospital protocol such patients are subjected to a series of diagnostic lumbosacral SNRBs. Patients with maximum pain in dermatome L4 were included in this prospective, randomized, double blinded, crossover pilot study. Patients were recruited in accordance with the rules of the Declaration of Helsinki. The Hospital Ethics Committee approved the study. Written informed consent was obtained from each patient.

Inclusion criteria were: over 18 years of age, pain present for at least 6 months, and a Verbal Numeric Rating Scale (VNRS; 0 is no pain, 10 is intolerable pain) score of ≥ 5 at the moment of inclusion in the study. Exclusion criteria were: planned surgery, symptomatic neurological deficits, known hypersensitivity to amino-amide-type local anaesthetics or iodide, presence of blood coagulopathy, or mental disorders. All included patients were scheduled for test blocks with local anaesthetics at spinal level L4. Each patient underwent, on separate occasions, two test blocks with commonly used local anaesthetic agents in random order, one with lidocaine 1% and one with ropivacaine 0.25%, as each other's control to raise the validity of the block response. We assumed the ratio for the relative anaesthetic potencies for lidocaine and ropivacaine to be 1:4 [17]. The duration of effect was not a study goal. The hospital pharmacist performed randomization for the first L4 treatment with lidocaine or ropivacaine via sealed numbered envelopes. The second test block at L4 was performed on another day with the other drug.

Three anaesthesiologists specialized in invasive pain treatment performed the blocks. A research fellow, unfamiliar with the local anaesthetic agent used, assessed sensory function 30 minutes before and 30 minutes after the SNRB. The patients' sensation was tested by pinprick (Hypo^{R}, 825044A, 27G, MPL Technologies Inc., Franklinpark, IL USA) by 2 cm interval circles from the distal end of the feet up to dermatome T12. The patient was asked to state whether sensation was normal, less or more intense compared to the unaffected leg. Areas with sensory changes, if present, were marked and photographed digitally (Sony MVC-FD7) with a ruler for calibration. Sizes of areas were calculated with a specially developed software program (JvE). A change in area size of less than 10% was considered clinically insignificant. Pre- and post block VNRS pain scores were also recorded. A decrease in VNRS score ≥ 2 points was considered clinically significant [18].

SNRB was performed under fluoroscopic guidance using sensory and motor electrostimulation with frequencies of 50 Hz and 2 Hz, respectively, for spinal nerve root identification. After visualizing the nerve root by using 0.3 ml contrast dye (Omnipaque® 180 mg/ml; Nycomed Ireland, LTD, Cork), 0.7 ml of the study solution (lidocaine 1% or ropivacaine 0.25% - Astra Pain Control AB Södertälje Sweden - with Omnipaque® 15%) was injected. For a more detailed description of the SNRB procedure see Wolff and colleagues (10). All data were initially processed using Microsoft Excel 2000.

Statistical analysis

Changes in size of area with altered sensory and pain VNRS were analyzed by Statistica software package (Release 6, Statsoft Inc., Tulsa OK 74104, USA). Using Mann Whitney U testing we compared pre and post block areas and pain for the grouping variables lidocaine vs. ropivacaine and block order. Comparison of pre vs. post block VNRS was performed by Wilcoxon matched pair testing, and pre and post block areas were compared using Friedman's 1-way ANOVA. Relationships between pain and size of areas were tested using Spearman correlation. The relationship between duration of complaints and pre-block summed hypoaesthetic areas was assessed by linear regression analysis. P values < 0.05 were considered significant.

Results

Ten patients (6 male, 4 female, mean age 47 yr, SD 12, range 25-63) were included to undergo a total of 20 SNRBs. Patient characteristics and details of their medical history are presented in table 1.

Baseline measurements

In 7 patients areas with hypoaesthesia for pinprick were found in the affected limb before both blocks, but in three patients no pre block hypoaesthesia was detected. In none of the patients was hypoaesthesia observed in the unaffected limb. No patients showed hyperaesthesia in the affected or unaffected limb. In all patients hypoaesthetic areas did not correspond to the pain radiation pattern, and showed a non-dermatomal distribution (figure 1 and table 2).

The median pre block pain VNRS was 5 (interquartile range or IQR 4-7 [range 2-8]). In 3 cases, pre block VNRS scores differed at least 2 points between first and second session (patients 1, 5 and 9), but for the group as a whole the difference between sessions 1 and 2 was not significant. No major differences were observed in mean sensory or motor electrostimulation thresholds between the two sessions, but sensory thresholds were significantly lower when the number of painful dermatomes was higher (Spearman $R = -0.56$, $P<0.05$). There was no relation between the level of electrostimulation thresholds and pre block VRNS.

Table 1 **Patient characteristics and medical history**

Patient	m/f, age [yr]	Duration complaints [months]	Radiological diagnosis (MRI, CT, X-ray)	Spinal level	Previous surgery	Medication
1	f, 50	24	facetarthrosis, spondylarhrosis bulging disc, rupture annulus	L5-S1 L4-5	-	NSAID, codeine
2	m, 52	144	facetarthrosis, lateral recess, spinal stenosis epidural fibrosis	L3-4 L2-3	2 x laminectomy	acetominophen
3	f, 63	60	lateral facetarthrosis, herniated disc	L4-5	4 x hernia operation	acetaminophen
4	f, 25	18	bulging disc	L4-5	-	acetaminophen
5	m, 58	360	lateral recess, spinal stenosis	L4-5	-	NSAID
6	m, 53	8	herniated disc	L3-4	-	acetominophen
7	m, 40	12	herniated disc	L5-S1	-	acetominophen
8	f, 42	36	bulging disc herniated disc	L4-5 L5-S1	-	acetaminophen, codeine
9	m, 30	108	herniated disc, discopathy discopathy	L4-5 S1-S2	chemonucleolysis	NSAID
10	m, 55	120	arthrosis, L4-5 small foramen, and discopathy	- L5-S1		acetaminophen

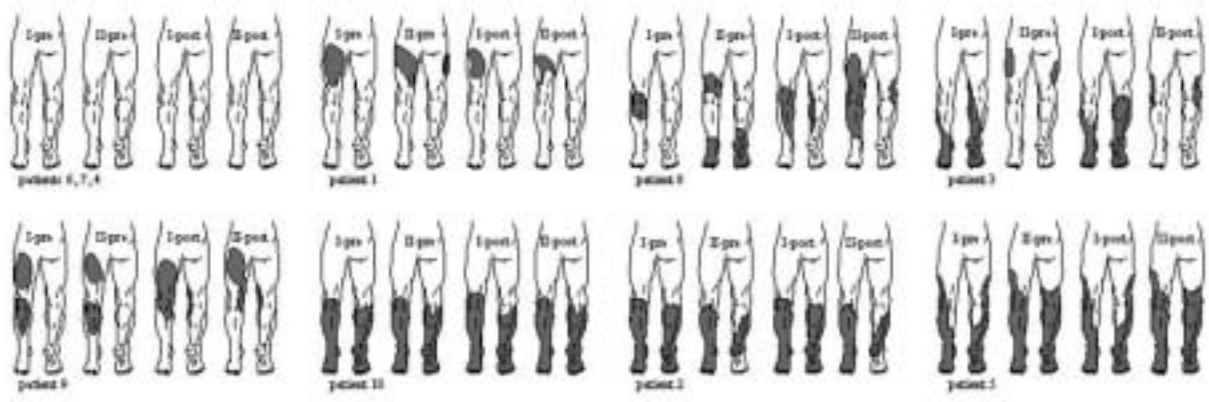

Figure 1 Dermal maps presenting areas with hypoaesthesia for pinprick before and after the two sessions with SNRB, grouped per patient. Each group of figures represents, respectively, the measured areas before the first SNRB (I-pre), before the second block (II-pre), after the first block (I-post) and after the second block (II-post). Left legs represent the ventral part of the affected leg, right legs the dorsal part.

Table 2 Results

Patient No	1	2	3	4	5	6	7	8	9	10
Duration of pain [mnths]	24	144	60	18	360	8	12	36	108	120
1st SNRB										
1st Local anaesthetic	ropi	lido	lido	ropi	lido	ropi	lido	ropi	ropi	lido
Pre-block hypoaesthesia-1 [mm²]	253	1082	495	0	593	0	0	223	1364	1271
Post-block hypoaesthesia-1 [mm²]	69	1085	637	0	591	0	0	394	986	1489
Δ area (%)	-73	0	+29	0	0	0	0	+77	-28	+17
Pre-block hypoaesthesia-1 dermatome	L1-4	L3-S2	L3-S2	0	L4-S2	0	0	L3-5	L2-5	L3-S2
Post-block hypoaesthesia-1 dermatome	L2-4	L3-S2	L3-S2	0	L4-S2	0	0	L3-S2	L2-5	L3-S2
Δ NRS 1	-3	0	-8	0	-1	-3	-4	0	-5	-1
2nd SNRB										
2nd Local anaesthetic	lido	ropi	ropi	lido	ropi	lido	ropi	lido	lido	ropi
Pre-block hypoaesthesia-2 [mm²]	512	653	237	0	1474	0	0	789	1014	1418
Post-block hypoaesthesia-2 [mm²]	210	659	209	0	1485	0	0	951	1418	1420
Δ area (%)	-59	0	-12	0	0	0	0	-59	40	0
Pre-block hypoaesthesia-2 dermatome	L1-5	L3-S2	L3-5	0	L4-S2	0	0	L3-S2	L2-5	L3-S2
Post-block hypoaesthesia-2 dermatome	L2-4	L3-S2	L4-S1	0	L4-S2	0	0	L2-S1	L2-5	L3-S2
Δ NRS 2	0	0	0	-2	-3	0	-3	0	-6	0
Summed pre block areas [mm²]	765	1735	732	0	2067	0	0	1012	2378	2689
Summed post block areas [mm²]	279	1744	846	0	2076	0	0	1345	2404	2909
Δ Summed hypoaesthetic areas	-64	+0,5	+16	0	+0,4	0	0	+33	+1	+8

Post-SNRB measurements

In patients with a baseline hypoaesthesia, SNRB produced variable, but neither statistically nor clinically significant changes in extent and distribution of hypoaesthetic areas (figure 1 and table 2). There was no group statistical difference in total post block hypoaesthetic area between session 1 and 2, even when patients without hypoaesthesia were excluded. Hypoaesthesia was absent in the non-affected limb, hyperaesthesia was absent in both legs.

Post block, median pain VNRS decreased from 5 (IQR 4-7 [2-8]) to 4 (IQR 1.5-5 [0-8]). Median change in VNRS was –1 (IQR –3-0 [–8-0]) and was not different between the two sessions. Change in VNRS did not correlate with pre block pain VNRS or the extent of pre- and post block hypoaesthesia. Clinically significant pre-post block decreases in VNRS (≥ 2 points) were found in 8 of the 20 SNRB sessions (table 2).

No differences were found for lidocaine vs. ropivacaine or for first vs. second treatment with respect to pre and post block incidence and extent of hypoaesthesia or for changes in pain VNRS.

Discussion

Most patients in this small preliminary study had pre-existing hypoaesthetic areas in the affected limb, not corresponding to pain radiation patterns and non-dermatomal in distribution. This suggests that for correct SNRB interpretation, post block sensory assessment alone is insufficient. The net hypoaesthetic effects of SNRBs were neither consistent nor significant, and a clinically significant pain reduction was only found in a minority of blocks.

As far as we know, this is the first time that such effects have been described. Earlier reports [10,14,15,19] have described pain-induced changes in pain thresholds and motor function in patients with CLBP-r as well as in chronic cervicobrachialgia patients [20,21]. However, these studies provide no information regarding size and variability of hypoaesthetic areas. A clear explanation for the baseline presence of hypoaesthetic areas in CLBP-r patients cannot be given. However, this phenomenon of areas not concordant with known innervation territories of nerve roots, is in keeping with reported extraterritorial spread of sensory dysfunction in chronic neuropathic pain patients [22]. We have interpreted these areas as non-dermatomal in distribution, although one could also argue that this distribution is perhaps the result of the patients not displaying dermatomes with definite, fixed boundaries. Furthermore, CLBP-r patients should be considered to form a heterogeneous population in which involvement of adjacent spinal levels cannot be excluded. Moreover, pre block hypoaesthetic areas often differed before blocks in our study, suggesting spontaneous variability in sensory function. Thus, the interpretation of sensory dysfunction and SNRB effect on sensory function remains extremely difficult.

Two possible mechanisms may be proposed to explain the presence of these hypoaesthetic areas, namely nerve damage (small fibre neuropathy) and/or inhibitory neuroplasticity.

We cannot exclude small fibre neuropathy. The pattern of changes we found is typical for this, with its presentation of pain accompanied by patchy and asymmetrical sensory changes. Pathological processes in the dorsal ganglion, such as demyelinization or ion channel re-distribution[15], are held responsible for this type of small fibre neuropathy[23], but identification of such processes was not possible in our patients. To formally establish the diagnosis of small fibre neuropathy, more specific complementary diagnostic tests assessing somatic and autonomic fibre system would be necessary (23).

It is well-accepted that various forms of neuroplasticity can accompany pain chronification [13,24]. When we grouped our data according to duration of complaints, the summed pre- block hypoaesthetic areas appeared to be larger in size and more fixed when the duration of pre-existing pain was longer (R = 0.67; p=0.03; figure 2).

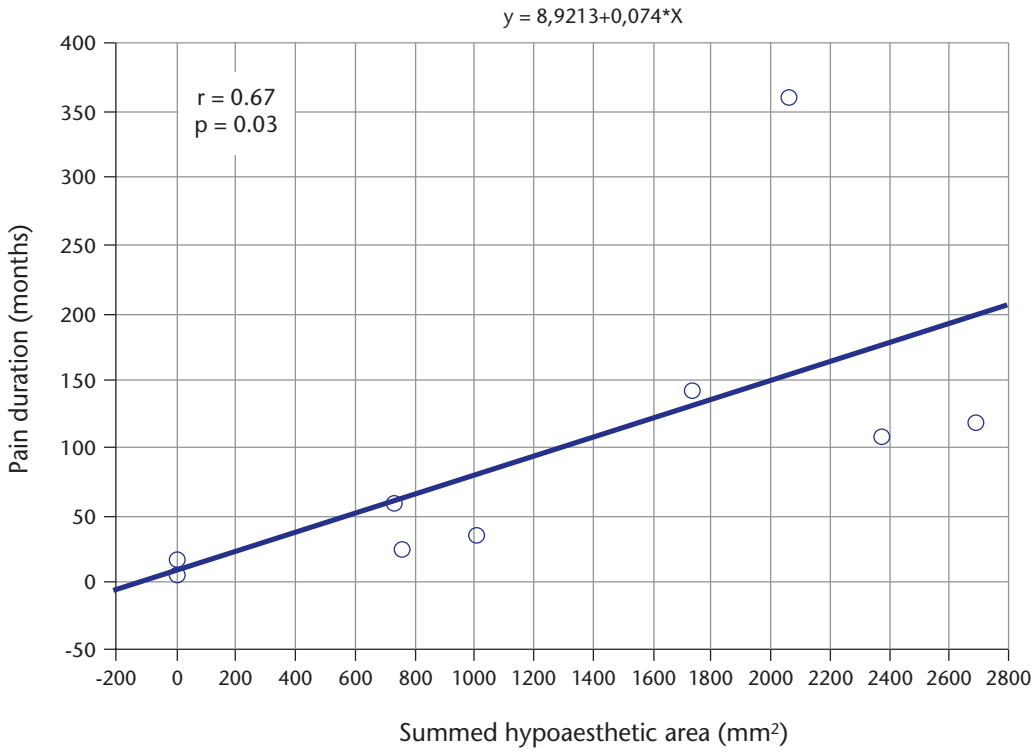

Figure 2 Relationship between duration of complaints and extent of summed pre-SNRB hypoaesthetic skin areas (n=10)

Further support for the involvement of neuroplasticity is found in our observation that electrostimulation thresholds were significantly lower when the number of painful dermatomes was higher, indicative of pain-induced central sensitisation. Thus it is tempting to postulate that the extent, the variability and the location of the hypoaesthetic areas may be time-related to increasing chronicity of the painful condition. However, considering the small numbers of patients in the present study one should be cautious. This hypothesis needs to be formally explored further by studying a large population of CLBP-r patients covering the complete spectrum of short to long existing chronic pain. Because pinprick testing alone may miss sensory changes, the use of Quantitative Sensory Testing (QST) in this context offers the possibility of detecting more subtle differences and acquiring more quantified information on the sensory function.

Lack of distinct SNRB effect

The lack of a distinct net effect of SNRB is surprising in view of the generally assumed axiom that SNRB should lead to dermatome related hypoaesthesia and correlated pain reduction. SNRB effects may remain unexpressed because of overlap with neighbouring dermatomes [25]. Other reasons may include the small number of patients or technical failure, although all blocks were performed under fluoroscopic guidance and were accompanied by clear paraesthesias and muscle contractions. Furthermore, radiological control demonstrated that in all cases the study drug reached the segmental nerve root L4 without unintended intravascular injection or epidural spread. It is conceivable that a more consistent post block hypoaesthesia pattern would have been revealed if larger local anaesthetic doses had been used. Complete abolition of intercostal somatic sensory evoked potentials (SSEP) was reported in thoracic paravertebral blocks using bupivacaine [26] in high doses (bupivacacaine 0,5% 1.5 mg kg^{-1}). Equivalent inhibition of SSEPs has not been achievable with epidural and spinal anaesthesia [27-29]. The volume and concentrations of local anaesthetics that we administered were within commonly used equipotent range, although to our knowledge no controlled dosage-effect studies have been performed up to now in this context [16,9]. Agents, such as steroids, when added to local anaesthetics in SNRBs are also responsible for pain relief [30] and can potentiate a local anaesthetic blocking effect [31]. Our study, however, was aimed at the effects of local anaesthetics only. Differences in pharmacokinetic behaviour between the two study drugs [16], e.g., differential sensitivity to local anaesthetic agents by different-sized neural fibres, are not addressed by this study, but cannot be ruled out. SNRB effects might further be attenuated by the inability to block alternative sensory pathways that are part of a multisegmental neural network [32,33]. Clearly, our results need confirmation with a larger number of subjects.

Conclusion

In this preliminary study SNRBs failed to demonstrate uniform or distinct effects on sensory function. Prior to the block, asymptomatic hypoaesthetic areas, non-dermatomal in distribution, were observed in many patients. In patients with longer duration of pain, pre block hypoaesthetic areas tended to be larger. Post block assessment only must be considered insufficient for SNRB assessement, since much of the observed hypoaesthesia was already present prior to the block. Careful pre block assessment of sensory function is an essential prerequisite for interpretation of SNRB effects.

Acknowledgement

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Chapter 5

LUMBAR SEGMENTAL NERVE ROOT BLOCKS WITH LOCAL ANAESTHETICS, PAIN RELIEF AND MOTOR FUNCTION: A PROSPECTIVE DOUBLE-BLIND STUDY BETWEEN LIDOCAINE AND ROPIVACAINE

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Summary

Introduction. Selective segmental nerve blocks with local anaesthetics are applied for diagnostic purposes in patients with chronic back pain to determine the segmental level of the pain. We performed this study to establish myotomal motor effects after L4 spinal nerve blocks by lidocaine and ropivacaine and to evaluate the relationship with pain.

Methods. Twenty patients, of which 19 finished the complete protocol, with chronic lumbosacral radicular pain without neurological deficits underwent segmental nerve blocks at L4 with both lidocaine and ropivacaine. Pain intensity scores (verbal numeric rating scale, VNRS) and the maximum voluntary muscle force (MVMF; using a dynamometer expressed in newtons) of the tibialis anterior and quadriceps femoris muscles were measured on the painful side and on the control side.

Results. Median VNRS decrease was 4.0 ($p<0.00001$; Wilcoxon) without significant differences between ropivacaine and lidocaine (Mann Whitney U-test). A difference in effect on MVMF was found for affected versus control side ($P=0.016$, Tukey test). Multiple regression revealed a significant negative correlation for change in VNRS score versus change in median MVMF (Spearman $R = -0.48$: $P = 0.00001$).

Conclusion. This study demonstrates that in patients with unilateral chronic low back pain radiating to the leg, pain reduction induced by local anaesthetic segmental nerve (L4) block is associated with increased quadriceps femoris and tibialis anterior MVMF, without differences for lidocaine and ropivacaine.

Introduction

Selective segmental nerve blocks with local anaesthetics are applied for diagnostic purposes in patients with chronic back pain to determine the segmental level of the pain [1-5]. Most patients with chronic pain are treated in day-care and must therefore have sufficient motor control to be discharged. In many pain clinics, lidocaine is used because of its intermediate-acting effect. Ropivacaine, a long-acting local anaesthetic, provokes a less intense motor deficit than bupivacaine [6] and possibly also less than lidocaine. These pharmacokinetic and pharmacodynamic characteristics of ropivacaine might be of benefit in spinal segmental nerve blocks. No reports have appeared on the use of ropivacaine in segmental nerve blocks, and, specifically, on its effects on segmental motor function.

In one study, the sensory effects of lumbosacral (L1 to S1) segmental nerve blocks by local anaesthetics were found to exhibit [7] a large variability in size and location of hypoaesthetic dermal areas, but with less variability for elicited paraesthesias. It was concluded that for a proper segmental diagnosis, one should also consider the overlapping of neighbouring dermatomes [6,8-11]. Determination of loss of motor function is equally part of the diagnostic segmental evaluation in invasive pain treatment. Because myotomes are also innervated multisegmentally [8], overlap of muscular innervation and the recruitment of inactive motor units [12] could theoretically mask motor deficits after segmental nerve blocks by local anaesthetics. A decrease in pain might further contribute to an increase in motor function, because motor function can be inhibited by pain [13,14].

This study focused on the motor effects induced by L4 spinal nerve blocks with lidocaine 1% versus ropivacaine 0.25%, assuming a ratio of 1:4 for the anaesthetic relative potencies for lidocaine and ropivacaine [6]. The fourth lumbar segmental nerve was chosen since it is the main motor supplying nerve for two muscles whose force can easily be measured (i.e., the quadriceps femoris and tibialis anterior muscles). The aims of this study were: 1) to establish whether there is also large variability in motor effects after L4 spinal nerve blocks by local anaesthetics; 2) to compare the motor effects of the 'standard' local anaesthetic lidocaine versus equipotent doses of ropivacaine; and 3) to evaluate the relationship between pain intensity and the effect of a segmental nerve block on motor function. Assessment of duration of effect was not a study goal.

Methods

We consecutively recruited patients with unilateral chronic low back pain radiating to the leg who were referred to the pain clinic for symptomatic invasive pain treatment. All patients were examined extensively, including computed tomography, magnetic resonance imaging, and electromyelography, and were diagnosed by a neurologist or an orthopedic surgeon as having lumbosacral radicular syndrome without neurological deficit (n= 44). Inclusion critera were: pain present for at least 6 months and a verbal numeric rating scale score for pain (VNRS; 0 = no pain; 10 = unendurable pain) of at least 5 at the moment of inclusion in the study. According to the hospital's standard protocol, these patients were

candidates for a series of lumbosacral segmental nerve test blocks, including L4 (n=22). Exclusion criteria were: availability of causal therapy, known hypersensitivity to amino-amide-type local anaesthetics or iodide, presence of blood coagulopathy, or mental disorders. Patients were recruited in accordance with the rules of the Declaration of Helsinki. The study was approved by the Hospital Ethics Committee, and each patient gave written, informed consent. Two patients refused inclusion in the study. Twenty patients were ultimately recruited, of which 19 patients finished the complete protocol. One patient was excluded because of too much pain during the measurement procedures, as a result of which the muscle force data became unreliable.

Patients always started their test series with a test block at a level other than L4, which was used for patient instruction and practice according to the study protocol. All other blocks were done on separate days. The second test block was performed at L4 with a randomly assigned local anaesthetic - Xylocaine® 1% (lidocaine) or Naropin® 0.25% (ropivacaine) - and vice versa for the third block. Randomization for starting with ropivacaine (Group RL) or lidocaine (Group LR) was done by the hospital pharmacist, who provided closed, numbered envelopes. At the end of the study period, 20 patients had undergone 40 diagnostic segmental nerve blocks at L4 according to the experimental protocol. The blocks were performed by three experienced anesthesiologists specialized in invasive pain treatment. All motor function measurements were performed by a research fellow, who was blinded for the type of local anaesthetic, the painful side, and the side of the nerve block.

After patients arrived in the pain treatment room, 5 minutes before the test block, the VNRS score was recorded and the patient was positioned prone with a pillow under the abdomen to decrease lordosis. Under fluoroscopic guidance, the insertion site of the needle was marked on the skin at the painful side by a pencil. The opposite side was also marked symmetrically to prevent unblinding of the observer. After lidocaine infiltration anaesthesia of the skin, a 10-cm electrode (23-gauge, Top®, Sanofi Santé) was inserted in the dorsocranial quadrant of the intervertebral foramen L4-5 (lateral view) and advanced until the tip was positioned one third to half way along the pedicle column (anteroposterior view). To confirm the position of the needle point, an electric current generated by a radiofrequency pulse- and lesion- generator system (RFG-3B, Radionics, Burlington, MA, USA) was applied, thereby stimulating the spinal nerve or its dorsal root ganglion (DRG). Paraesthesias were evoked by stimulating with a frequency of 50 Hz and muscular contractions were evoked by stimulating at 2 Hz with a motor stimulation threshold of at least 1.5 times the sensory stimulation threshold (0.2-2 V). The anesthesiologist recorded the voltages (0-2 V, as displayed on the lesion generator system) necessary to evoke the paraesthetic sensations (experienced by the patient) and muscular contractions (observed by the anesthesiologist by seeing and feeling the muscle contractions by hand). Subsequently, 0.3 ml of contrast dye (Omnipaque® 180 mg/ml, Nycomed Ireland, Ltd, Cork) was injected to confirm adjacency of the DRG, and radiographs were taken in the anteriorposterior and lateral direction. Finally, 0.7 ml of the lidocaine study solution (lidocaine 1% and Omnipaque 0.15%) or

0.7 ml of the ropivacaine study solution (ropivacaine 0.25% and Omnipaque 0.15%) was injected. Forty-five minutes after the test block the VNRS was recorded again.

Baseline maximal muscular contraction forces were assessed at least 30 minutes before injection. The maximum voluntary forces (MVMF) of the tibialis anterior and quadriceps femoris muscles were both measured during a maximal effort of 10 s and repeated twice at 5-min intervals to enable muscle recovery. After 30 minutes the whole procedure was repeated on the other leg.

To measure MVMF, a special device was developed to perform the exercises in a standard way. This device enabled the patient to have a half-sitting and half-lying posture, which was necessary to optimize the test exercise (Fig. 1). The patient's head was supported by a pillow in a neutral position. The trunk was held at an angle of 45° to the horizontal and supported by an adaptable support for the back. Hips and knees were both flexed to an angle of 90°. The Microfet hand held Dynamometer™ (Hoggan Health Industries, South Droper, UT, USA) was fixed in this device to measure the MVMF (in newtons). To test the MVMF of the quadriceps muscle, the dynamometer was attached just proximal to the ankle, in the midline between the medial and lateral malleolus. The patient had to extend the lower part of the leg at the knee at maximal strength against the fixed dynamometer for 10 s. To test the MVMF of the tibialis anterior muscle, the dynamometer was attached just proximal to the head of the first metatarsal bone. The patient had to flex the foot at the ankle at MVMF for 10 s.

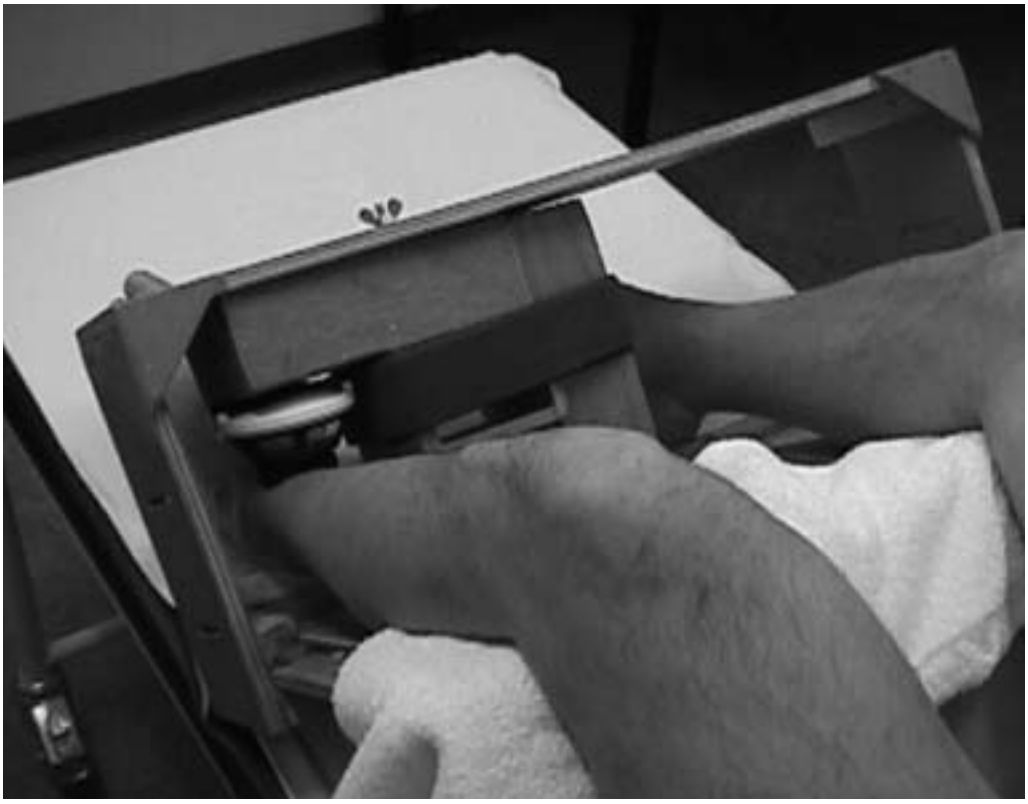

Figure 1 Device developed for experiment exercises. In this position the maximal voluntary contraction force of the quadriceps muscle can be tested. The dynamometer is attached just proximal to the ankle, in the midline between the medial and lateral malleolus.

The data were processed on using Statistica for Windows (release 4.5, Statsoft Inc., Tulsa, OK). A minimal decrease of 2 points in the VNRS score was considered as clinically significant [15]. Between-group demographic data differences were tested using Student's t-test. Intervention order effect (first versus second treatment), drug effect (ropivacaine versus lidocaine), side effect (treatment side versus control side), site effect (motor effect on quadriceps femoris or tibialis anterior muscle), and dermatome effect (whether maximum pain was in L4 dermatome) on the median of MVMF were evaluated by analysis of variance (ANOVA). For *post hoc* analysis Tukey testing was used.

Nonparametric testing (Mann-Whitney U test and Wilcoxon's signed rank test) was used to evaluate pre block versus postblock pain. Spearman regression analysis was used to assess the various relationships between pre intervention VNRS, change in VNRS, change of MVMF, and sensory and motor thresholds ($r > 0.3$ was considered relevant with 95% confidence; $P < 0.05$ were considered statistically significant).

Results

Nineteen (total of 38 segmental nerve blocks) of the 20 patients finished the study. In all but two cases, hypoaesthesia was found by pinprick in the corresponding dermatome after local anaesthetic injection. Independent assessment of the radiographs revealed no epidural spread of radiocontrast dye.

Table 1 **Patient characteristics (n=19)**

Age: mean SD, range [yrs]	46.8; 12.3; 25-63	
Sex: M/F [n]		10/9
Duration of complaints: mean SD, range [mnth]	49.7; 39.4; 6-244	
Radiological diagnosis (MRI, CT, X) [n]	HNP	12
	discopathy	3
	spine degeneration	5
	epidural fibrosis	5
Previous surgery [n]	herniotomy	6
	PFD	6
	RF-LTrOS	3
Medication [n]	acetominophen	8
	NSAID	14
	tramal	4
	opioid	2
	amitryptiline	1
	gabapentin	1

Patient characteristics with respect to sex, duration of complaints, radiological diagnosis, relevant history of surgery and medication. Abbreviations: PFD = percutaneous facet denervation; RF-LTrOS = radiofrequency lesion of lumbar sympathetic trunk.

Group RL contained five male and five female patients with a mean age of 48.7 years (range, 36-66 yr; SD, 10.9 yr); Group LR consisted of five male and four female patients with a mean age of 55.7 yr (range, 40-79 yr; SD, 13.0 yr). The differences in age between groups were not statistically significant (P = 0.23; Student's t-test). Patient characteristics are described in table 1.

Table 2 shows the effects of segmental nerve block on motor function and pain, expressed as relative changes in MFMF and absolute change in VNRS scores, respectively. Some patients did not show any decrease in VNRS after segmental nerve block, but for the entire group, the median pain VNRS decrease was 4.0 (before versus after: $P < 0.00001$; Wilcoxon's signed rank test). The median pain VNRS (interquartile range; range) was 7.0 (6.0-8.0; 0-10) pre block and 3.0 (0.5-6.0; 0-8.5) post block. In one case in the RL group, the patient underwent a segmental nerve block with lidocaine without any pain at that moment. This case was excluded from further data analysis. There were no significant differences in pre block VNRS, post block VNRS, and change in VNRS between ropivacaine and lidocaine (Mann-Whitney U-test). Figure 2 shows the pre- and post injection median MVMF's on the affected and on the control side.

Table 2 **Results**

	Affected side		Control side			
	∂ median (%)#		∂ VNRS°		∂ median (%)#	
ropivacaine quadriceps	**-7**	(-43, 44; 21)	**-3.0**	(-9, 1; 2.4)	**7**	(-25, 58; 21)
lidocaine quadriceps	**-12**	(-67, 17; 19)	**-3.3**	(-10, 1; 2.9)	**1**	(-25, 45; 18)
ropivacaine tibial	**4**	(-49, 71; 32)	**-3.0**	(-9, 1; 2.4)	**3**	(-37, 115; 43)
lidocaine tibial	**-2**	(-42, 43; 23)	**-3.3**	(-10, 1; 2.9)	**3**	(-25, 62; 22)
totals	**-4**	(-67, 71; 24)	**-3.1**	(-10, 1; 2.6)	**4**	(-27, 115; 24)

Differences between post- vs pre block values of quadriceps or tibial muscle forces [Newtons] and VNRS (n=19) for the affected and control side, after ropivacaine or lidocaine induced segmental nerve block at L4. Data of muscle forces are expressed as % change in mean force. Values shown between brackets are % change of maximal decrease and increase, and standard deviation.

mean % difference between post- vs pre block values of muscle forces (medians of 3 measures are compared)

° mean difference between post vs pre block values of Numeric Rating Pain Scale (VNRS)

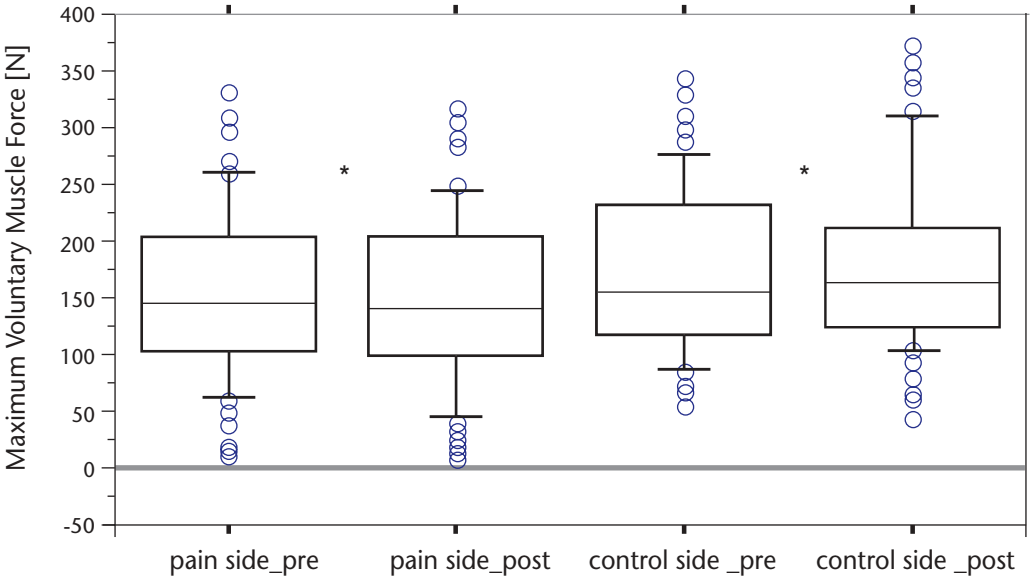

Figure 2 Box Plot representing median MVMF's (maximum voluntary mucle forces) at the affected (pain) side vs control side before and after local anaesthetic induced segmental nerve block at L4. A difference in effect on MVMF was found for affected vs control side (* P=0.016, Tukey).

Analysis of variance demonstrated no significant effect on MVMF for the following independent factors: first versus second intervention (i.e., order effect), drug injected (ropivacaine or lidocaine), site (quadriceps femoris or tibialis anterior muscle), and whether the maximum pain intensity was in the L4 dermatome or not (both for the standard and adapted dermatomal map)[7]. A statistically significant difference in effect on MVMF was found for affected versus control side (P = 0.016; Tukey test). When the results were pooled (both muscles together) for the affected side, a decrease of the MVMF was found for median (mean, 4.2%; range, –65% to 71%; SD, 24.3%) values. For the control side, an increase was observed for median (mean, 4.5%; range, -37% to 115%; SD, 24.3%) values.

The data were pooled for multiple regression to assess correlations between factors on the affected side. A significant negative correlation was found for change in VNRS score versus change in median MVMF (Fig. 3; Spearman R = -0.48: P = 0.00001): the larger the decrease in VNRS score, the larger the increase in MVMF on the affected side. No statistically significant correlations were found for pre block VNRS score versus change in median and sums of MVMF. Further significant correlations were found for the affected side for pre block VNRS versus post block VNRS (Spearman R = +0.53; P = 0.000001) and the change in VNRS score versus post block VNRS (Spearman R = +0.69; P = 0.0000001).

No significant correlations were found either for change in VNRS or for change in MVMF for the control side. For both sides, there was no significant correlation for pre block VNRS score versus sensory and motor electrostimulation thresholds, or for the pre block sensory or motor electrostimulation threshold versus change in the median or sums of MVMF.

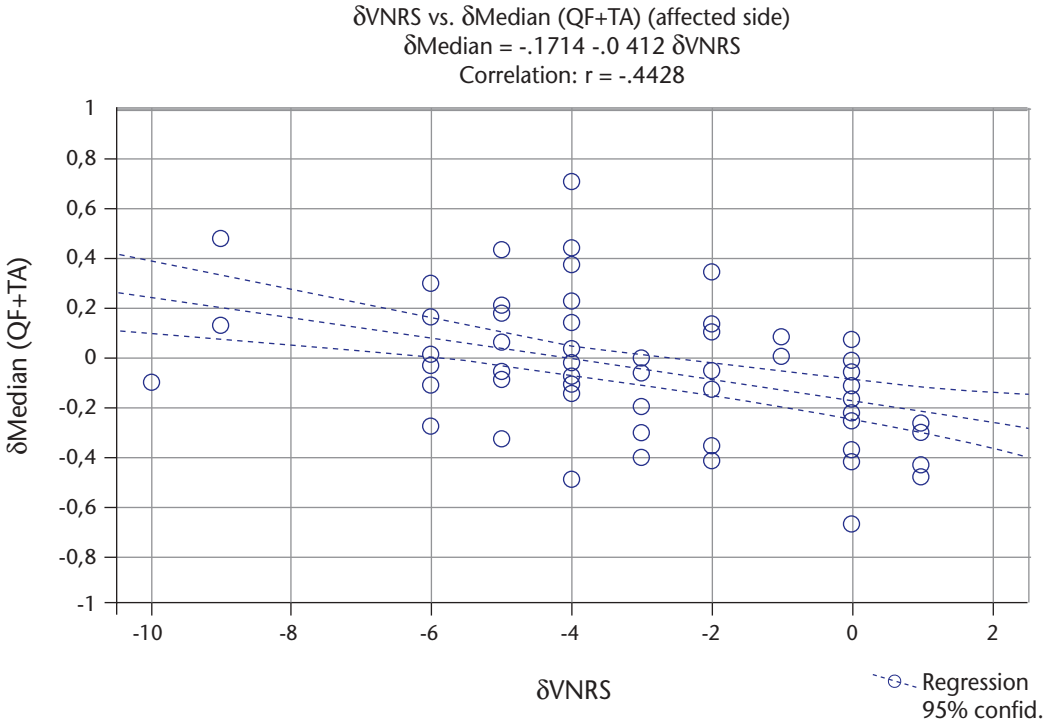

Figure 3 Change of mean VNRS vs change of MVMF in percentage of baseline muscle force in newton (affected side). A negative correlation is found with Spearmans multiple regression (Spearman R: -0.48: p=0.00001).

Discussion

The regression results of the study demonstrate that alleviation of pain by segmental nerve block with local anaesthetics can be accompanied by an increase of MVMF in the musculature innervated by that segmental nerve. The larger the decrease in pain, the larger the increase in force. This is the first time that this phenomenon has been described in human subjects undergoing segmental nerve blocks with local anaesthetics. This result was unexpected, because one would anticipate segmental nerve block by local anaesthetics to decrease MVMF. A plausible explanation is that pain causes inhibition of motor function [16] and that when pain decreases, motor inhibition is reduced, in accordance with our results. However, for the group taken as a whole, the median MVMF on the affected side decreased after segmental nerve block. This is probably the effect of the cases in which nerve block did not decrease pain.

Le Pera et al. [16] demonstrated that tonic muscle pain can inhibit the motor system by using motor evoked potentials from the right abductor digiti minimi by transcranial magnetic stimulation of the left primary motor cortex in human subjects. To provoke pain, hypertonic (5%) saline was injected into the right and left abductor digiti minimi, into the right first dorsal interosseus, and into the subcutaneous region of the right abductor digiti minimi. Motor evoked potentials were significantly reduced in amplitude during pain induced in the right abductor digiti minimi and right first dorsal interosseus, but not during pain in the left abductor digiti minimi or during subcutaneous pain. An ipsilateral muscular and possibly

a myotomal relationship was suggested. Paik et al.[13] studied the effect of conditioning stimulation of a peripheral nerve on responses of spinal dorsal horn cells and motor neurones in 16 decerebrate-spinal cats. Noxious mechanical and noxious thermal stimuli applied to the receptive fields reduced the activity of dorsal horn cells and motor neurones recorded from a filament of ventral rootlet divided from either the L7 or S1 root. One of the conclusions the authors reached was that the conditioning stimulation of a peripheral nerve produced a powerful inhibition of the responses elicited by noxious stimuli, suggesting that inhibition is an antinociceptive effect. Le Bars et al.[14] described diffuse noxious inhibitory controls in animals and humans, where neurones in the dorsal horn of the spinal cord can be strongly inhibited by a nociceptive stimulus applied to any part of the body distinct from their excitatory receptive fields. Diffuse noxious inhibitory control is most likely sustained by a loop which includes supraspinal structures and is therefore different from segmental inhibition. In both of the phenomenona described above, nociceptive signals can be modulated by powerful controls. All above described mechanisms have in common that pain can inhibit central and/or motor neurone activity and probably represent natural mechanisms meant to protect a subject from further harm. A segmental nerve block potentially decreases pain-induced motor inhibition. This might explain the unexpected increase of MVMF after local anasthestic segmental nerve block-induced pain reduction in patients with lumbosacral radiating pain in our study.

The dynamometer we used has a high intraobserver reliability[17,18] and the specially developed device made it possible to measure MVMF for 10 seconds. Submaximul efforts, avoided by instruction, increase the risk of not using all motor units and, hence, the possibility of recruiting motor units of other myotomes[12]. When the effort was not done in the proper way, the measurement was excluded from further data processing, which happened in one patient. We paid special attention to keep a steady muscle temperature by covering the legs under wool blankets, thus preventing changes in stimulus conduction[19].

This study could not demonstrate differences in effects on MVMF and pain between lidocaine and ropivacaine. In all but one case, the local anaesthetics were applied at the correct location. In only one case (after injection with ropivacaine) the DRG and its segmental nerve could not be visualized with contrast dye. It is possible that lidocaine and ropivacaine are equally potent in segmental nerve blocks in the applied dosages. However, the number of patients might be too small to demonstrate such an effect. There seems to be, except for a theoretical difference in duration of effect (not a study goal), no advantage from one local anaesthetic over the other.

We would suggest that, on the basis of the results of this study, the value of local anaesthetic segmental nerve blocks in diagnosing and predicting interventional outcomes must be treated with caution. Many factors play a role in causing this uncertainty in this context, including our lack of knowledge on the precise mechanisms of pain involved, the many variants of neurophysiology and pathophysiology, placebo effects, and technical aspects[20]. In this study, we have made attempted to illuminate motor aspects of this complex interaction. Further investigation is needed to achieve a better understanding of the underlying complexity of the effects of local anaesthetic-induced segmental nerve blocks.

We conclude that in patients with unilateral chronic low back pain radiating to the leg, pain reduction induced by nerve (L4) block is associated with increased MVMF of the quadriceps femoris and tibialis anterior muscles. There are no differences in effect on MVMF between lidocaine and ropivacaine. The larger the pain decreases, the more the MVMF increases. This study is the first to report these phenomena, which can be important for the interpretation of segmental nerve blocks.

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Chapter 6

SELECTIVE LUMBOSACRAL NERVE ROOT BLOCKS AND INADVERTENT EPIDURAL SPREAD: A CAUTION

Submitted

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Summary

Background. In patients with chronic low back pain radiating to the leg (CLBP-r) segmental nerve root blocks (SNRBs) are performed to predict surgical procedure outcome and identify the putative symptomatic spinal nerve. Epidural spread may lead to false interpretation, affecting clinical decision-making. Systematic fluoroscopic analysis of epidural local anaesthetic spread and its relationship to needle tip location has not been published to date. Study aims include assessment of epidural local anaesthetic spread and its relationship to needle position during fluoroscopy-assisted SNRB.

Methods. CLBP-r patients scheduled for L4, L5 and S1 SNRB were included in this prospective observational study. Under fluoroscopy and electrostimulation they received 0.5 ml of a mixture containing lidocaine 5 mg and Iohexol 75 mg. X-rays with needle tip and contrast were scored for spread epidurally or to adjacent nerve roots.

Results. Seventy-one patients (18 L4, 29 L5, 24 S1) entered the study, 65 were analyzed for epidural spread, 62 for needle position. Epidural spread occurred in 47% of L4 and 28% of L5 blocks, and inadvertent spread to an adjacent nerve root in 3 blocks (5%; L5 n=1, S1 n=2). For lumbar SNRBs the needle was most frequently found in the lateral upper half of the intervertebral foramen. Epidural spread occurred more frequently with medial needle positions.

Conclusion. Fluoroscopically detected epidural spread with lumbosacral SNRBs is common and at lumbar level more frequent with medial intraforaminal needle positions. Spread to adjacent nerve roots occurs occasionally. Epidural spread decreases selectivity and necessitates caution regarding the role of SNRBs in clinical decision-making.

Introduction

Segmental nerve root blocks by local anaesthetics (SNRBs) are performed to identify the putative symptomatic spinal nerve [1-7] and to predict the outcome of surgical treatment in low back pain patients [8,9]. There is moderate evidence for the effectiveness of SNRB as a diagnostic tool in spinal pain disorders with radicular complaints [10] but selectivity and specificity of this procedure, as well as the reproducibility of its clinical effects, have been questioned [11-17]. Fluoroscopy and, sometimes, CT are used to guide needle position and to document spread of radio contrast dye. In patients with chronic low back pain radiating to the leg (CLBP-r) CT-guided lumbar SNRBs with a low volume of 0.5 ml of contrast dye showed epidural spread in 50% and inadvertent spread to adjacent nerve roots in almost 25% of the cases [18]. Higher volumes resulted in higher incidences of epidural spread. Epidural spread outside the area of the segmental nerve root will result in a diminished selectivity of the block. Up to now epidural spread with SNRB has not been assessed for fluoroscopy, although at present most SNRBs are performed using this procedure. Furthermore, it is not known if there is any relationship between needle tip position in the intervertebral foramen and the occurrence of epidural spread.

This study was performed to assess: 1) the incidence of epidural spread in lumbosacral SNRBs using fluoroscopy and 2) to determine if there is a relationship between the needle tip position in the intervertebral foramen and occurrence of inadvertent spread of the injected agent. We applied the lowest volume (0.5 ml) that was used by Castro et al to enable comparison of results [18].

Patients and methods

Patients with chronic low back pain unilaterally radiating beyond the knee, planned for diagnostic lumbosacral SNRBs, were included in this prospective, observational study. Patients were recruited in accordance with the rules of the Declaration of Helsinki. The Hospital Ethics Committee approved the study and informed consent was obtained from each patient.

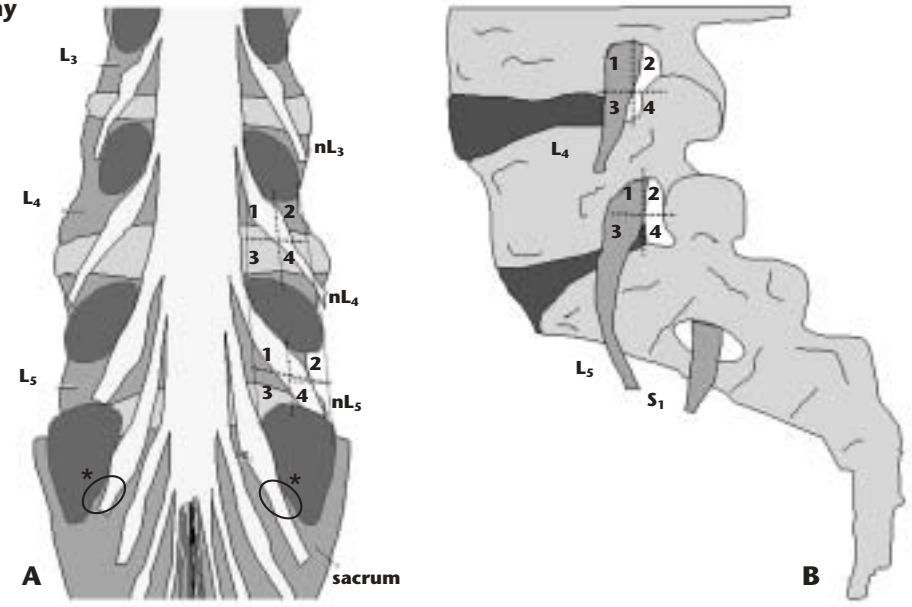
All patients were diagnosed as having a 'radicular syndrome without symptomatic neurological deficit' by a neurologist or neuro- or orthopaedic surgeon after extensive examination, including CT, MRI and EMG. Patients were scheduled for diagnostic SNRBs at L4, L5 and S1. All patients were over 18 years of age.

Exclusion criteria were: planned surgery, known hypersensitivity to amino-amide-type local anaesthetics or iodide, presence of blood coagulopathy, or mental disorders.

After arrival in the pain treatment room the patient was positioned prone with a pillow under the abdomen to decrease lordosis. The insertion site of the needle was marked by a pencil on the skin of the painful side. Following infiltration anaesthesia of the skin with 1 ml of lidocaine 1.5% subcutaneously, a 10 cm insulated electrode (23G, Top®, Sanofi Santé) with a 5 mm insulation-free tip was inserted under fluoroscopic guidance (Philips image intensifier BV25, Philips, Best, The Netherlands) into the dorsocranial quadrant of the L4

or L5 intervertebral foramen (lateral view) and advanced until the tip was positioned one-third to half way the pedicular column (AP view). For S1 the needle was advanced in anterior-posterior direction through the posterior foramen into the caudal spinal canal.

Figure 1 **Anatomy**



Schematic drawing of lumbosacral spine with nerve roots. **A**. AP view showing medio- (1), laterocranial (2), medio- (3) and laterocaudal (4) quadrants. *Posterior foramen S1. **B**. Lateral view with ventro- (1), dorsocranial (2), ventro- (3) and dorsocaudal (4) quadrants.

To confirm the position of the needle tip, an electrical current generated by a radiofrequency pulse and lesion generator system (RFG-3B, Radionics®, Burlington MA, USA) was applied, thereby stimulating the spinal nerve root or its dorsal ganglion (DRG). Paraesthesias were evoked by stimulating with a frequency of 50 Hz and muscular contractions were evoked by stimulating at 2 Hz. X-ray pictures were taken in anterior-posterior and lateral direction with the needle in position. Subsequently 0.5 ml of the study mixture was injected slowly (exclusive the volume of the needle and catheter). The study mixture was made by mixing Xylocaine 2%® (Astra Pain Control AB Södertälje Sweden) and Omnipaque 300® (Omnipaque Nycomed Ireland, LTD, Cork) in a ratio of 1:1, resulting in 5 mg lidocaine and 75 mg Iohexol in 0.5 ml. X-ray pictures in AP and lateral direction were taken again. Three anaesthesiologists experienced in invasive pain treatment performed the blocks. Two investigators blinded for the patients and experienced in the interpretation of these images assessed the radiographs independently (AW, GG). Disagreements in interpretation (3 cases) were resolved by discussion. Presence or absence of epidural spread and the position of the needle in the intervertebral foramen of L4-5 and L5-S1 were recorded for L4 and L5 blocks using the following criteria: contrast dye medial to the medial border of the pedicle and/or cranial to the caudal border of the upper pedicle [19], both in AP view. For S1 SNRB only assessment of spread to an adjacent nerve root block was done, since in S1 SNRB injection is always in the epidural space.

Needle tip position was assessed pre- and post block by dividing the intervertebral foramen in 4 quadrants in the AP view (i.e. medio- and laterocranial and medio- and

laterocaudal; Fig. 1A) and in 4 quadrants in the lateral view (i.e. ventro- and dorsocranial, ventro- and dorsocaudal; Fig. 1B). Needle tip position for S1 was assessed by dividing the caudal spinal canal in a ventral, an intermediate and a dorsal third (lateral view). Chi-squared testing was used to determine differences in the incidences of epidural spread (for L4 and L5) or spread to adjacent nerve root (S1) for different needle positions in medial vs lateral halves of the intervertebral foramen. Differences were considered significant for $p<0.05$.

Results

A total of 71 patients were enrolled into the study. Six cases (L4 n=1; L5 n=4; S1 n=1) were excluded because of poor quality of the images, leaving 65 cases for analysis (L4 n=17, L5 n=25, S1 n=23). Age, gender and radiological diagnoses are presented table 1. The mean sensory and motor electrostimulation thresholds were 0.62 V (range 0.10 – 1.40; sd 0.30) and 1.21 V (0.20 – 3.0; sd 0.66) respectively. In 3 more cases (L4 n=2, L5 n=1) needle tip position could not be determined because of inadequate X-ray direction, leaving 62 cases for that analysis.

Table 1 **Patient characteristics**

	All	%	L4	%	L5	%	S1	%
pts n / %	65	**100**	17	**26**	25	**38**	23	**35**
m/f	23/42		8/9		8/17		7/16	
Age (mean ± SD, range)	47 ± 13 (26-81)		48 ± 13 (26-72)		48 ± 12 (26-81)		45 ± 13 (16-72)	
radiological diagnosis								
herniated disc	22	**34**	6	**35**	8	**32**	8	**35**
bulging disc	3	**5**	0	**0**	1	**4**	2	**9**
disc degeneration	19	**29**	5	**29**	9	**36**	5	**22**
spinal stenosis	4	**6**	1	**6**	2	**8**	1	**4**
epidural fibrosis	4	**6**	2	**12**	2	**8**	0	**0**
facet arthrosis	5	**8**	1	**6**	2	**8**	2	**9**
nerve root compression	3	**5**	1	**6**	1	**4**	1	**4**
surgery	22	**34**	5	**29**	10	**40**	7	**30**

Epidural spread

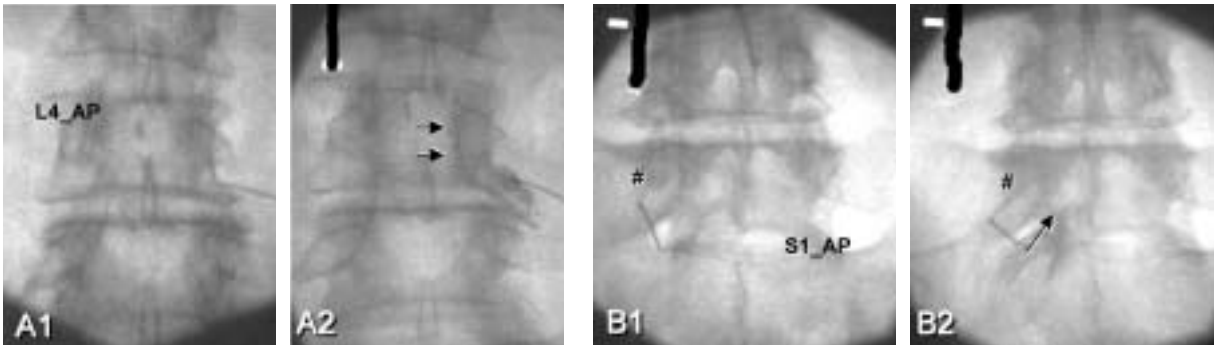
In none of the cases was the post block needle tip position changed compared to pre block. Epidural spread was found in 15 of the 42 lumbar cases (36%), 8 at L4 blocks (47%), 7 at L5 blocks (28%; table 2) and, as expected, in all S1 cases. For L4 epidural spread

was observed medial to the medial border of the pedicle as well as cranial to the caudal border of the upper pedicle in 5 cases (Fig. 2A), for L5 this occurred in 4 cases (table 2). Spread to adjacent ipsilateral nerve roots was found in 1 L5 block (to S1) and 2 S1 blocks (to S2; Fig. 2B).

Table 2 **Incidence of epidural spread with SNRB**

	L4	%	**L5**	%	**S1**	%
pts n, %	**17**	25	**25**	41	**23**	34
Epidural spread						
medial to medial border pedicle	**8**	47	**7**	28	-	-
cranial to caudal border upper pedicle	**5**	29	**4**	16	-	-
epidural spread	**8**	47	**7**	28	**23**	100
second nerve visible	**0**	0	**1**	4	**2**	9

Figure 2 **Fluoroscopy images before and after injection with SNRB**



AP view of SNRB prior to (left figures) and just after the blocks (right figures). **A** level L4, female, 52 yrs showing epidural spread medial to medial border of pedicle and cranial to caudal border of upper pedicle (arrows). **B** Level S1, female, 45 yrs showing spread to S2 nerve root (arrow). # needle

Needle tip position

Thirty-nine lumbar cases were evaluated for needle position. No differences were observed between L4-5 and L5-S1 levels. The majority of all needle tips were localized in the lateral part of the upper half of the intervertebral foramen (27; 69%) of which 15 (38%) were located dorsally and 12 (31%) ventrally. The remaining needle tips were found in the lateral caudal half of the foramen (n=6; 4 ventral, 2 dorsal) and in the medial cranial half of the foramen (n=5; 2 ventral, 3 dorsal). In 1 case the needle tip was located dorsally in the mediocaudal quadrant of the intervertebral foramen (table 3).

Table 3 **L4 and L5 SNRB needle position**

n=39		Lateral view (quadrant)			
		ventrocranial	dorsocranial	ventrocaudal	dorsocaudal
Anterior-posterior view (quadrant)	mediocranial	2 (2)	3 (1)		
	laterocranial	12 (4)	15 (6)		
	mediocaudal			0	1 **[1]**
	laterocaudal			4 (0)	2 (1)

n = blocks; (n) = blocks with epidural spread; **[n]** = blocks with epidural spread to adjacent nerve root

Table 4 **S1 SNRB needle position**

n=23	**Lateral view of caudal canal**		
Anterior-posterior view (quadrant)	ventral	intermediate	dorsal
mediocranial	2	3 **[1]**	-
laterocranial	1	11	-
mediocaudal	1	2 **[1]**	-
laterocaudal	-	3	-

n = blocks with epidural spread; **[n]** = blocks with epidural spread to adjacent nerve root

Epidural spread was found in 15 of those 39 lumbar cases evaluated for needle position (39%) (tables 3 and 4). For L4 and L5 SNRBs with needle position in the medial half of the intervertebral foramen epidural spread was present in 67% of cases (4/6) vs 33% (11/33) for the lateral half of the foramen (p=0.06, Chi-squared test). Also, the one case with epidural spread to an adjacent nerve root showed a medial needle position. There were no statistical differences with respect to epidural spread for lumbar cranial (13/32) vs caudal (2/7) and for ventral (6/18) vs dorsal (9/21) intraforaminal needle positions.

For S1 SNRBs, epidural spread to an adjacent nerve root occurred in 33% (2/6) cases with needle tip in the medial half of the foramen, with no cases of spread to an adjacent nerve root (0/15) with a lateral needle position (p=0.015, Chi-squared test). No statistical differences were found for cranial (1/17) vs caudal (1/6) needle positions, and for ventral (0/4) vs intermediate (2/19) needle tip positions.

Discussion

In the present study on lumbosacral SNRBs using fluoroscopy, we observed a high frequency (i.e., 38%) of inadvertent epidural spread, while extension to an adjacent nerve root occurred in only a few cases. Epidural spread is more frequent with medial intraforaminal needle positions and the cases with spread to an adjacent nerve root also showed medial needle tip positions.

For CT-guided lumbar SNRB, Castro et al [18] demonstrated that epidural spread is common in this region. They reported epidural spread in 50% and spread to adjacent nerve roots in 25% of cases with their lowest volume (0.5 ml). In our study, using the same volume of injection fluid - equal to the lowest volumes reported in relevant studies (table 5) - we found a much lower incidence of spread to an adjacent nerve root. An explanation for this discrepancy might be our use of electrostimulation to locate the segmental nerves, in contrast to Castro et al [18]. Furthermore, in our study the needle was aimed at the lateral half of the intervertebral foramen, which position was adjusted according to electrostimulation parameters. The mean sensory threshold for electrostimulation in our patients was 0.6 V, which could indicate a mean distance of 3 mm between tip and nerve root [18]. Castro et al reported an overall mean distance between the tip of the needle and the nerve root of 3 mm as well [18]. However, this is debatable, for the 8 mm slice thickness in CT they used implies a large partial volume effect, suggesting that their figures might be overestimated.

However, at the same time our results might also be underestimated due to technical flaws. Fluoroscopy has a lower resolution than CT, which might decrease sensitivity for detecting inadvertent spread to adjacent nerve roots and thus induce false-negative results. Furthermore, since the lumbosacral SNRBs were part of a diagnostic procedure, our mixture also contained lidocaine, in contrast to Castro et al [18] who used only contrast dye. Although they did not mention the concentration of the injected contrast fluid, our mixture may be less radiopaque. We mixed lidocaine in a high concentration (2%) with 300 mg Iohexol, resulting in 75 mg Iohexol per 0.5 ml. In a pilot study this dosage of Iohexol appeared sufficiently radiopaque to be able to identify epidural spread. Other methods that enhance quality of monitoring spread, such as are real-time fluoroscopy and digital subtraction of contrast dye before and after injection, might have improved the results for epidural spread. However, these aspects are beyond the framework of the present study.

Table 5 **Contrast dye and local anaesthetics used in relevant SNRB studies**

Authors	Year	Contrast dye	mg/ml	Volume (ml)	Local anesthetic	mg/ml	Volume (ml)
Schutz et al [1]	1973	Iophendylate	NM	1	Procaine	NM	1.0
Krempen and Smith [2]	1974	Iophendylate	NM	NM	Lidocaine	10	1.0
Krempen et al [20]	1975	Iophendylate	NM	NM	Lidocaine	10	1.0
Tajima et al [3]	1980	Iothalamate Meglumine	600	> 2	Lidocaine	10	3.0
Haueisen et al [4]	1985	NM	NM	1	Lidocaine	10	1.0
Quinn et al [21]	1988	Diatrizoates	600	1	Lidocaine	10	3.0
Dooley et al [5]	1988	Ethyl Iodoundecylate	NM	1	Lidocaine Mepivacaine	10	1.0
Herron LD [8]	1989	NM	NP	NP	Lidocaine Bupivacaine	5 - 10	1.0
Castro et al [18]	1994	Iothalamate	NM	0.5- 1- 2	NP	NP	NP
Hasue et al [19]	1989	Metrizamide	NM	2	Lidocaine	20	2.0
van Akkerveeken [22]	1993	NM	NM	< 1.0	Bupivacaine	5	0.2 - 0.5
Nitta et al [23]	1993	NM	NM	NM	Lidocaine	NM	1.5
North et al [12]	1996	NP	NP	NP	Bupivacaine	5	3.0
Porter et al [24]	1999	NP	NP	NP	Bupivacaine	5	1.5
Manchikanti et al [7]	2001	NM	NM	0.3-1.0	Lidocaine	20	0.3 - 1.0
Wolff et al [15]	2001	Iohexol	180	0,3	Iohexol + Lidocaine	45 + 10	0.75
Macadaeg et al [25]	2001	NM	NM	NM	Lidocaine	20	0,5 - 0,75
Wolff AP et al [16]	2004	Iohexol	180	0.3	Iohexol + Lidocaine or Ropivacaine	105 + 7 or 1.75	0.7
Huston et al [26]	2005	NM	NM	0.5-2	Lidocaine	20	2.0
Geurts et al [27]	2003	Iohexol	240	1.0	Lidocaine	20	0.5

NM = not mentioned; NP = Not Performed

Although the target area of the needle tip was the lateral half of the dorsocranial quadrant of the intervertebral foramen, i.e. the so-called safe triangle, the tip was found elsewhere in 61.5% of the cases. The safe triangle is cranially bounded by the caudal border of the upper pedicle, laterally by a line connecting the lateral borders of the upper and lower pedicle, and medially by the spinal nerve root. It is considered a safe entry zone for the needle to come nearest to the segmental nerve before starting electrostimulation. Redirection of the needle based upon electrostimulation criteria will lead to other needle positions than the initial ones, as shown in this study. These results are in keeping with reported variations

in localization of lumbar DRGs in relation to the intervertebral foramen [19], e.g., L5 DRG localization may vary from extraforaminal to intraforaminal to inside the spinal canal. Furthermore, alterations in the local anatomy, such as bulging discs, facet arthrosis and spinal or foraminal stenoses may contribute to nerve root and DRG displacement.

Our findings suggest that epidural spread is related to medial needle tip position. Indeed, in four of the six lumbar cases (66%) where the tip was medially located epidural spread occurred, compared to eleven of the 33 (33%) laterally positioned needle tips. Further, in all blocks with spread to an adjacent nerve root, the tip of the needle was observed medially. It would appear that placement of the tip of the needle in the medial half of the foramen (L4-5, L5-S1) increases the possibility of epidural spread and, thus, of false positive interpretations. Also, needle placement with the tip in the medial half of the dorsal sacral foramen (S1) increases the risk of spread to an adjacent nerve root. However, in view of the small numbers, further studies are indicated to confirm these results.

The high incidence of epidural spread with an intraforaminal lumbar block implies that the local anaesthetic contained in the injection fluid will block adjacent neural structures as well: sinuvertebral nerves conveying nociceptive information from the outer annulus fibrosus, the ventral dura and posterior longitudinal ligament, and nearby rami communicantes [29]. Since these structures, when inflammation is present, may mimic radicular syndromes [30] false-positive results may be induced.

Our study again emphasizes that many lumbar SNRBs are not selective [15-18], even if low volumes are injected. This stresses not only a need to reconsider their role in the diagnostic and presurgical selection process of CLBP-r patients, but the necessity of redefining the concept of SNRB. The recently suggested matching of provoked nerve root response (i.e., paraesthesias provoked by electrical stimulation) with spontaneous pain should get more attention [31]. Repeat electrostimulation directly after the SNRB, and performing the same double electrostimulation procedure before and after block at supra- and subjacent levels could further improve insight in the segmental pain pattern. Paraesthesias in corresponding dermatomes are reliably reproducible, as we have demonstrated in a previous study [15].

Conclusion

The high incidence of epidural spread after diagnostic lumbar SNRB found by fluoroscopy results in a decreased selectivity since adjacent spinal structures are also blocked, and warrants caution in SNRB interpretation. Inadvertent spread to adjacent nerve roots can occur in up to 9% of cases. Lumbar epidural spread and lumbosacral spread to an adjacent nerve root are greater with medial needle position in the intervertebral foramen.

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Chapter 7

GENERAL DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

General considerations

SNRBs are performed in patients with specific radicular pain to predict the outcome of surgical procedures. They are also applied in patients with chronic back pain radiating to the leg to identify the putative symptomatic spinal nerve if history, physical examination, imaging and electrophysiological examination are inconclusive [1,2]. These CLBP-r patients represent a large patient population and form a major part of the referral to pain clinics. Some would argue that such referrals are more or less useless, since SNRB as an additional diagnostic tool will not be able to identify nerve root involvement, as a patho-anatomical cause was not demonstrated in these patients. However, this overestimates the importance of the diagnostic imaging and electrophysiological techniques. Daily clinical practice shows otherwise, since there is no clear relationship between imaging results, electrophysiogical findings and patient complaints. Even in so-called specific radicular syndromes there is no absolute consensus on clinical signs and symptoms, critical MRI findings and the structure that is eventually causing the pain. Only the findings at surgery related to outcome are certain. For the above-mentioned group of CLBP-r patients, in which no underlying cause is or can generally be found, diagnostic insecurity is much higher. Nevertheless, even in this group of patients with generally negative nerve root MRI findings, the positive finding of an inflamed nerve root is often found at spinal endoscopy [3]. This suggests that at least part of our diagnostic procedures is still insufficient. For SNRBs the situation is worse: a specific patho-anatomical diagnosis upon which to base a gold standard can only be made (e.g. during surgery or spinal endoscopy) in a small part of the population. A gold standard against which to compare SNRB effects is thus lacking for the larger part of CLBP-r patients. Consequently, we have to rely upon consistency of the clinical-physiological effects that are induced by SNRB of segmental nerve root blocks. Surprisingly, data on this are limited [4]. Therefore, the main aim of this thesis was to determine if SNRB effects on pain reduction and on corresponding segmental sensory and motor function are consistent in CLBP-r patients.

Patient selection for SNRBs

All patients included in our studies were patients with intractable radiating pain who underwent evaluation according to a multidisciplinary model. After an extensive history, physical examination and evaluation of radiological imaging results, attempts were made to establish clinical diagnoses. An algorithm as proposed by Bogduk and McGuirk [5], and also described in evidence-based practice guidelines for interventional techniques in the management of chronic pain [2], was used in our patients.

To select patients with specific monoradicular pain for surgery, pain reduction of 100% with SNRB is used as a diagnostic criterion [6], although systematic volume-dose effect studies on the optimal volume and concentration of the local anesthetic needed for this effect are lacking. In SNRBs performed in CLBP-r patients, it is not known if pain is uniquely the result of changes in the targeted spinal nerve root. Most CLBP-r patients express pain that is multifactorially determined, consistent with its chronic nature. In these patients it has to be established to what degree the targeted spinal nerve root is part of the problem,

since it is known that radicular pain can be mimicked by referred pain originating from nociceptive (peri-)spinal structures such as facet joints, sacro-iliac joints, intervertebral disc and ventral dura [2,7-13]. Furthermore, any epidural spread to adjacent structures needs to be identified, implying that the local anaesthetic should be mixed with a highly radiopaque contrast dye, which is not always the case. Total selective pain relief as standard diagnostic criterion may therefore be a utopia. Partial pain relief might be a more realistic goal. At present, it is unknown which percentage of pain reduction should be used to reliably assess effects of SNRBs in CLBP-r patients. In our series we adopted a pain reduction of 30% or minimally 2 points on the Numeric Verbal Rating Scale [14,15] as acceptable for assessing nerve root involvement in radiating pain.

Because there is no functional gold standard to compare with and because placebo effect has to be minimized, we used controlled blocks [5,8,16] in studies on L4 SNRBs (chapters 4 and 5). Although we did not evaluate duration of effect, the variability in response to both local anaesthetics we found questions the usefulness of these controlled blocks, especially since they are only focussed upon block induced pain reduction. The use of placebo (i.e., saline injections) in SNRBs in patients suffering from intractable pain is considered unethical and was therefore not used in our studies. Another method to improve the diagnostic reliability is to perform always SNRBs at minimally 3 spinal levels on separate occasions. That is also what usually happened to our patients in their individual treatment sequence. However, this was not part of our study methods.

Complications

In none of our patients complications were reported, however, documentation of complications and adverse events was not a primary study goal. Complications can occur as with any other invasive action and may be related to needle placement or drug administration [2]. They include direct trauma to the nerve root, damage to neural vasculature resulting in haematoma with neural infarction [17] or intravascular injection. Potential major complications are death, paralysis, spinal nerve injury, infection or allergic reactions. Minor complications are exacerbation of pain, pain at the injection site, bleeding, dural puncture, headache and vasovagal responses. Houten and Enrico [18] reported 3 cases of paraplegia after lumbosacral (2 L3, 1 S1) steroid injection, which was attributed to vascular damage and subsequent embolisation of steroid emulsions. In a prospective non-randomized controlled trial Huston and Slipman [19] recorded complications and side effects immediately after SNRB, and after 1 week and 3 months. A total of 151 patients underwent 306 SNRBs, and 60 patients who had not undergone any intervention served as control group for the 1-week evaluation. The authors reported no major complications with lumbosacral SNRBs. Immediate effects described as side effects were reported by 39,4% of the patients (pain at injection site, 17,1%; exacerbation of pain, 8,8%; light-headedness, 6,6%; increased spinal pain, 5,1%; nausea, 3,7%; non-specific headache, 1,4%; vomiting, 0,5%). Surprisingly, after one week no differences were observed in incidence of "side effects" between the two groups (9%), except for pain at the injection site, which was more frequent in the active group. Only one patient suffered from non-specific complaints after 3 months. This suggests that only pain at the

injection site can be considered as a temporary side effect. Risk of complications can be minimized by performing the procedure in patients who are awake, by using imaging techniques such as fluoroscopy, by aspirating through the needle before injection, and by dynamic imaging of the contrast dye injection that precedes the definite injection.

Main thesis questions and conclusions

In this paragraph the main questions in this thesis as presented in the general introduction will be discussed.

What is the present basis for the application of SNRBs in CLBP-r patients?

SNRBs are applied in patients that complain of radiating pain to the leg with a dermatomal distribution. If a patho-anatomic cause is identified, but signs of neurological deficit and positive spine nerve tension tests are absent, these patients are described as having radicular pain (chapter 2). If such signs are present, the patients are considered to have a *radiculopathy*. In these patients, a high sensitivity, specificity and predictability are attributed to SNRBs if they are used to predict outcome of surgery, although most studies are retrospective [6,20-24]. In many of CLBP-r patients, however, a clear patho-anatomic substrate cannot be demonstrated with the **presently** available diagnostic tools. Nevertheless, patients may experience pain that follows a segmental or a segment-like pattern, which pain is best described as *segmental pain*. Presently, data are lacking whether the segmental nerve root actually generates the pain, but even if this is not the case, we cannot come to a decisive conclusion, since the resolution of our current diagnostic tools is insufficient. We cannot at present fully verify if a root is irritated, and thus we cannot suggest effective therapy for CLBP-r patients in the absence of a clear view of the patho-anatomic background or degree of neuroplastic changes. The only basis on which SNRBs might at present be rationally applied is that a reasonable alternative diagnostic tool is not available. Therefore, it seems logical to suggest that the role of SNRBs in CLBP-r patients and the conceptual framework of "segmental pain" both need to be reconsidered. More sophisticated diagnostic tools clearly need to be developed to better establish diagnosis in CLBP-r patients.

Are SNRB effects expressed in a dermatome-related fashion?

A segmental nerve root block is supposed to act on the segmental nerve and should, therefore, display segmental effects. In our series with lumbosacral SNRBs (chapter 3), we found that concomitant occurrence of pain, pain reduction, paraesthesias elicited by electrostimulation and hypoaesthetic areas was hardly consistent, particularly when related to the dermatome of the treated segmental nerve root. Furthermore, size and location of post block hypoaesthetic areas showed a large variability. In contrast, elicited paraesthesias showed consistent segmental patterns. In 98% of the time they occurred in corresponding extended dermatomes and in 80% in classic dermatomes. The use of dermatomal maps representing overlap by neighbouring dermatomes may improve understanding of dermatomal representation of pain, paraesthesias, hypoaesthesia and pain.

Do SNRBs exert consistent effects on sensory function?

In this study (chapter 4) we tested the consistency of segmental sensory effects of lumbar SNRBs at one lumbar spinal nerve (L4) with a short acting (lidocaine) and long acting (ropivacaine) local anaesthetic. We found no clear differences in effects between lidocaine and ropivacaine. Since in an earlier study we had observed post block sensory effects without knowing if pre-block sensory signs were already present in these patients, the net effect of SNRBs was assessed by comparing pre – and post block sensory measurements. We found that areas with hypoaesthesia were already present *before* SNRB in the majority of the studied CLBP-r patients in a non-dermatomal, mainly distal, distribution. Their size tended to be larger if duration of pain was longer. Furthermore, SNRBs did not markedly affect pre-existing alterations of sensory processing. Thus, SNRBs do not exert consistent net sensory effects. Until now, we presumed that the block was technically successful if SNRB caused hypoaesthesia in the corresponding dermatome. Absence of hypoaesthesia nevertheless does not mean that the block is not successful because neighbouring dermatomes overlap each other by half[25]. Furthermore, pre-existent neuroplasticity may affect sensory function resulting in non-dermatomal areas of hypoaesthesia before and after block. Therefore, to evaluate sensory effects caused by SNRBs, it is mandatory that sensory function be assessed before and *after* block with the following aims in mind: to establish the presence of neuropathic sensory changes, to establish if neuroplastic changes have occurred and to determine if the SNRB induced hypoaesthesia is concordant with the corresponding dermatome.

Do SNRBs exert consistent effects on motor function?

SNRBs at L4 variably induced a decrease or increase in maximal voluntary muscle force in the corresponding myotomes amongst the studied CLBP-r patients (chapter 5). A non-specific pain reduction with block in the affected limb leads to an increase in muscle force. SNRB induced motor function alterations do not play a role in monitoring the technical SNRB quality and in establishing the putative spinal segmental level in CLBP-r patients for pain diagnosis. Assessing motor function quantitatively is a complex matter. It needs standardized circumstances to obtain reliable results. Testing motor function is therefore not suitable for monitoring quality and effect of the block in daily practice. Measuring corresponding myotome related muscle force with SNRB has for the time being no diagnostic consequences for individuals with chronic radiating low back pain[26] and is therefore not advocated in individual assessment.

Is there any role for SNRBs as a diagnostic tool in CLBP-r patients?

Fluoroscopically monitored inadvertent epidural spread is commonly found in lumbosacral SNRBs, whereas extension to an adjacent nerve root is not, although in this study (chapter 6) the occurrence of spread to adjacent nerve roots may have been underestimated. In lumbar nerve root blocks epidural spread was observed relatively more frequent when the tip of the needle was positioned more medially in the intervertebral foramen. This epidural spread affects selectivity of the nerve root block[27,28]. This conclusion is in keeping with the results of recently published systematic reviews on the diagnostic utility of selective

nerve root blocks[1,2]. Limited evidence was found for the effectiveness of a selective nerve root injection as a diagnostic tool in spinal disorders in the absence of disc herniation and negative provocative discography. However, these reports were based upon studies that used SNRBs as a standard selection tool without systematic measurements of the effects of local anaesthetics on sensory and motor function.

Our results indicate that evaluation and technique of SNRBs should be altered to make them a useful diagnostic instrument. In the absence of consistent effects and a gold standard to compare with, we found support for the idea that matching elicited paraesthesias with the patients' segmental pain patterns (chapter 3) may contribute to the development of a diagnostic gold standard for SNRBs[29]. Haynsworth[30] suggested an algorithm, using both electrostimulation and conduction anaesthesia of the spinal segmental nerve root, in which matched elicited paraesthesias and pain should disappear after nerve root block. This procedure can be repeated systematically for various spinal levels within one session. In the future, more sophisticated diagnostic methods, as spinal endoscopy and high resolution MRI (> 2.0 Tesla compared to the 1.5 Tesla for standard MRI) may provide the ability to detect nerve root processes that have remained concealed until now.

In view of potential, albeit usually minor, complications with SNRB[19] - which always should be taken into account with every invasive procedure - we have to counterbalance the pros and cons. Despite a lack of knowledge about the basic effects of SNRBs, or perhaps just because of this lack of knowledge, we feel that the potential of SNRBs has not been fully explored and needs further elucidation. Moreover, the low positive predictive value of imaging studies[12] and low diagnostic contribution of neurological examination in the chronic radiating low back pain problem[31] make additional interventional diagnostic techniques necessary. SNRB technique should be adapted to improve segmental selectivity. It justified that we put all our efforts into improving the diagnostic quality and effectiveness of lumbosacral SNRBs in CLBP-r patients, because there is no better alternative for the time being.

With respect to needle point positioning in SNRB, the electrode tip can be positioned extra- or intraforaminally. Clearly, intraforaminal tip position has the disadvantage that epidural spread may occur resulting in decreased block selectivity. Injection of a local anaesthetic with extra- or paraforaminal needle position[32] may lead to anaesthesia of the mixed spinal nerve that may impair motor function, affecting patients' ability to provoke their pain. There are no studies available that describe motor dysfunction after extraforaminal block. However, we demonstrated that motor function might increase or decrease after intraforaminal block in a variable manner (chapter 5). A study comparing motor function with intra- and extraforaminal SNRB should be conducted to elucidate this subject.

Future work and recommendations

Spinal endoscopy

Various findings and developments, such as identification of involvement of DRG neurons in radiating pain by spontaneous repetitive firing[33], diagnostic transforaminal segmental nerve root blocks[34], interventional treatment of the DRG[35], identification of nerve

root irritation by autologous nucleus pulposus [36], and (transforaminal) epidural injection of steroid agents [37,38] have contributed to the present concept of segmental radiating pain in patients without radiologically confirmed diagnosis. Segmental pain, having no clear underlying patho-anatomic diagnosis, is thus at present part of a conceptual framework that has to be reconsidered. Inflammatory processes of the nerve root and DRG [39] may induce radiating pain. Inflammation may involve surrounding tissues via inflammatory exudates [40]. This may be a further reason why segmental processes exceed dermatome territories. In case of inflammation, local anaesthetics may not be effective due to altered tissue acidity and should be combined with steroid agents. Evidence is growing that steroid injections are effective in patients suffering from radicular pain due to nerve root irritation [41]. Studies on establishing a diagnosis related to a spinal segmental level may therefore in future include agents that are active on inflammatory processes. With the available diagnostic tools it is not easy to detect neuroinflammation, but spinal endoscopy is a promising modality that provides an opportunity to observe fibrotic adhesions and inflammatory changes in the epidural space involving structures such as spinal nerves, dura and fibrotic adhaesions [3,42-46]. Spinal endoscopy enables us to visualize all this in a fashion that cannot be done yet or achieved by CT or MRI. A direct view of pathological processes in the epidural space with an opportunity to further diagnose local processes by taking biopsies and analysing biochemical inflammation markers may help us to better understand underlying mechanisms. Moreover, a more targeted application of anti-inflammatory agents is possible in this context [3]. Recent developments in imaging techniques will increase diagnostic resolution enormously, with high-field MRI (7.0 Tesla) having the potential to eventually monitor in vivo processes in humans with a high spatial resolution [47].

Neuroplasticity

Findings indicating the presence of (chronic) pain induced neuroplastic changes emphasize that pain is associated with a nervous system subjected to complicated dynamic processes [48-52]. A concomitant result of a systematic observation of SNRB effects on sensory-, motor function and pain in CLBP-r patients is that the changes observed also provide insight not only in the mechanism of SNRBs, but also into pain related neuroplastic processes. In our series we used pin prick to assess sensory function, because it is easy and fast for mapping areas with changed sensory function. It is commonly used and reliable enough to test hypoaesthesia after nerve blocks [53]. However, the use of Quantitative Sensory Testing (QST) techniques will offer greater opportunities for sophisticated assessment [54,55] and will enable the identification of more subtle changes in sensory pain processing. The assessment by QST of sensory changes induced by SNRBs in healthy volunteers, and the systematic evaluation of pain and neuroplastic processes in the acute, subacute and chronic phase of patients via long term follow up, will most probably lead to a better understanding of (chronic radiating) pain and underlying mechanisms.

Anesthesiology and pain treatment: a diagnostic challenge?

Anesthesiology and pain treatment are strongly related to each other on historical grounds. Attractive medical aspects of both disciplines offer great opportunities to raise

insights in pain. Until recently, pain treatment was strongly directed to symptom related pain reduction and less related to the establishment of a diagnosis. Symptomatic treatments such as intravascular drug injection, direct modulation of the peripheral or central nervous system with or without indwelling catheters, and the application of potent drugs have been widely applied. However, pain treatment as a medical field has now entered a challenging pathway to mechanism-based therapy [50]. The growing knowledge in molecular biological, physiological and neuro-psycho-social aspects, the development of diagnostic computerized tools, such as new generation functional MRI, echoscopes, endoscopes, QST, and (infrared) thermography, will all together finally change our insight in the mechanisms of pain. This will fundamentally alter the pain clinicians' view of diagnosis and therapy. It should further be emphasized that, because of its complexity, the solution of the puzzle of pain will only be achieved via interdisciplinary co-operation.

For this, extended networks of (para-)medics, scientists, government, industry and investors, and the use of sophisticated ICT platforms are necessary. This should guarantee a more efficient development process. The pain clinician has the potential to play a central role in this multifactorial approach, if he has a complete overview and has the ability to integrate all relevant developments on pain. Traditional frameworks in health care and medical science need to be surpassed to further improve diagnosis and achieve effective treatment to alleviate the individual and societal burden of chronic pain. A giant challenge is waiting to be resolved. It is an opportunity that should bring more light to the darkness of pain.

Final conclusions

There is a large variability in the changes of sensory and motor function induced by SNRB. Multiple factors, such as multisegmental innervation of spinal structures, overlap of neighbouring dermatomes, chronic pain induced neuroplasticity and epidural spread result in limited reliability of the blocks with respect to consistency and interpretation of effects. Of the described concomitant effects after SNRB only paraesthesias induced by electrical nerve stimulation show a consistent pattern, potentially making these suitable for improving pain diagnosis and monitoring the technical quality of SNRBs. The findings of this thesis do not support that SNRB, as presently used, is an adequate diagnostic tool to relate radiating pain in the leg in chronic low back pain patients to a specific spinal segmental level. Future work should focus on distinguishing segmental pain from non-segmental (referred) pain by matching paraesthesias not only to pain at the stimulated level, but also with pain reduction induced by the nerve root block. Furthermore, the relationship between paraesthesias in irritated vs non-irritated nerve roots needs to be established. Selectivity of the nerve root block should be improved to reduce false interpretations of block outcome. Increasing the resolution of modern imaging techniques (e.g., MRI, spinal endoscopy) may help to develop a gold standard for SNRB in CLBP-r patients. Finally, better insight into development, duration and the dynamics of neuroplastic changes is mandatory, especially in CLBP-r patients.

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Chapter 8

SUMMARY

Summary

Chapter 1

A general introduction is given on the goal of this thesis with its main questions and on the conducted studies. In patients with (chronic) low back pain radiating to the leg (CLBP-r) diagnostic segmental nerve root blocks (SNRBs) are performed to predict the outcome of surgical procedures and to identify the putative symptomatic spinal nerve. Chronic back pain patients often lack a specific diagnosis and form a large population. Questions rose with respect to the selectivity, sensitivity, specificity, and predictability of the blocks in CLBP-r patients and thus with respect to their diagnostic value. Because there is in CLBP-r patients no anatomical and functional gold standard to compare SNRB diagnosis with, SNRBs should at least be a clinical entity with consistent clinical physiological effects.

The goal of this thesis is to study if SNRBs in CLBP-r patients without overt focal neurological deficits generate consistent effects on sensory and motor function to be considered as a reliable diagnostic tool in CLBP-r patients.

To map these effects, studies are performed on the variability and consistency of:

- location and extend of paraesthesias elicited by electrostimulation at the segmental nerve root;
- location and extend of changes in sensory function;
- changes in motor function;
- epidural spread with SNRBs monitored with fluoroscopy, which is the most commonly used imaging technique to guide SNRBs.

Chapter 2

In this chapter we discuss the diagnostic value of SNRBs in CLBP-r patients and the most important problems related to pain diagnosis according the relevant literature. Many uncertainties with respect to anatomical, neurophysiological and pathophysiological aspects complicate the attempts to establish an equivocal diagnosis in these patients. Doubt seems to be justified to question the existence of "segmental pain", i.e., radiating pain following a dermatomal pattern while no specific patho-anatomic diagnosis can be established. Nevertheless, inflammatory and immuno-pathologic processes may cause radiating pain that can hardly be observed by presently available imaging techniques as CT and MRI. "Segmental pain" as conceptual framework should be reconsidered and the role of SNRBs still has to be established within that framework.

Chapter 3

We describe an observational prospective double blind study on the variability and interpretation of SNRB effects on the sensory function. Pinprick is used to assess dermatome related hypoaesthesia that developed after lumbosacral SNRBs in CLBP-r patients without neurological deficits. Sites with maximum experienced pain, pre block elicited paraesthesias, and local anaesthetic induced hypoaesthesia with lumbosacral SNRB are

documented according to a map with standard dermatomes and a newly developed map representing dermal overlap of segmental innervation.

After SNRB, a large variability in size and location of hypoaesthetic areas is found that is much more variable than considered up to now. Elicited paraesthesias are more consistently reproduced if related to the dermatome corresponding to the treated spinal segmental level. The spread of hypoaesthesia seems to be in keeping with the overlapping innervation pattern of dermatomes and re-emphasizes the fact that dermatomes are more extensive than depicted in standard dermatomal maps. The understanding of the variability of concomitant clinical physiological effects with SNRB as hypoaesthesia, elicited paraesthesias and pain reduction in relation to the presumed dermatome, is improved when the overlap of neighboring dermatomes is taken into account. This is an important aspect with respect to assessment of SNRB quality. Only electrical elicited paraesthesias are, if related to the corresponding dermatome, consistently reproducible.

Chapter 4

In this chapter, we present a case series of CLBP-r patients without overt focal neural deficits undergoing L4 SNRBs in a prospective randomised controlled cross over fashion with lidocaine and ropivacaine in equipotent doses. This study was conducted to assess changes in pre- and post block extend and location of hypoaesthesia.

Pre block hypoaesthesia is present in 70% of the cases but the patterns are not clearly dermatome-like. SNRBs do not have significant effects on sensory function within prior existing alterations of sensory processing. Relating duration of complaints to extend of hypoaesthetic skin areas suggest a tendency indicating that the presence and extend of pre block sensory changes in CLBP-r patients are positively related to the duration of pre-existing pain. No differences are found for SNRB effects on pain and changes in hypoaesthesia area between ropivacaine and lidocaine.

The findings in this study are suggestive for the presence of pre block sensory function changes that are related to duration of pain. A co-founding that dorsal root ganglion electrostimulation thresholds are lower when the number of painful dermatomes is higher, supports the idea that neuroplasticity is present. The presence of these pain induced pre block sensory changes influence the SNRB effects on the sensory function and complicate the assessment and interpretation of SNB effects. This limits the clinical value of SNRBs in CLBP-r patients without overt focal neurological deficit, who represent a major population of chronic pain patients. If sensory function is evaluated with SNRB, net effects have to be assessed.

Chapter 5

Here we present a prospective randomised controlled cross over study conducted to examine L4 SNRB effects in CLBP-r patients on pain and muscle force comparing lidocaine and ropivacaine. We related pain reduction and changes in maximum voluntary myotomal muscle force to each other to assess the role of pain and SNBs with respect to motor function.

Although SNRBs do cause variably muscle force increases and decreases in the individual patients, the group maximum voluntary muscle force decreases in the painful limb. However, patients who experience pain reduction, also if maximum pain was not in dermatome L4, show a statistically significant pain reduction related increase of the maximal voluntary muscle force. No differences are found for SNRB effects on pain and maximal voluntary muscle forces between ropivacaine and lidocaine.

This study demonstrates that in CLBP-r patients, non-specific pain reduction induced by local anaesthetic SNRB is associated with increased muscle force in musculature mainly innervated by the treated corresponding spinal nerve. This finding is unexpected because one would anticipate SNRB to decrease muscle force, which actually happens for the whole patient group at the affected side. Pain reduction with SNRB, accompanied by muscle force increase, happens independently of the presence of maximum pain in the corresponding dermatome L4 and is therefore non-specific. This muscle force increase with block impresses as dis-inhibition of pain induced muscle force loss. Supraspinal mechanisms such as Diffuse Noxious Inhibitory Control (DNIC) are suggested.

Chapter 6

In this chapter we present a study concerning inadvertent epidural spread with SNRB that may lead to decreased selectivity of the block and false positive outcome influencing the clinical decision making. Systematic analysis of fluoroscopy guided epidural spread of local anaesthetics mixed with contrast dye, of the position of the needle point in the intervertebral foramen and assessment of the mutual relationship was not done so far.

In this prospective observational study, X-ray pictures with needle tip and contrast, made before and after lumbosacral SNRBs with 0.5 ml of a radiopaque mixture, were analyzed by 2 investigators blinded for the patients' background for epidural spread (L4, L5) or spread to adjacent nerve roots (L4-S1).

Epidural spread occurs in 47% of the L4 and in 28% of the L5 blocks and inadvertent spread to an adjacent nerve root is detected only in 3 blocks (L5 n=1, S1 n=2). For lumbar SNRBs the needle is most frequently found in the lateral part of the upper half of the intervertebral foramen, but the rate of lumbar epidural spread is related to medial position of the needle in the intervertebral foramen. In the cases with epidural spread to an adjacent nerve root, medial needle position is found also. Thus, epidural spread decreases selectivity and necessitates caution regarding the role of SNRBs in clinical decision-making.

Chapter 7

In chapter 7 the thesis findings are discussed. There is a large variability in the changes of sensory and motor function induced by SNRB. Multiple factors, such as multisegmental innervation of spinal structures, overlap of neighbouring dermatomes, chronic pain induced neuroplasticity and epidural spread result in limited reliability of the blocks with respect to consistency and interpretation of effects. Of the described concomitant effects after SNRB only paraesthesias induced by electrical nerve stimulation show a consistent pattern, potentially making these suitable for improving pain diagnosis and monitoring the

technical quality of SNRBs. The findings of this thesis do not support that SNRB, as presently used, is an adequate diagnostic tool to relate radiating pain in the leg in chronic low back pain patients to a specific spinal segmental level. Future work should focus on distinguishing segmental pain from non-segmental (referred) pain by matching paraesthesias not only to pain at the stimulated level, but also with pain reduction induced by the nerve root block. Furthermore, the relationship between paraesthesias in irritated vs non-irritated nerve roots needs to be established. Selectivity of the nerve root block should be improved to reduce false interpretations of block outcome. Increasing the resolution of modern imaging techniques (e.g., MRI, spinal endoscopy) may help to develop a gold standard for SNRB in CLBP-r patients. Finally, better insight into development, duration and the dynamics of neuroplastic changes is mandatory, especially in CLBP-r patients.

Chapter 9

SAMENVATTING

Samenvatting

Hoofdstuk 1

Hierin wordt een algemene introductie gegeven over het doel van dit proefschrift, over de belangrijkste onderzoeksvragen en de uitgevoerde studies. Diagnostische segmentale zenuwwortelblokkaden worden uitgevoerd bij patiënten met (chronische) lage rugklachten met uitstraling naar het been om de uitkomst te voorspellen van een operatieve ingreep waarbij een ruggenmergszenuw ontlast wordt of om de vermoedelijke symptomatische segmentale ruggenmergszenuw te identificeren. Bij patiënten met chronische uitstralende lage rugklachten kan vaak geen specifieke diagnose worden gesteld en deze patiëntengroep vormt een grote populatie. Begrippen als selectiviteit, sensitiviteit, specificiteit en voorspelbaarheid van segmentale zenuwwortelblokkaden bij deze patiënten roepen veel vragen op. De vraag is nu wat de diagnostische waarde is van deze zenuwblokkaden bij dit type patiënten. Omdat er bij patiënten met chronische uitstralende lage rugklachten geen anatomische en functionele goudstandaard voorhanden is, waarmee het resultaat van een segmentale zenuwwortelblokkade vergeleken kan worden, zou deze zenuwblokkade op zijn minst moeten leiden tot consistente klinisch-fysiologische effecten.

Het doel van dit proefschrift is om vast te stellen of segmentale zenuwwortelblokkaden bij patiënten met chronische uitstralende lage rugklachten stelselmatig effecten hebben op gevoel en spierkracht, zodat ze als een betrouwbaar diagnostisch instrument beschouwd kunnen worden.

We voerden een aantal studies uit om te kijken naar de variabiliteit en consistentie van de volgende effecten:

- lokatie en uitbreiding van paresthesieën ("gevoelsprikkels"), welke opgewekt werden door middel van elektrische stimulatie van een ruggenmergszenuwwortel;
- lokatie en uitbreiding van veranderingen van de gevoelsfunctie;
- veranderingen van de spierfunctie;
- verspreiding van de injectievloeistof binnen de epidurale ruimte (de ruimte binnen de wervelkolom welke het harde ruggenmergvlies omgeeft en tevens de ruimte, die de ruggenmergszenuwwortels passeren op weg naar buiten).

Hoofdstuk 2

De diagnostische waarde van segmentale zenuwwortelblokkaden bij patiënten met chronische lage rugklachten uitstralend naar het been en de belangrijkste problemen die zich voordoen bij het stellen van de diagnose worden besproken aan de hand van de meest relevante literatuur.

Er zijn veel onzekerheden met betrekking tot anatomische, neurofysiologische en pathoanatomische aspecten waarmee we rekening moeten houden bij patiënten met chronische lage rugpijn met uitstraling naar het been. Daardoor kan het moeilijk zijn om een eenduidige diagnose te stellen. Op basis van de huidige inzichten lijkt er gerede grond te zijn om te twijfelen aan het bestaan van "segmentale pijn", ofwel pijn die uitstraalt volgens het patroon van een dermatoom (huidgebied dat door één ruggenmergszenuw geïnnerveerd

wordt) zonder dat er een specifieke pathoanatomische oorzaak kan worden vastgesteld. Desondanks kunnen er verklarende oorzakelijke factoren aanwezig zijn voor rugklachten met uitstralende pijn, welke nauwelijks kunnen worden vastgesteld met de op dit moment ter beschikking staande beeldvormende technieken als CT en MRI. "Segmentale pijn" als conceptueel denkraam zou herzien moeten worden en de werkelijke rol van de segmentale zenuwwortelblokkade moet binnen dat kader nog steeds worden vastgesteld.

Hoofdstuk 3

In dit hoofdstuk beschrijven we in een observationele, prospectieve, dubbelblinde studie de variabiliteit en interpretatie van de effecten op de gevoelsfunctie, die veroorzaakt worden door segmentale zenuwwortelblokkaden. Dit onderzoek werd gedaan bij patiënten met chronische lage rugklachten met uitstraling naar het been zonder neurologische uitvalsverschijnselen.

Pinprick wordt gebruikt om dermatoom-gerelateerde gevoelsverminderingen vast te leggen na lumbale en sacrale segmentale zenuwwortelblokkaden met een lokaal anestheticum. De huidgebieden waar de meest ernstige pijn, paresthesieën en gevoelsvermindering voor pinprick worden ervaren, worden in kaart gebracht. Hiervoor wordt een kaart gebruikt met standaarddermatomen en een kaart waarop dermatomen worden weergegeven waarbij rekening is gehouden met overlap van dermatomen.

Er wordt een grote variabiliteit gevonden in de grootte en lokatie van huidgebieden met gevoelsvermindering. Deze variabiliteit is groter dan tot nu toe werd aangenomen. Paresthesieën worden wel consistent ervaren in het dermatoom (zowel standaard als aangepast), dat correspondeert met het niveau waarop de segmentale zenuw is gestimuleerd. De verspreiding van de gevoelsvermindering lijkt samen te hangen met het patroon van dermatoomoverlap en benadrukt het gegeven dat dermatomen veel uitgebreider zijn dan voorgesteld in de gemiddelde praktijk. De variabiliteit van de na de wortelblokkade optredende klinisch-fysiologische effecten (gevoelsvermindering, paresthesieën en pijnreductie in het dermatoom waarin de meeste pijn zit), lijkt beter begrepen te worden als we rekening houden met de overlap met naburige dermatomen. Dit aspect is van groot belang voor de interpretatie van segmentale zenuwwortelblokkaden. Alleen de door electrische stimulering van de segmentale ruggenmergszenuwwortel opgewekte paresthesieën, zijn in het bijbehorende dermatoom goed reproduceeerbaar.

Hoofdstuk 4

In dit hoofdstuk presenteren we een reeks patiënten met chronische lage rugpijn met uitstraling in het been zonder tekenen van neurologische uitval, waarbij in alle gevallen segmentale zenuwwortelblokkaden werden uitgevoerd op hetzelfde niveau (L4). In deze prospectieve, gerandomiseerde, gecontroleerde cross-over studie werden lidocaine en ropivacaine in equipotente doseringen met elkaar vergeleken. Doel was het huidgevoel voor pinprick vóór en ná het uitvoeren van de segmentale zenuwwortelbehandeling met elkaar te vergelijken.

In 70% van de gevallen blijkt dat er vóór het aanbrengen van de wortelblokkade reeds gebieden met gevoelsvermindering aanwezig is, echter zonder een duidelijk dermatomaal patroon. Segmentale zenuwwortelblokkaden hebben géén significante effecten op de reeds bestaande gevoelsveranderingen voor pinprick. Er is een trend gevonden dat, naarmate de pijn langer aanwezig is, de reeds bestaande gevoelsvermindering groter is en meer aan de uiteinden van het been is gelokaliseerd. Tussen lidocaine en ropivacaine worden geen verschillen gevonden als het gaat om effecten van de segmentale zenuwwortelblokkaden op pijn en gevoel.

De bevindingen van deze studie suggereren dat de aanwezigheid van de veranderingen van de gevoelsfunctie vóór de wortelblokkade samenhangen met de bestaansduur van de pijn. Een bijkomende bevinding dat de paresthesie-drempels voor electrostimulatie van de segmentale zenuwwortel of van het dorsale zenuwwortel ganglion lager zijn wanneer het aantal dermatomen met pijn groter is, ondersteunt het idee dat deze verschijnselen toegeschreven kunnen worden aan neuroplastische veranderingen bij deze patiënten. De aanwezigheid van pijn geïnduceerde pre-blok gevoelsveranderingen beïnvloedt de interpretatie van de effecten van de segmentale zenuwwortelblokkade op het gevoel. Het beperkt de klinische waarde van de segmentale zenuwwortelblokkaden bij patiënten met chronische lage rugpijn met uitstraling in het been. Verder moet, als de gevoelsfunctie wordt geëvalueerd bij zenuwwortelblokkaden, altijd het netto effect (d.w.z. het verschil tussen de metingen voor en na het blok) onderzocht worden.

Hoofdstuk 5

In dit hoofdstuk beschrijven we in een prospectieve, gerandomiseerde, gecontroleerde cross-over studie de effecten van segmentale zenuwwortelblokkaden op niveau L4, uitgevoerd met lidocaine en ropivacaine, op pijn en spierkracht bij patiënten met chronische lage rugpijn met uitstraling in het been. Om de rol van pijn en segmentale zenuwwortelblokkaden te evalueren voor de spierkracht, werden pijnvermindering en veranderingen in de vrijwillig maximaal opgewekte spierkracht binnen het overeenkomende myotoom aan elkaar gerelateerd.

Ondanks dat segmentale zenuwwortelblokkaden een grote variabiliteit veroorzaken in toename en afname van spierkracht bij de individuele patiënten, daalt de vrijwillig maximaal opgewekte spierkracht gemiddeld voor de gehele patiëntengroep in het bijbehorende myotoom in het been met de pijn. Echter, patiënten die pijnvermindering ervaren na het blok, ook als de maximale pijn niet in dermatoom L4 zat, tonen een statistisch significante stijging in de vrijwillig maximaal opgewekte spierkracht, welke samenhangt met hun pijnvermindering. Kort gezegd: pijnvermindering na een L4 blok leidt tot toename van spierkracht in het bijbehorend myotoom, terwijl de maximale pijn niet in dermatoom L4 zelf hoeft te zitten. Er worden geen verschillen gevonden tussen lidocaine en ropivacaine voor wat betreft de effecten van het blok op pijn en spierkracht.

Deze studie laat zien dat niet-specifieke pijnvermindering, door patiënten ervaren na segmentale zenuwwortelblokkaden met een lokaal anestheticum, leidt tot een toename in de spierkracht in spieren, die voornamelijk worden geïnnerveerd door de geblokkeerde zenuw.

Deze bevinding is verrassend, omdat men zou verwachten dat een zenuwblokkade leidt tot spierkrachtverlies, wat gemiddeld ook gebeurt voor de hele patiëntengroep in het been met pijn. Deze niet-specifieke toename van spierkracht na wortelblokkade kan worden geïnterpreteerd als opheffing van verlies van spierkracht, dat tevoren werd veroorzaakt door de aanwezigheid van pijn. Het is denkbaar dat supraspinale mechanismen als "Diffuse Noxious Inhibitory Control", ofwel DNIC, hierin een rol spelen.

Hoofdstuk 6

In dit hoofdstuk presenteren we een studie naar het vóórkomen van onbedoelde epidurale verspreiding van de injectievloeistof bij segmentale zenuwwortelblokkaden. Epidurale verspreiding kan de selectiviteit van de wortelblokkade verlagen en tot fout-positieve uitkomsten leiden, hetgeen de klinische besluitvorming beïnvloedt. Een systematische analyse van epidurale verspreiding van lokaal anestheticum met röntgencontrastvloeistof, vastgelegd met behulp van röntgendoorlichting, waarbij gekeken wordt naar de naaldpositie in het foramen intervertebrale en naar de relatie met epidurale verspreiding, is tot dusverre niet gedaan.

In deze prospectieve en observationele studie werden vóór en ná injectie van 0,5 ml röntgencontrastvloeistof röntgenfoto's gemaakt, om de positie van de naaldtip in het foramen intervertebrale en de verspreiding van contrastvloeistof te beoordelen. De foto's werden onafhankelijk geanalyseerd door 2 onderzoekers die geblindeerd waren voor de patiënten. Er werd onder meer gekeken naar epidurale spreiding (bij blokkade op niveau L4 en L5) en naar spreiding naar naburige ruggenmergszenuwwortels (bij wortelblokkade op niveau L4, L5 en S1).

Epidurale spreiding komt voor in 47% van de L4 wortelblokkaden en in 28% van de L5 wortelblokkaden. Onbedoelde spreiding naar een naburige zenuwwortel wordt vastgesteld na 3 wortelblokkaden (L5 n=1, S1 n=2). Bij de lumbale blokkaden wordt de naaldtip meestal in het laterale deel van de bovenste helft van het foramen intervertebrale gevonden, maar het vóórkomen van epidurale verspreiding hangt samen met een mediale positie van de naaldtip in het foramen intervertebrale. In die gevallen waarbij epidurale spreiding naar een naburige zenuwwortel wordt vastgesteld, blijkt de naaldtip óók mediaal in het foramen te zijn gepositioneerd.

Geconcludeerd wordt dat epidurale verspreiding de selectiviteit van het zenuwwortelblok verlaagt en dat voorzichtigheid geboden is ten aanzien van de rol van dit blok in de klinische besluitvorming.

Hoofdstuk 7

In dit hoofdstuk worden de bevindingen van dit proefschrift besproken, worden eindconclusies gegeven en worden aanbevelingen gedaan ten aanzien van studies die in de toekomst kunnen worden uitgevoerd.

Er wordt een grote variabiliteit gevonden met betrekking tot veranderingen van het gevoel en de spierkracht wanneer segmentale zenuwwortelblokkaden worden toegepast. De consistentie en interpretatie van deze effecten wordt beïnvloed door vele factoren, zoals

multisegmentale innervatie van de wervelkolom en overlap van naburige dermatomen, pijn-gerelateerde neuroplasticiteit en verspreiding van het injectaat in de epidurale ruimte. Van de onderzochte effecten is alleen het opwekken van paresthesieën goed reproduceerbaar, als het gaat om de relatie tussen de gestimuleerde zenuwwortel en het bijbehorende dermatoom. Het verdient aanbeveling om elektrisch opgewekte paresthesieën zowel voor als na het blok vast te stellen. Dit komt de kwaliteit van het wortelblok en dientengevolge ook het diagnostisch proces ten goede.

In de toekomst zou men zowel paresthesieën als pijnvermindering moeten relateren aan het pijnlijke spinale niveau om een onderscheid te maken tussen segmentale en niet-segmentale of gerefereerde pijn. De relatie tussen elektrisch opgewekte paresthesieën bij geïrriteerde en niet-geïrriteerde zenuwwortels zou moeten worden onderzocht. De selectiviteit van de zenuwwortelblokkade moet worden verbeterd om de kans op foute interpretaties van effecten te verminderen. Ten aanzien van de diagnostiek zou het verhogen van de resolutie van moderne beeldvormende technieken zoals MRI en spinale endoscopie kunnen bijdragen aan de ontwikkeling van een goudstandaard voor de uitkomst van zenuwwortelblok bij patiënten met chronische lage rugklachten met uitstraling naar het been. Ten slotte is, vooral met betrekking tot rugpijnpatiënten, meer inzicht gewenst in de ontwikkeling en dynamiek van neuroplastische veranderingen.

Chapter 10

CURRICULUM VITAE (ENGLISH)

Curriculum vitae André P. Wolff

Professsional: André Wolff graduated in 1987 in Medicine at the Catholic University Nijmegen and specialized subsequently in anaesthesiology at the Radboud University Nijmegen Medical Centre. From 1992 until 2000 he worked in the St Anna Hospital in Oss as anesthesiologist and started to specialize in Pain Medicine. From 1996 until 2000 he was chairman of the multidisciplinary Regional Pain Centre in north-east Brabant. From 2000 until 2003 he worked as anaesthesiologist and consultant in Pain Medicine in the Bernhoven Hospital and was medical co-ordinator of the multidisciplinary Regional Pain Centre. André Wolff introduced neuromodulation and epiduroscopy in Oss and from 1999 to 2003 he was the leader of a multidisciplinary transmural project on the prevention of chronic pain. In 2002 he combined his activities with a part time function as a consultant in Pain Medicine at the department for pain treatment at the University Medical Centre of Utrecht. In 2003 he switched to the Radboud University Nijmegen Medical Centre (department for Anaesthesiology) and continued also as consultant in Pain Medicine at its Pain Treatment Centre. In 2006 he also became chef de clinique at the department for Anesthesiology.

Scientific: In 1986, André Wolff was in North-Sulawesi, Indonesia, for a research program on the regional epidemiology of Hepatitis-B. From 1992 to 1995 he joined in studies on animals in the animal laboratory of the department for Anaesthesiology at the Radboud University Nijmegen. From 1995, André Wolff worked also for the Pain Knowledge Centre Nijmegen and co-operated in various projects, such as pain classification, prevention of chronic pain and epiduroscopy. He performed the studies for his PhD thesis on Segmental Nerve Root Blocks in Patients with Chronic Radiating Low Back Pain in Oss. His special interests are chronic (low back) pain, prevention of chronic pain and invasive diagnostic and therapeutic procedures. He is author of a number of publications and he is lecturer at various national and international meetings and congresses. He also organized scientific symposia and meetings on pain and pain treatment and teached medical and para-medical professionals in pain management. In 2006 André Wolff has become Head of the Pain Knowledge Centre Nijmegen.

Other: André Wolff is member of various national and international scientific and professional societies on pain and anaesthesiology. He is board member of the Pain Chapter of the Dutch Society for Anesthesiology (NVAsP), the Dutch Chapter of the International Association for the Study of Pain (NVBP), representative in the Platform for Pain and Pain Management (SWVP), and board member of the National Working group and foundation LANSET (spinal endoscopic techniques). André Wolff collaborated in national working groups with respect to guidelines on pain management (invasive techniques, chronic non-specific low back pain).

André Wolff married with Brigit Bossers, dentist, and they have 4 children: Wouter, Geert, Stijn and Bas.

Chapter 11

CURRICULUM VITAE (NEDERLANDS)

Curriculum vitae André P. Wolff

André Wolff werd op 2 december 1959 geboren in Eindhoven en groeide op in Veldhoven en Eindhoven. In 1978 behaalde hij zijn Atheneum-B diploma aan het van Maerlant Lyceum in Eindhoven en in 1987 het arts-examen aan de Radboud Universiteit Nijmegen (destijds Katholieke Universiteit Nijmegen). In 1985 verbleef hij in Minahassa, Sulawesi, Indonesië, alwaar hij bij Prof. dr. N. Pangalila (universiteit van Manado, Indonesië) en Prof. W. Dolmans (Academisch Ziekenhuis St Radboud) onderzoek deed naar het voorkomen van Hepatitis-B onder de lokale bevolking. In 1987 begon hij aan de opleiding anesthesiologie. Hij werd opgeleid onder verantwoordelijkheid van respectievelijk prof. dr. J. Crul, plaatsvervangend opleider prof. dr. H. Beneken-Kolmer en prof. dr. L. Booij. Zijn registratie als anesthesioloog vond plaats in 1992. Van 1992 tot 2000 werkte hij als anesthesioloog in het Sint Anna ziekenhuis te Oss en van 2000 tot en met 2003 in ziekenhuis Bernhoven Oss/Veghel. In deze periodes was hij actief in vele ziekenhuis commissies.

Vanaf 1992 bekwaamde hij zich ook in pijnbestrijding. De behandelmogelijkheden werden door hem uitgebreid met neuromodulatie (electrostimulatie van het ruggenmerg via de epidurale ruimte en continue toediening van medicatie bij het ruggenmerg middels implanteerbare pompen). Hij was van 1996 tot en met 2003 respectievelijk voorzitter en coördinator van het multidiciplinaire Regionaal Pijn Centrum noord-oost Noord-Brabant. Wolff richtte er onder meer een interdisciplinaire poli “vroeg”-diagnostiek op (“Carrousel-poli”) en introduceerde er in 2002 epiduroscopie ten behoeve van verbetering van diagnostiek en behandeling bij patiënten met het zogenaamde failed back surgery syndroom. Gedurende het jaar 2002 was Wolff óók werkzaam voor het pijncentrum van het Universitair Medisch Centrum Utrecht.

Tijdens zijn opleiding tot anesthesioloog deed Wolff onderzoek op het gebied van de regionale anesthesie onder begeleiding van dr. M. Gielen. Van 1992 tot 1995 was hij deeltijds werkzaam ten behoeve van onderzoek aan het dierenlaboratorium verbonden aan de afdeling anesthesiologie van het Academisch Ziekenhuis St Radboud te Nijmegen bij dr. R. Dirksen. Sinds 1995 is Wolff verbonden aan het Pijn Kennis Centrum (hoofd Prof. dr. B. Crul). Daar nam hij deel aan diverse projecten, waaronder pijnclassificatie en preventie van chronische lage rugpijn. Hij initieerde zijn onderzoek naar de waarde van de diagnostische segmentale zenuwwortelblokkaden bij patiënten met chronische uitstralende rugpijn in Oss om het vervolgens in Nijmegen af te maken (Promotor Prof. dr. B. Crul en co-promotores dr. G. Groen en dr. O. Wilder-Smith). Sinds oktober 2003 is hij als anesthesioloog werkzaam voor de afdeling anesthesiologie (hoofd Prof. dr. G.J. Scheffer) en als pijnspecialist voor het pijnbehandelcentrum (hoofd dr. R. van Dongen) aan het Universitair Medisch Centrum St Radboud te Nijmegen. Ook hier introduceerde Wolff epiduroscopie (2004) ten behoeve van diagnostiek, behandeling én onderzoek bij patiënten met uitstralende lage rugklachten. Na een aantal jaren actief te zijn geweest voor het Pijn Kennis Centrum Nijmegen volgde hij met ingang van 2006 Prof. dr. B. Crul op als hoofd

van het PKC. Vanaf diezelfde datum functioneert hij tevens als Chef de Clinique van de afdeling Anesthesiologie aan het Universitair Medisch Centrum St Radboud.

André Wolff gaf en organiseerde (o.a. voor het Pijn Kennis Centrum) regelmatig nascholingen op het gebied van pijn en pijnbestrijding voor huisartsen, verpleegkundigen en medisch specialisten en was spreker op nationale en internationale symposia en congressen. Verder werkte hij mee aan het tot stand komen van de Nederlands Richtlijnen Anesthesiologische Pijnbestrijding, een samenwerking tussen de NVA en CBO (1996) en aan de CBO Richtlijnen de Behandeling van Aspecifieke Lage Rugklachten, een multidisciplinaire samenwerking tussen vele beroepsorganisaties (2002). Hij is lid van diverse landelijke en internationale wetenschappelijke verenigingen en is als bestuurslid actief van de sectie pijn van de Nederlandse Vereniging voor Anesthesiologie, is vertegenwoordiger van de NVA in het Platform voor Pijn en Pijnbestrijding (SWVP), is bestuurslid van de Nederlands Vereniging ter Bestudering van Pijnbestrijding en van de landelijke werkgroep en stichting LANSET (LANdelijke werkgroep ter bevordering van Spinale Endoscopische Technieken).

André Wolff is getrouwd met Brigit Bossers, tandarts. Zij hebben samen 4 kinderen, Wouter (1988), Geert (1991), Stijn (1992) en Bas (1994).

Chapter 12

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Chapter 13

DANKWOORD

Dankwoord

Onderzoek doen betekent een proces ingaan waardoor je groeit. Je ontwikkelt kennis, analytisch denk- en abstractievermogen en komt tot nieuwe denkwijzen. Je ondergaat vele momenten van verwondering en leert om te gaan met tegenslagen. Onderzoek doen verrijkt je. Ik heb dit al die jaren met veel plezier gedaan en zal er ook nooit mee klaar zijn. Gedurende dit proces heb ik hulp gehad van anderen. Veel mensen hebben hierin bijgedragen in actieve, passieve, bewuste of onbewuste vorm. Deze mensen ben ik dan ook heel dankbaar voor wat zij voor mij hebben kunnen betekenen.

In chronologische volgorde wil ik graag mijn dank uitspreken.

Allereerst aan mijn opleiders. Het zijn er diverse. Jan Crul nam mij aan. Herman Beneken Kolmer leidde mij tussentijds op en Leo Booij zei toen ik "de periferie" in ging om te werken bij een toen al uitstekende maatschap Anesthesiologie in Oss, dat hij mij nog wel verwachtte terug te zien in "de Academie".

Mijn interesse voor pijnbestrijding werd gewekt toen ik mijn stage pijnbestrijding deed in mijn opleidingstijd bij Ben Crul, die toen net uit de periferie was terugkomen om pijnbestrijding verder te ontwikkelen in het St Radboud ziekenhuis. Hij was het die mij in 1995 vroeg om deeltijds voor het Pijn Kennis Centrum (PKC) in Nijmegen te komen werken.

Inmiddels was ik al in Oss begonnen, in het St. Anna ziekenhuis. Daar heb ik geleerd het vak uit te oefenen, anesthesiologie en pijnbestrijding, en een betere maatschap kon ik mij niet wensen met als maten Karel Slegers, Huub Spoormans en Gerard Braak. Beste Karel, Huub en Gerard, met jullie werken is uiterst plezierig en waardevol geweest. Jullie hebben een open instelling, zijn constructief en collegiaal. Niet voor niets zei de toenmalige directeur van het St. Anna ziekenhuis, Sijbrand Gerritse, dat de maatschap anesthesiologie de parel van het ziekenhuis was toen hij mij belde om me te vertellen dat ik uitverkoren was na de sollicitatie procedure. En niet voor niets behoort de maatschap anesthesiologie in ziekenhuis Bernhoven tot de best functionerende maatschappen in Nederland én huisvest hun praktijk sinds 2004 ook arts-assistenten anesthesiologie voor hun perifere deel van de opleiding. Ik heb ook de samenwerking na de fusie per 1 januari 2000 met de maatschap in Veghel (met collegae Hans van der Zee, Victor van Cauter, Peter Baaijens, Eric van Ark en later met Marcel Schenkels) voornamelijk als prettig ervaren. De maatschap anesthesiologie heeft altijd mijn onderzoek gesteund en mede dank zij jullie heb ik al mijn patiënten kunnen includeren in de diverse studies. Bij 3 van die studies hebben Marianne Bijman, Esther van Eggelen en Marc van de Heijden mij bijzonder geholpen door hun afstudeer opdrachten af te stemmen op mijn onderzoek. Hun rollen als onafhankelijke onderzoekers is hierbij onmisbaar geweest. Verder gaat mijn dank uit naar Marlies Baas, Geertje Deerns, Trudy Berns en Estella Meulendijks. Mede door jullie goede zorgen liepen de spreekuren en pijnbehandelingen in Oss "als een trein". Mede dankzij jullie heb ik al mijn onderzoekspatiënten kunnen behandelen.

Met de hulp van Gerard en Karel heb ik mij in Oss vele pijnbestrijdingstechnieken eigen gemaakt. Jullie beiden zijn praktisch doch kritisch ingesteld. Pijnpatiënten behandelen deden we verder onder anderen samen met Fons Sijbers, klinisch psycholoog en Hendrik-Jan Mennema, neuroloog. Beiden waren verbonden aan het multidisciplinaire pijnteam dat al sinds ongeveer 1980 functioneerde in Oss. Beste Fons en Hendrik-Jan, jullie behoren tot de professionals die vanaf het eerste uur bij pijnbestrijding betrokken waren. Veel tijd hebben wij samen doorgebracht, ook om ná de pijnteambesprekingen samen bomen op te zetten over pijn, patiënt, mens, samenleving en vele onbegrepen zaken. Holistisch denken was in die tijd al gemeengoed. De basis voor mijn huidige visie op pijn heb ik in die tijd voor een groot deel met jullie ontwikkeld.

In mijn Osse periode ben ik dus begonnen met het opzetten van het onderzoek waar deze thesis het resultaat van is. Ben Crul gaf me destijds de gelegenheid om deel te nemen aan diverse projecten van het Pijn Kennis Centrum Nijmegen en om mijn ideeën aangaande mijn onderzoek vorm te geven onder de vlag van het PKC Nijmegen. Beste Ben, jouw faciliterende rol is van groot belang geweest, niet in de laatste plaats ook, omdat jij als hoogleraar en voorvechter van pijnbestrijding sterk hebt bijgedragen in de toenemende aandacht voor pijn en pijnbestrijding.

Vervolgens kwam ik in contact met Gerbrand Groen uit het AZU. De eerste impuls hiervoor werd gegeven tijdens een uiterst aangenaam pijncongres op Tenerife. Beste Gerbrand, heel veel uren spraken wij over pijn en onderzoek, maar daar bleef het niet bij. Zo zitten we samen ook in meerdere besturen van organisaties die actief zijn op het gebied van pijn en pijnbestrijding. Vanuit veel onderzoek- en onderwijservaring, met goede pijptabak of een goede sigaar erbij, ben je altijd een onnavolgbare gids geweest. Jouw vlijmscherpe analytische vermogen en je talent om een boodschap glashelder weer te geven zijn voor mij altijd van grote steun geweest. Jouw inhoudelijke bijdrage in dit werk is van onschatbare waarde. Een mooie vriendschap is hier bovendien uit voortgekomen die ik altijd zal blijven koesteren.

Nadat Oliver Wilder-Smith naar Nijmegen was gekomen is al snel een vruchtbare samenwerking tot stand gekomen. Oliver, jouw onderzoekservaring en visie brachten andere dimensies in mijn onderzoek. De dynamiek van pijn als proces kreeg een betere plaats. We delen veel in de visie over pijn en onderzoek en over het faciliteren van voorwaarden om pijnonderzoek kwalitatief naar grotere hoogten te brengen. “Making pain visible” is voor jou een hoger doel en verschaft ook mijn onderzoek een goede basis. Inzicht verkrijgen in het chronisch worden van (rug)pijn zal ons nog lang bezig houden!

Robert van Dongen vroeg als hoofd van de afdeling pijnbestrijding in 2002 of er bij mij misschien toch interesse was om terug te keren naar “het Radboud”. Beste Robert, van deze switch heb ik geen spijt gehad, al had ik het goed in Bernhoven. Vele uitdagingen wachtten mij tot nu toe en wachten mij nog steeds in Nijmegen en ik ben je dankbaar dat je mij de kans bood om deze uitdagingen aan te gaan. We hebben een prettige samenwerking en dat is voor een groot deel ook aan jou te danken.

Directe collegae Monique Stegers, Will Gerrits, Lieven Dick en sinds kort ook Willem Brinkert en, belangrijk, de komst van Kris Vissers als hoogleraar Palliatieve Zorg dragen in belangrijke mate bij aan een goede werksfeer binnen het pijncentrum. Het bieden van en het verbeteren van patiëntenzorg, het samen verder structureren van de afdeling en het opleiden van assistenten en jonge stafleden behoort tot de mooie uitdagingen van ons vak.

De rol van de pijn-verpleegkundigen is prominent binnen ons pijncentrum. Vooral Paul Verstegen, maar ook Lily Frederix en Mieke Luckers wil ik (zonder de anderen te kort te willen doen!) bedanken voor hun inspanningen bij het mee opzetten van epiduroscopie in het UMC St Radboud. Daarnaast is de steun van de secretariaten van het Pijn Centrum en het Pijn Kennis Centrum voor ons functioneren onmisbaar. Vooral Anne van Muijen, maar ook Anita Jacobs voor het pijncentrum en Anneke Brand (tot 1 februari 2006) en Dedi Rijkers voor het PKC zijn bijzonder behulpzaam en organiseren het reilen en zeilen van allerlei patiënten- en kennisactiviteiten. Marianne van Leeuwen en Jeske Bongers nemen daarbij nog een speciale rol in als het gaat om organisatie en het zetten van "de puntjes op de i". Aansturing van het PKC maar ook projecten als preventie van chronische rugklachten, waarin we samen werken met o.a. Eric van Rijswijk, huisarts, en Andrea Evers, medisch psychologe, is zonder jullie onmogelijk. De komende tijd, zullen we samen met de overige medewerkers van het PKC Nijmegen de kennisactiviteiten verder gestalte geven.

De afdeling anesthesiologie wordt geleid door Gert Jan Scheffer. Beste Gert Jan, jouw enthousiasme en visie om de afdeling verder vorm te geven, samen met de aanwezigheid van veel goede mensen bieden ons allen goede kansen om een mooie toekomst tegemoet te gaan. Hoewel pijnbestrijding niet jouw primaire vak is, begrijp je als geen ander dat weefselschade, nociceptie en pijn onlosmakelijk met elkaar verbonden zijn en daarmee ook anesthesiologie en pijnbestrijding. Samen met Marcel Hasenbos (Chef de Clinique) en Dirk van Diejen (de Chef de Poli-Clinique), zal ik de komende tijd graag mijn bijdrage leveren als mede-Chef de Clinique om van onze grote afdeling een nog mooiere te maken, waar alle stafleden, arts-assistenten en overige medewerkers, maar ook algemene en wetenschappelijke ontwikkelingen goed tot hun recht komen. Samen met al onze collega stafleden moet het gaan lukken om de komende jaren onze missie succesvol te maken. En….hierbij is voor ons functioneren als Chef de Clinique de bijdrage van Mariska van de Berk onmisbaar!

Speciale dank gaat uit naar mijn paranymfen, Eric van Laarhoven en Karel Slegers. Als eerste Eric, vriend, studiegenoot, vroegere huisgenoot, dispuutgenoot, getuige bij mijn huwelijk, orthopedisch chirurg (en ook nog opgeleid door mijn schoonvader!): Beste Eric, bij onze vriendschap doen tijd en afstand er niet toe. Friendship forever! Jouw vriendschap is mij altijd bijzonder waardevol geweest. En Karel, collega anesthesioloog, meer dan maat in de maatschap: Beste Karel, met jou volgde ik de röntgenhygiëne cursus al voordat ik in Oss als anesthesioloog was begonnen. De toon was gezet. Jíj gaf me thuis op de keukenvloer een epiduraal injectie toen mijn rug niet meer mee wilde doen en ik letterlijk geen millimeter meer vooruit kon en…. het hielp! Overigens had Gerard dat kunstje ook al eens met succes

geflikt, maar dan in het ziekenhuis, netjes aan de monitor. Het voordeel hiervan is dat ik het vak pijnbestrijding ook van de andere kant heb mogen ervaren...

Vrienden Ben Prins en Bart Poierrié hebben beide op eigen wijze een voor mij belangrijke rol gespeeld in de totstandkoming van mijn proefschrift. Vrienden ben je door dik en dun, in betere en slechtere tijden. Ik ben dankbaar dat we elkaars vrienden mogen zijn. Dank wil ik ook uitspreken aan Jolanda van Gent, voor haar bijdrage aan mijn manuscript.

Maar nu de allerbelangrijkste mensen voor mij: Lieve Brigit, de vrouw van wie ik hou, mijn allergrootste steun en toeverlaat en "vriend". Je dacht en zei vaak: joh, kijk nou eens goed naar al je activiteiten, maak keuzes. Soms doe ik dat ook, maar als bezige bij zit ik nu eenmaal zó in elkaar, dat mijn kar behoorlijk geladen moet zijn om me lekker te voelen. En met deze kar ben ik altijd op pad en jij geeft me de ruimte daarvoor. Alles wat ik doe, inclusief mijn activiteiten buiten mijn werkgebied, heeft mij mede gevormd en dat kost tijd. "Onderweg" zijn is al een genot…. En in wat mij gevormd heeft, heb jij wel een heel belangrijke rol gespeeld. Overigens, als geliefde, levenspartner, moeder, huismanager, tandarts met eigen praktijk en wedstrijdsecretaris, en dan nog met al de rollen die je daarbuiten nog bekleedt, kun jij er ook aardig wat van. Je bent óók nog een goede sparring partner. Dank je voor alles.

Wouter, Geert, Stijn en Bas. Jullie zijn een ongelooflijk mooi stel jongens en rakkers bij elkaar. Met veel energie en vele talenten zijn jullie rijkelijk gezegend. Gedurende al de jaren van mijn onderzoek hebben jullie ook wel interesse in mijn activiteiten gehad. Echter, de vele uren thuis achter mijn computer maakten mij er niet altijd gezelliger op. Jullie betrokkenheid in de vorm van "hé pap, wanneer ben je nou eens klaar?", en, "wanneer is het feest?", en…. "je promoveert toch wel onder schooltijd, hè?" kan ik wel waarderen. Helaas Bas, het is woensdagmiddag geworden.…Misschien zijn jullie je het niet bewust, maar ik leer veel van jullie. Mij spiegelen is iets waar jullie je niet van onthouden als jullie het nodig vinden. Dank jullie wel hiervoor.

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André Wolff
Nijmegen, 10 mei 2006

Grünenthal

Grünenthal is van oorsprong een Duits bedrijf, gevestigd in Aken, dat in 1845 is gesticht als zeepfabriek. Het is sinds 1888 100% eigendom van de familie Wirtz. Uit deze fabriek ontstond in 1946 het farmaceutische bedrijf Grünenthal. De zeepfabriek bestaat voort als cosmeticabedrijf (Mäurer & Wirtz, o.a. bekend van het merk Tabac). Aanvankelijk worden medicinale producten op basis van plantenextracten en schimmels bereid zoals penicilline en digitalis. Vandaag de dag is de productie van antibiotica nog een belangrijke activiteit.

Tramal wordt in 1963 door Günenthal gesynthetiseerd en gekarakteriseerd als een effectieve pijnstiller. Omdat de firma niet actief is in pijnbestrijding duurt het tot 1973 voor het is uitontwikkeld en beschikbaar is voor patiënten. Met de ontdekking van endorfinen en opioid receptoren in de 70'er jaren neemt de belangstelling voor het unieke werkingsprofiel van tramadol sterk toe. In de 80er jaren beginnen artsen het met groot succes in te zetten bij zeer verschillende vormen van pijn. Hierna wordt Tramal geregistreerd in bijna alle landen. Tramal is sinds 1998 wereldwijd het meest voorgeschreven opioïd.

De strategie van Grünenthal is om een zelfstandig, onafhankelijk familiebedrijf te blijven met een oriëntatie op de lange termijn. Ongeveer 15% van de omzet wordt gestoken in eigen Research & Development, aangevuld met strategische allianties (b.v. Takeda, Johnson & Johnson) en in-licenciering van producten, waar gewenst. Pijnbestrijding is het allerbelangrijkste aandachtsgebied van de firma.

De laatste jaren heeft Grünenthal met succes Zaldiar®, een combinatie van paracetamol met tramadol op de markt gebracht. Daarnaast is zojuist ClaroSip®, een klassiek antibioticum in een innovatieve kindertoedieningsvorm, en Colistin®, een niche-antibioticum bij de behandeling van Cystic Fibrosis beschikbaar gekomen. De komende jaren wordt Transtec®, een matrix patch met het opioïd buprenorphine, en een product voor de behandeling van postherpetische neuralgie verwacht. Als opvolger voor tramadol zijn thans een 5-tal substanties in fase 2 van ontwikkeling, die allen een multiple mode of action hebben. Daarnaast wordt op het gebied van orale anticonceptie en antibiotica nieuwe producten verwacht.

Grünenthal heeft eigen vestigingen Zuid-Amerika, Mexico, West & Midden Europa en China. Wereldwijd werken bij Grünenthal ca. 5000 mensen waarvan ongeveer 25 op de vestiging in Nederland.

Voor nadere informatie

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André P. Wolff is anesthesiologist and consultant in pain medicine. His interest in pain, patients suffering from pain and pain treatment inspired him to try bringing more light into the darkness of pain for patients suffering from chronic radiating low back pain. André P. Wolff was born in 1959 and currently works as head of the Pain Knowledge Centre in Nijmegen and as chef de clinique at the Institute for Anesthesiology at the Radboud University Nijmegen Medical Centre.

Establishing a clear diagnosis can be complicated in a large population of patients suffering from chronic radiating low back pain. Improved insight into the value of Segmental Nerve Root Blocks should bring us further in understanding underlying mechanisms in these patients, which is essential to raise the efficacy of their pain treatment. The author has performed various studies on the role of lumbosacral Segmental Nerve Root Blocks in patients with chronic radiating low back pain. The studies are interesting and the results are surprising. They challenge present-day medical science and care givers, active on the area of pain, to change the historical and current opinions with respect to diagnosis, treatment and clinical decision making.