Diagnosis and minimally invasive treatment of chronic discogenic low back pain

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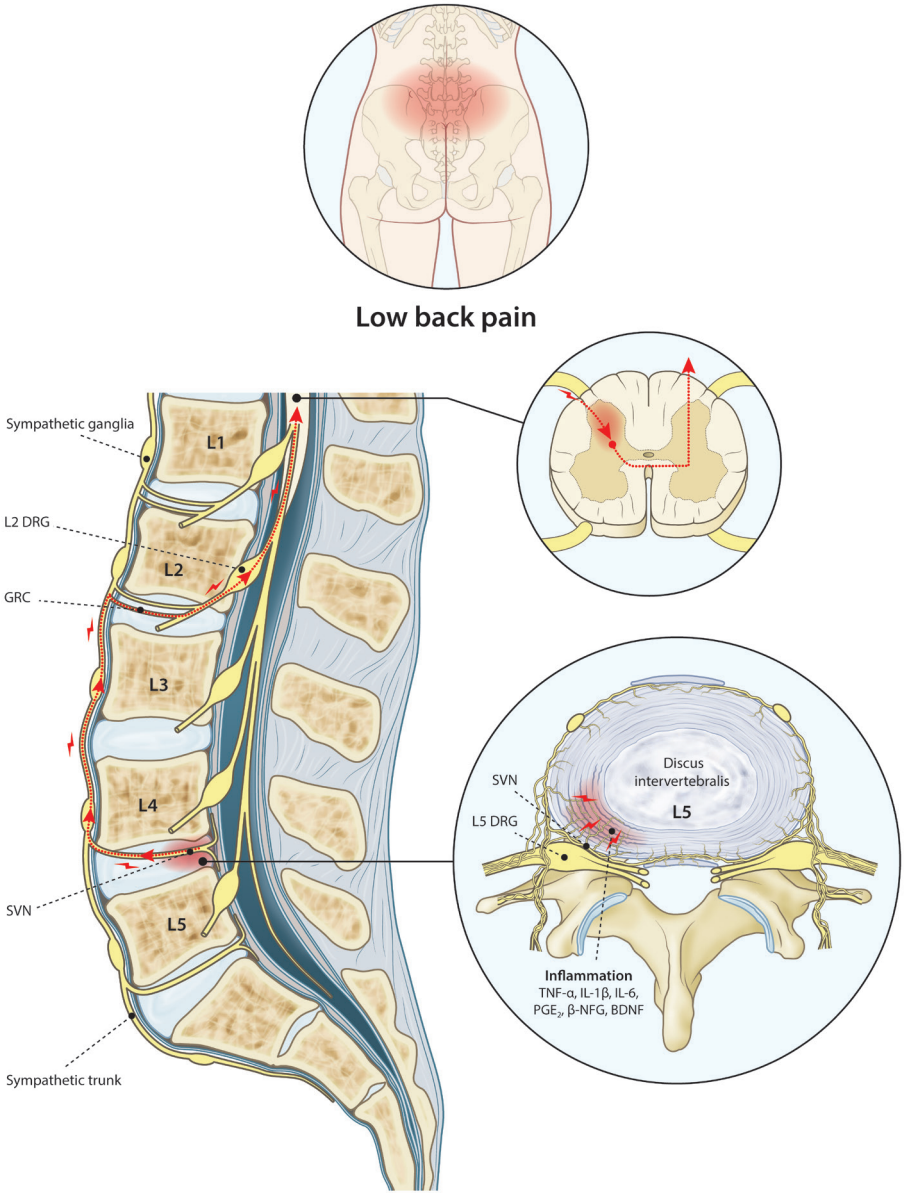

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Cover image: Anatomical design of the intervertebral disc
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Diagnosis and minimally invasive treatment of chronic discogenic low back pain

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit van Maastricht,
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Jan Willem Kallewaard

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CHAPTER 1

General Introduction and Aim of the Thesis

Background

Low back pain

Low back pain (LBP) is a major cause of disability and has almost endemic prevalence in Western societies. Most adults will have low back pain at some point. The median 1-year prevalence in the adult population is around 37%, it peaks in mid-life, and is more common in women than in men.[1-3]

The global burden of disease study[4] found low back pain to be responsible for around 65 million years lived with disability (YLD) in 2017, thus occupying the first place in the ranking of diseases causing YLD.

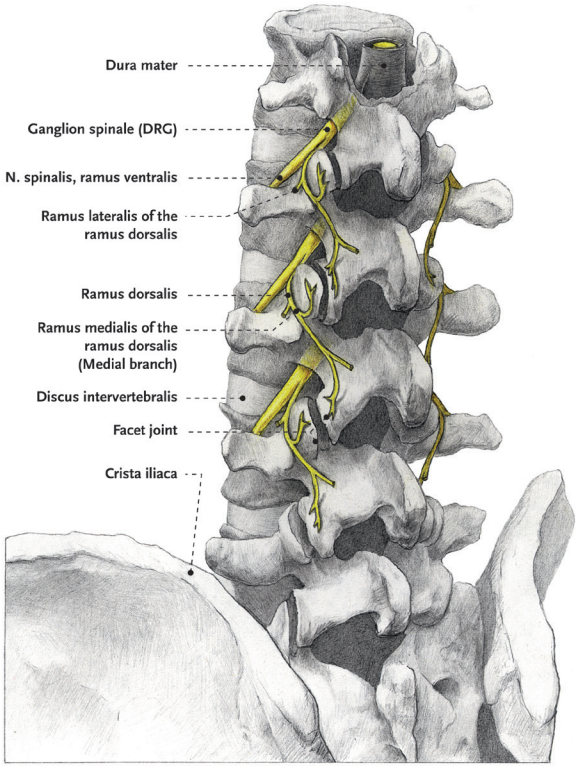

Figure 1: Anatomy of the lumbar spine. Illustration Rogier Trompert Medical Art

LBP can be classified according to duration of pain: acute up to 4-6 weeks, sub-acute for 6-12 weeks and chronic when the pain persists beyond 12 weeks. It is generally accepted that LBP disappears in the majority of patients within weeks. However, two literature reviews suggest that a significant number of patients[5] still suffer from LBP one year after

diagnosis. The first literature review found that 62% of patients still have pain at 12 months, and 16% are still disabled at 6 months.[6] The second literature review assessed patients with nonspecific low back pain for less than 3-months duration who sought treatment in a primary care clinic. About one-third of the patients had spontaneous recovery in the first 3 months after onset. The majority (65%) still experienced pain after 1 year. This percentage varied between 57% and 67% depending on the definition of persistent pain.[2]

There are different potential causes of LBP. The minority, estimated to be around 5%-10%, are identified as the result of tumor, infection, vertebral fracture or ankylosing spondylitis.[7] The remaining 90%-95% are commonly indicated as "nonspecific LBP". Waddell[8] suggested a simple and practical classification, which divides low back pain into three categories: (1) pain caused by specific spinal pathology, e.g. tumor, infection or trauma, (2) nerve root or radicular pain and (3) nonspecific low back pain, which constitutes a large heterogenous group of patients (about 85% of total cases[9]). In these patients imaging often reveals signs of degeneration of one or more intervertebral discs, such as disc space narrowing, vertebral endplate changes[10, 11], annular disruption[12, 13] and/or facet joint arthropathy. These degenerative findings, however, can also be observed in asymptomatic subjects[14] and are consequently nonspecific for low back pain.

Nonspecific LBP may be caused by the anterior and posterior longitudinal ligaments, dura mater; the periost and muscles.[15] (see figure 1)

Patients presenting with LBP should first be screened for a specific spinal disorder. The so-called "red flags" can serve as guidance. In case of suspicion of an underlying disease, appropriate further diagnosis and treatment should be performed (see table 1 in appendix). Several factors, such as fear, depression, stress, working conditions etc. are documented to influence the severity and duration of low back pain.[16] The risk for chronification should be identified relying on the yellow flags, a list of psychological indicators suggesting an increased risk of progression to long-term distress. Initial treatment of non-specific low back pain includes conservative therapies such as physical therapy and rehabilitation, pharmacological management and, if psychosocial risk factors are present, biofeedback and cognitive behavioral treatment. When pain proves to be refractory to conservative treatment or the medication causes significant side effects, interventional pain treatment may be considered.[17]

The facet joints are true synovial joints that form the so-called three joint complex, that is formed by the three articulations between adjacent vertebrae: one disc and two facet joints.[18] Disc degeneration is thought to automatically induce facet joint arthritis.[18] In addition, the sacroiliac joints are true synovial joints which consist of two surfaces held together by fibrous capsule and enjoined with synovial fluid.[19] To optimize potential

interventional pain management, which is target specific, efforts are made to identify the source of pain, thus changing non-specific LBP into specific LBP.

There is some controversy regarding the clinical signs of facet joint pain. Revel described 5 criteria which are predictive for positive placebo-controlled blocks: pain worsened by coughing; pain not worsened by straightening from flexion, pain not worsened by extension-rotation, pain not worsened by hyperextension, pain improved in the supine position.[20, 21] Subsequent studies failed to confirm these findings.[22-24] Paravertebral tenderness is, however, indicative for facetogenic pain.[25] The pain from the upper facet joints often extends into the flank, hip and lateral thigh; if the pain originates from the lower facet joints it typically radiates into the posterior thigh. Pain distal to the knee is rarely associated with facet pathology.[26] (see figure 3)

Diagnostic blocks consist of either intra-articular injection of local anesthetic or the block of the medial branch (MB) of the dorsal ramus, that innervates the facet joint. International pain associations discourage the use of intra-articular injections,[27-29] because intra-articular injections are more painful for patients, and due to technical difficulties, the failure rate to reach the intra-articular space ranges between 29% and 38% per joint, and between 46% to 64% per procedure.[30, 31]

Cohen et al.[32] described a prevalence of facet joint pain identified with a single block ranging from 8% to 94%. With comparative blocks a prevalence range of 9% to 42% was reported.

Pain originating from the sacroiliac joints has a variety of characteristics. The most relevant referral pattern is buttock pain that extends into the posterolateral thigh.[33] (see figure 3) The physical examination consists of a series of provocative maneuvers which are positive when they reproduce the patient's typical pain. Of the compression test; distraction test; flexion, abduction, and external rotation test; Gaenslen test; thigh thrust test; and Gillett test at least 3 should be positive for patients to be considered for a diagnostic block.[34-36]

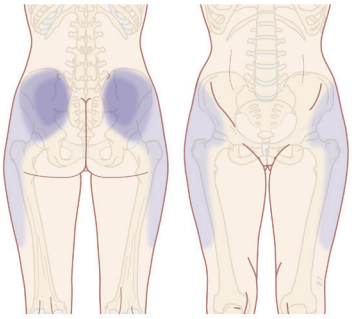

Figure 2: ain referral pattern of lumbar facet Pain adapted from McCall et al.[26] Illustration Rogier Trompert Medical Art

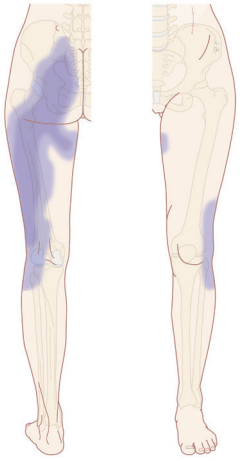

Figure 3: Referral pattern of sacroiliac joint Pain. Illustration Rogier Trompert Medical Art

Discogenic pain

Definition

According to the International Association for the Study of Pain (IASP), the definition of lumbar discogenic pain is lumbar spinal pain, with or without referred pain to the lower limb girdle or lower limb, stemming from a lumbar intervertebral disc. The diagnosis hinges on the fact that the pain must be shown to be conclusively from the intervertebral disc.[37]

A cross-sectional study of patients with chronic low back pain showed that 39% of the patients had the criteria for disc disruption based on clinical examination, MRI and CT scan and provocation discography.[38] A retrospective chart review of patients presenting to a spine center with LBP refractory to conservative treatment, found that in 41.8% of patients the intervertebral disc was the cause of low back pain; utilizing the clinical examination as a first triage and provocative lumbar discography to confirm the diagnosis discogenic pain.[39]

Pathophysiology

The innervation of the lumbar spine depends on the somatic nervous system and on the sympathetic nervous system. The intervertebral disc, the ventral surface of the dura mater, the longitudal dorsal and ventral ligaments are innervated by the sinu-vertebral nerves

and the rami communicantes, which are sympathetic nerves. The sinu-vertebral nerve is implicated in diffuse low back pain. It cannot directly reach the somatic element of each level of the lumbar spine.[40] The cutaneous innervation from L3 to L5 must therefore pass through the nearest somatic nervous system structure which is the spinal ganglion L2. Therefore, the ramus communicantes and the bilateral dorsal root ganglion L2 are considered targets for interventional pain treatment.

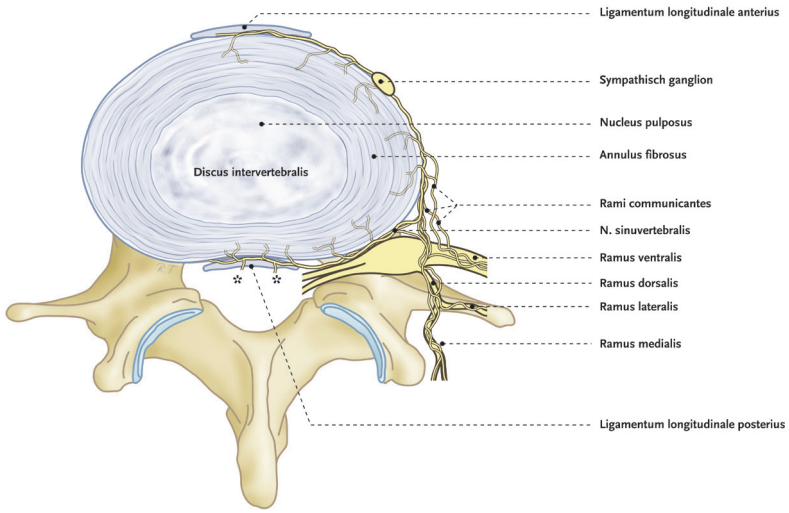

Figure 4: Schematic drawing of the lumbosacral innervation. Connections to the dural nerve plexus. Illustration Rogier Trompert Medical Art

From the rationale that a structure must have a sensory nerve supply to be capable of causing pain, the innervation of the intervertebral disc has been extensively studied and documented.[41] Bogduk described the innervation of the lumbar intervertebral disc in 1983. The anterior and lateral portions of the annulus fibrosis (AF) are supplied by branches of the grey rami communicantes of the sympathetic trunk. The posterior aspect of the AF is supplied by the sinuvertebral nerve, which is a combination of a branch from the ventral ramus and a branch of the grey ramus communicantes of the corresponding segment.[42] (see Figure 1)

In a normal disc, only the outer one third of the AF is innervated. However, in patients with discogenic pain, it is found that there is innervation all the way into the inner third of the AF and even into the nucleus pulposus (NP). The tears in the AF, which are commonly in the posterior part, caused the formation of a vascularized granulation tissue starting from the outer part of the AF into the disc. Within this granulation tissue, nerve fibers are found, and these abnormal nerves are the likely cause for the nociception of the intervertebral disc.[42-44]

The innervation of the degenerative intervertebral disc is supposed to be promoted by the ingrowth of blood vessels. An immunohistochemistry study on human intervertebral discs shows a large proportion of nerves in the inner AF and the nucleus pulposus of the degenerative discs. The nerve ingrowth is also observed in absence of blood vessels.[45]

The clinical significance of this is that most of the various percutaneous intradiscal therapies are targeted at obliterating these abnormal nerves and thus stopping discogenic pain. In addition to the abnormal sensory innervation described above, inflammation within the intervertebral disc also plays a role in the pathogenesis of discogenic pain. In degenerated discs, there is an increased concentration of pro-inflammatory molecules like tumor necrosis factor–α, prostaglandin E2 and interleukin-6 . These factors may be a cause for the sensitization of the nerve fibers of the disc.[46]

Physical examination

As interventional pain treatment is target specific, identification of the pain source is important. In absence of a generally acknowledged reference test for identifying the pain source in patients with nonspecific low back pain, identification of a possible source is based on medical history, clinical examination and additional tests.

There are no typical characteristics of discogenic pain in the physical examination. Biphasic straightening from flexion to extension is considered by some to be an indication of disc pathology. Pain as a result of pressure on the processus spinosus is considered characteristic of discogenic low back pain ("Federung"). Pain radiating from the disc due to provocation with a tuning fork pressed on the processus spinosus of the affected segment was described.[47] Although suggestive, these physical examination characteristics have not been validated.[38, 48-50]

Additional tests

Imaging techniques such as CT and MRI are effective means of demonstrating detailed anatomical abnormalities in the vertebral column.[13, 14, 51, 52] Findings identified in people with low back pain are also common in people without such pain,[14, 53] and their importance in diagnosis is a source of much debate.

Aprill and Bogduk[12] described the high-intensity zone (HIZ) on MR images of the lumbar spine. HIZ is a high-intensity focal signal on T2-weighted sequences in the posterior annulus fibrosus with a considerably brighter signal intensity than nucleus pulposus that is distinctly dissociated.[54, 55] HIZ are present in 28-59% of symptomatic patients. The HIZ may be an indication of an annular tear that extends to the outer third of the annulus. The HIZ

may be caused by the presence of inflammatory cytokines. Conflicting findings have been reported in the literature concerning this topic. On the one hand, a study done by Wolfer and Derby[56] showed an 80% correlation between the HIZ and discogenic pain. Carragee, on the other hand, claimed that this HIZ regularly occurs in asymptomatic control patients as well.[14, 53, 57] Modic changes, visualized on MRI, represent bone marrow lesions. These changes have a high specificity for discogenic low back pain.[58] Modic changes are seen in the endplates of a degenerated disc.[59] Modic changes of any type (1-3) were noted more frequently in patients with low back pain compared to asymptomatic subjects.[60] The sensitivity of Modic changes for the relation with discogenic low back pain is low.[61-63]

In a study performed by H. Albert et al.[64] cultures from discs removed under sterile conditions showed infection with Propionibacterium acnes and Corynebacterium proinquum in 53% of the patients. Based on this information the potential efficacy of long-term antibiotic (amoxicillin/clavulanate) treatment was assessed in a randomized placebo-controlled trial. Antibiotic treatment significantly decreased discogenic pain compared with no or minimal pain reduction in the control group.[64] This study has not yet been reproduced and the debate on the potential hazards of long-term antibiotic use is ongoing.

The current *gold standard* used by interventional pain specialists for confirming the clinical diagnosis of discogenic pain is a positive low-pressure discogram, with a negative control disc and the demonstration of a Grade 2-4 annular tear as defined by the Dallas discogram scale.[12, 65, 66] (see table 2 in appendix)

Morphologically, these discs are Grades 2 to 3 based on the Dallas Discogram Scale.[65] The international (IASP and ISIS) guidelines are based on these operational criteria**:**[67]

Absolute discogenic pain:
- Stimulation of target discus reproduces concordant pain.
- The intensity of this pain has a Numeric Rating Scale (NRS) score of at least 7 on an 11-point scale.
- The pain is reproduced by a pressure of less than 15 psi above the opening pressure.
- Stimulation of the two adjacent discs is not painful.

Minimally Invasive Interventional Management of Discogenic Pain

Several minimally invasive interventional treatments have been described for the management of chronic discogenic low back pain.

Intradiscal corticosteroids

The intradiscal injection of corticosteroids is documented in a case series and 3 controlled trials.[68-71] The quality of the evidence is low and showed no better effect of corticosteroid injections compared to intradiscal saline.[72] Comparison of injection of methylprednisolone with injection of local anesthetic showed no difference between groups.[71]

There is conflicting evidence on the clinical effect of intradiscal corticosteroid injections. A recent-review showed two negative and 1 positive RCT's. The latter was subject to serious criticism[73] such as a 5-point pain reduction which has not been seen in other studies. In addition, there was an absence of improvement in the saline injection group. Between the two groups, the outcome is strikingly uniform, despite the small numbers. The duration of apparent effect is at least 6 months which is not corresponding with the pharmacological duration of action of the agents used. The evidence on intradiscal corticosteroid injections is of low quality and the inherent risks justify a weak recommendation for this treatment.

Radiofrequency treatment of the ramus communicans

Radiofrequency treatment of the communicating ramus produced improvement in pain and function in a study with methodological weaknesses.[74] Another study found no difference between radiofrequency treatment and sham intervention.[75] Although there was no consensus in selecting patients with presumed chronic discogenic low back pain, patients in this study were selected by means of a test block of the communicating ramus. No MRI or other diagnostic tools were used to select patients and "affected levels".

The evidence is of very low quality and the lack of effect justifies a weak recommendation for this treatment.

Radiofrequency treatment of the intervertebral disc in chronic discogenic low back Pain

Radiofrequency treatment of the intervertebral disc was studied in two RCT's.[76, 77] The study comparing intradiscal RF with sham procedure found the treatment to be ineffective at 8 weeks follow-up.[76] The second study compared the results of intradiscal RF treatment of different duration (120 sec and 360 sec) in patients with a positive provocative discography. The pain reduction observed at 1, 2 weeks and 1 month was no longer present at 6 months. The quality of the evidence is judged to be low and there is a weak recommendation against.

Intradiscal electrothermal therapy

Intradiscal electrothermal therapy (IDET) was studied in two RCT's that had divergent findings.[78, 79] The first study found a significant improvement of VAS and ODI scores in the IDET group compared to sham intervention.[78] The second study found no differences between the active and the sham group.[79] A prospective trial showed maintained

improvement over 24 months follow-up.[80] The GRADE evaluation showed that these studies were of low quality and there is a weak recommendation for this treatment.[72]

Intradiscal pulsed radiofrequency treatment
An uncontrolled prospective cohort study showed that pulsed radiofrequency treatment in the nucleus pulposus resulted in pain relief for 3 and 12 months. This study was of very low quality and the treatment has a weak recommendation.[81]

Intradiscal cooled radiofrequency (biacuplasty)
The use of intradiscal cooled radiofrequency (biacuplasty) was studied in 2 pilot studies[82, 83] and a prospective matched controlled groups study comparing biacuplasty and RF annuloplasty.[84] The latter trial was of high quality and showed better outcome with biacuplasty. A randomized controlled trial compared intradiscal cooled radiofrequency with conventional medical management, showing a significant better outcome in the intradiscal cooled radiofrequency group.[85] The quality of the evidence is moderate, and the strength of recommendation is also moderate.[72]

Intradiscal methylene blue
In 2007 the Chinese group of Peng et al. published the spectacular outcome of intradiscal methylene blue injection in patients with positive discography who were scheduled for fusion surgery. After a mean follow-up period of 18.2 months, 87% of the patients reported disappearance or marked alleviation of low back pain.[86] The publication of the RCT in Pain in 2010[87] that reported for the methylene blue group a mean reduction in VAS of 52.5 %, a 35. 8% mean reduction in the Oswestry disability scores and a 91.6 % satisfaction rate compared with 0.70%, 1.68%, and 14.3%, respectively, in placebo treatment group, gave rise to skepticism. As Bogduk in the accompanying editorial stated: "If the results of Peng et al.[87] are true, this intervention will revolutionize the treatment of low back pain. Spinal surgery for back pain will be rendered essentially obsolete."
As with any treatment, the results of this study should be replicated.

In 2012 two different groups reported their findings with intradiscal methylene blue injections. Kim et al.[88] included 20 patients with discogenic pain proven by provocative discography. They found a significant decrease in VAS and ODI at 1- and 3-months follow-up in 55% of the patients. This effect weaned off at 6 months and at 12 months follow-up only 20% of the patients had satisfactory pain relief. Gupta et al.[89] published a case series of 8 patients with discogenic pain diagnosed by provocation discography. One patient was considered a clinical success and 4 patients had a time-limited clinical response. Another prospective study assessed the clinical outcome and the MRI documented changes of the intervertebral disc after intradiscal methylene blue injection in 33 patients.[90] They found a 2-point pain reduction at 1, 3- and 6-months follow-up but at 12 months this was no

longer achieved. The MRI findings suggested that intradiscal methylene blue injection might even improve disc degeneration 6 and 12 months after treatment.

These conflicting findings justify replication of the RCT on IMBI by Peng[87] using exactly the same protocol.

Aim of this thesis

There have been many theories, diagnostic and therapeutic tools, researched over the years, with the ultimate goal of treating CD-LBP. Obviously lumbar spine surgery is an option for a well selected group of patients. Some patients might benefit from minimal invasive pain treatments.

Treatment of CD-LBP is only an option when other sources of low back pain have been ruled out and the disc seems to be the causative factor of CD-LBP.

The objectives of this thesis are to examine the accuracy of diagnostic testing in chronic discogenic low back pain; and to examine the effectiveness of various minimal invasive treatment strategies. Therefore, we addressed the following research questions:

Question 1A: What is the current knowledge regarding the diagnostic process of chronic discogenic low back (CD-LBP) pain?

Question 1B: What is current evidence for efficacy and effectiveness of minimal invasive treatments for CD-LBP (2010 and 2018)?

Question 2: Can pressure-controlled provocative discography be flawed by potential pressure transfer to an adjacent disc?

Question 3: Can the good and long-lasting effects of the injection of MB in the painful discs in patients with CD-LBP, as found by Peng et al., be reproduced and confirmed?

When all treatment options fail spinal cord stimulation might be a viable option for different pain syndromes. Understanding the innervation of the lumbar discs opens the research question of whether spinal cord stimulation might be an effective treatment in refractory patients with chronic discogenic low back pain, not being candidates for lumbar spine surgery.

Question 4: Can stimulation of the L2 dorsal root ganglion produce long term pain relief and improved disability in patients with chronic discogenic pain?

Outline of this thesis

Chapter 1: Introduction

In **Chapter 2a** systematic review concerning CD-LBP is performed, assessing the diagnostic process and the evidence (2010) of the minimally invasive treatments that are used in CD-LBP.[68]

Chapter 2b gives the updated evidence for minimally invasive treatments for CD-LBP (2018).

In **Chapter 3** we discuss the relevance of the single most important diagnostic test in CD-LBP: pressure controlled provocative discography. An animal study reporting increased intradiscal pressure in the adjacent discs, raised concern. These results were reproduced in a small human cohort.[91-92] We performed low-speed, pressure-controlled discography in 50 consecutive patients with intractable low back pain. With an arterial blood pressure monitoring system, the pressure in the adjacent discs were controlled.[93]

In **Chapter 4** we describe the results of a prospective study, on the effect of intradiscal methylene blue injection in patients with CD-LBP, using the same protocol as described by Peng et al.[87]

In **Chapter 5** we describe the results of an RCT, in which patients with CD-LBP, as confirmed by provocative discography, exactly copying the protocol of Peng,[87] were randomly assigned to receive intradiscal methylene blue or lidocaine (control group).

In **Chapter 6** we describe the effectiveness of DRG (dorsal root ganglion) stimulation in patients suffering from failed back surgery syndrome after discectomy. The implantation level was identified by the paresthesia pain overlap, with good coverage of low back pain being obtained with L2 stimulation.

In **Chapter 7** we show the results of a prospective study treating therapy resistant patients with CD-LBP with bilateral DRG L2 stimulation.

The general discussion (**Chapter 8**) summarizes the major findings as related to our research questions in the light of the findings of a recently finished renewed systematic review. Questions arising from our results are addressed and suggestions for future research are presented.

In **chapter 9**, the valorization, we explain from a patient and economic perspective the burden of CD-LBP and discuss the value of our studies for society.

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Appendixes Chapter 1

Table 1: Red flags

First appearance of back complaints before 20th or after 55th year
Trauma
Constant progressive back pain
Malignant disorder in the medical history
Long-term use of corticosteroids
Drug use, immunosuppression, HIV
(Frequent) general malaise
Unexplained weight loss
Structural deformities of the spinal column
Infectious disorders (e.g. herpes zoster, epidural abscess, HIV, Lyme disease)
Neurological loss of function (motor weakness, sensory disturbances, and/or micturition

Table 2: Classification of discs on the basis of the pressure at which pain arises[68]

- Discs that are painful at a pressure lower than 15 psi above opening pressure
- Discs that are painful between 15 and 50 psi above opening pressure
- Discs that are not painful in spite of the fact that the pressure is higher than 50 psi above opening pressure

CHAPTER 2a

2a

Discogenic Low Back Pain

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Abstract

An estimated 40% of chronic lumbosacral spinal pain is attributed to the discus intervertebralis. Degenerative changes following loss of hydration of the nucleus pulposus lead to circumferential or radial tears within the annulus fibrosus. Annular tears within the outer annulus stimulate the ingrowth of blood vessels and accompanying nociceptors into the outer and occasionally inner annulus. Sensitization of these nociceptors by various inflammatory repair mechanisms may lead to chronic discogenic pain.

The current criterion standard for diagnosing discogenic pain is pressure-controlled provocative discography using strict criteria and at least one negative control level. The strictness of criteria and the adherence to technical detail will allow an acceptable low false positive response rate. The most important determinants are the standardization of pressure stimulus by using a validated pressure monitoring device and avoiding overly high dynamic pressures by the slow injection rate of 0.05 mL/s. A positive discogram requires the reproduction of the patient's typical pain at an intensity of > 6/10 at a pressure of < 15 psi above opening pressure and at a volume less than 3.0 mL. Perhaps the most important and defendable response is the failure to confirm the discus is symptomatic by not meeting these strict criteria. Various interventional treatment strategies for chronic discogenic low back pain unresponsive to conservative care include reduction of inflammation, ablation of intradiscal nociceptors, lowering intranuclear pressure, removal of herniated nucleus, and radiofrequency ablation of the nociceptors. Unfortunately, most of these strategies do not meet the minimal criteria for a positive treatment advice. In particular, single-needle radiofrequency thermocoagulation of the discus is not recommended for patients with discogenic pain (2 B-). Interestingly, a little used procedure, radiofrequency ablation of the ramus communicans, does meet the (2 B+) level for endorsement. There is currently insufficient proof to recommend intradiscal electrothermal therapy (2 B±) and intradiscal biacuplasty (0). It is advised that ozone discolysis, nucleoplasty, and targeted disc decompression should only be performed as part of a study protocol. Future studies should include more strict inclusion criteria.

Key Words

discogenic low back pain, interventional therapy, evidence-based, intradiscal therapy, discography

Introduction

This review on discogenic low back pain is part of the series "Evidence-based Interventional Pain Medicine according to clinical diagnoses". Recommendations formulated in this chapter are based on "Grading strength of recommendations and quality of evidence in clinical guidelines" described by Guyatt et al.[1] and adapted by van Kleef et al.[2] in the editorial accompanying the first article of this series (Table 1). The latest literature update was performed in October 2009.

Each year, many people become disabled as a result of back complaints. Back pain is a multifactorial ailment. In approximately 45% of the cases, low back pain appears to be of discogenic in origin.[3,4] The sacroiliac joint or the facet joints are indicated as the cause of the pain in 13% and 15% to 40% of the cases, respectively.[4] Furthermore, in clinical practice, often, more than one cause can be found simultaneously that might be held responsible for the patients' pain. Discogenic pain shares clinical signs with lumbosacral radicular pain characterized by radiating pain in one or more lumbar or sacral dermatomes with or without neurological deficits. Discus herniation in patients under the age of 50 and spine degeneration in older patients are often associated with chronic low back pain. The development of interventional techniques to treat discogenic pain has stimulated the refinement of diagnostic procedures with a high specificity and sensitivity, to confirm or refute the hypothesis that the patients' pain is primarily due to a painful internally disrupted discus.

Table 1: Summary of evidence scores and implications for recommendation:

Score	Description	Implication
1 A +	Effectiveness demonstrated in various RCTs of good quality. The benefits clearly outweigh risk and burdens.	Positive recommendation
1 B +	One RCT or more RCTs with methodological weaknesses, demonstrate effectiveness. The benefits clearly outweigh risk and burdens.	
2 B +	One or more RCTs with methodological weaknesses, demonstrate effectiveness. Benefits closely balanced with risk and burdens.	
2 B ±	Multiple RCTs, with methodological weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens.	Considered, preferably study-related
2 C +	Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens.	
0	There is no literature or there are case reports available, but these are insufficient to prove effectiveness and/or safety. These treatments should only be applied in relation to studies.	Only study-related
2 C -	Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefit.	Negative recommendation
2 B-	One or more RCTs with methodological weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens outweigh the benefit.	

Anatomy of the discus intervertebralis

The discus intervertebralis is composed of the nucleus pulposus (NP), the annulus fibrosus (AF), and the vertebral end-plates (VE). The corpora vertebrae lie above and below the discus. On the posterior side, the discus is supported by two facet joints. Together, the weight- bearing joints provide support and stability, especially by limiting movement of the spine in all directions.[5] The healthy discus is avascular, and its nutrition depends on diffusion via the AF and the VE. The nucleus itself has no blood supply.

Nerve Supply

The nerve supply of the discus intervertebralis is complex. The sensory innervation of the discus intervertebralis occurs via branches of the truncus sympathicus.[6] The dorsal circumference of the discus annulus is innervated via branches of the nervi sinuvertebrales (or recurrentes meningei) (Figure 1), which stem from rami communicantes. The nervus sinuvertebralis runs ventral to the nerve root, back to the canalis spinalis, where the nerve splits into finer branches, which form nerve networks: one in the ligamentum longitudinale posterius (LLP) and a network in the ventral dura.[6] The nerve plexus is characterized by many left-right connections and many cranio-caudal connections. Ultimately, the posterior discus and corpus vertebrae are innervated via this nerve network in the LLP. The same accounts for the ventral dura. The ligamentum longitudinale anterius (LLA) also contains a network of nerves with many left-right and high-low connections of branching nerves. It is formed by branches from the trunci sympathici from both sides. The ventral and lateral sides of the discus intervertebralis are supplied by branches of the rami communicantes, direct branches of the truncus sympathicus, and by the LLA nerve plexus.[6] (Figure 1).

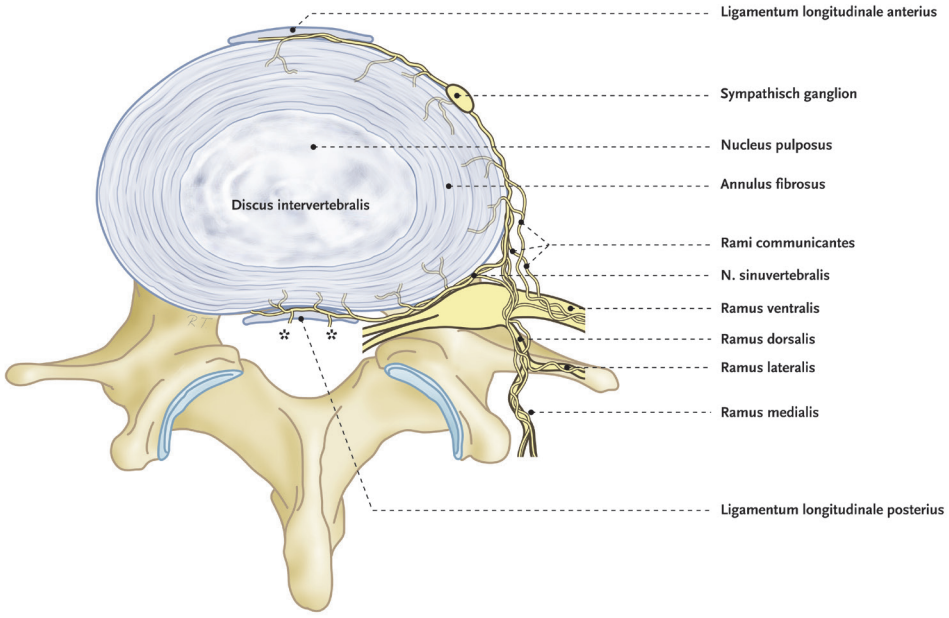

Figure 1. Schematic drawing of the lumbosacral innervation.[6] *Connections to the dural nerve plexus. Illustration: Rogier Trompert Medical Art. http://www.medical-art.eu.

Because many of the afferent fibers from the discus travel along with nervi sympathici, some investigators have sought to prove the discus has a sympathetic innervation and that both nerve networks consist of inter- connected nerves with somatic and autonomic branches from various lumbar spinal nerves.[6] This assumption has been endorsed by Suseki et al.[7] and indirectly supported by a recent RCT showing pain relief following radiofrequency (RF) lesioning of the rami communicantes.[8]

Significance of this innervation pattern

The observation of left-right and cranio-caudal connections in these nerve plexuses further suggest that lateralized disorders, in which nociceptive stimuli reach the spinal cord via nervi sinuvertebrales from the other side, can cause pain at a side that is contralateral to its origin. This could explain why patients complain about pain on the left side at one time and another time about pain on the right. Another implication is that the majority of spinal structures, including the disci, are innervated multi segmentally.[6] Via the mechanism of deep somatic referred pain, this innervations pattern leads to an overlap in distribution of referred pain areas from adjacent structures. As a result, the pain projections are not always reliable for determining the source of the pain. Finally, if the human disci receive significant afferent fibers via sympathetic pathways, their cell bodies may be primarily located in the ganglia spinalia (dorsal root ganglia, DRGs) of C8-L2 nerves, i.e., the levels at which the sympathetic nerve fibers leave the spinal cord.[6] Although it has yet to be proven true, some researchers have utilized this hypothesis to obtain a specific block of the nervus spinalis L2 for low lumbar discogenic pain.[9]

Diagnosis

History

There are no specific characteristics in the patient's history that confirm or disprove the diagnosis of discogenic low back pain.[10] More typical features include persistent, nociceptive low back, groin and/or leg pain that worsens with axial loading and improves with recumbence. Patients may have experienced a prior episode of acute, intense pain caused by an acute tear in the innermost part of the AF (although no scientific proof of this exists).

Discogenic low back pain is often localized medially in the back, and more detailed referral patterns were reported by Ohnmeiss et al. during provocative discography.[11,12] Discogenic pain originating from the L3/L4 level typically radiates to the front (anterior) side of the

thigh, L4/L5 to the outside (lateral) of the thigh, and sometimes to the back (posterior) of the thigh, and L5/S1 usually causes pain on the back of the thigh.

Physical examination

There are no typical characteristics of discogenic pain in the physical examination. Biphasic straightening from flexion is considered by some to be an indication of a discus complaint. Pain as a result of pressure on the processus spinosus is considered characteristic of discogenic low back pain ("Federung"). Vanharanta[13] has described pain radiating from the discus due to provocation with a tuning fork pressed on the processus spinosus of the affected segment. Although suggestive, these physical examination characteristics have not been validated, and the current criterion standard for confirming a clinical diagnosis of discogenic pain is a positive discogram and the demonstration of a Grade 3 annular tear.[14,15]

Additional tests

Imaging techniques such as CT and MRI are highly effective means of demonstrating detailed anatomical abnormalities in the vertebral column.[16,17] These imaging techniques are limited in that only an indication can be given for the cause of the pain. Recently, the presence of a high-intensity zone (HIZ) has been correlated with the presence of discogenic pain at that level. The HIZ may be an indication of an annulus tear that extends to the outer third of the annulus. The HIZ may be caused by the presence of inflammatory cytokines. Conflicting studies can also be found in the literature concerning this subject. On the one hand, a study done by Wolfer and Derby showed an 80% correlation between the HIZ and discogenic pain. Carragee, on the other hand, claims that this HIZ regularly occurs in asymptomatic control patients as well.[14,18] In spite of the regular appearance of conflicting literature, especially between Carragee's and Derby's groups, provocative discography remains the *gold standard* for the diagnosis of discogenic pain. Although MRI images are helpful in visualizing such pathology as discus degeneration and desiccation, HIZ's, and loss of disk height, the results commonly correlate poorly with clinical findings, leaving open the critical question of causality. To date, provocation discography is the only available method of linking the morphologic abnormalities seen on MRI with clinically observed pain, and its predictive value has been repeatedly questioned, mainly as a result of reported false positive rates.

Pathophysiology of Discogenic Pain and Discography

In the normal discus intervertebralis, sensory nerves innervate the outermost third of the annulus. In the degenerated discus, this innervation is deeper and more widespread; some

fibers even penetrate the NP.[19–26] By now, it is also an accepted fact that the discus can be a frequent and significant source of low back pain. Every discus has a nucleus that is surrounded by a fibrous structure, the AF. As a result of aging, an anomalous posture of the back, or injury, the discus intervertebralis can become weaker, and fissures and tears can arise in the annulus (Figure 2). These tears can cause chronic pain if the tear in the annulus extends to its outermost third.

Based on CT-discography studies, the annular tear is becoming more frequently implicated as the basis for discogenic pain. The emphasis lies more on the extent and the dimensions of the annular tear than on disc degeneration. Sachs et al.[27] developed the "Dallas Discogram Scale," a 4-point scale that specifies the degree of discus degeneration. Grade 0 indicates a discus in which the contrast agent remains entirely in the NP. Grades 1 through 3 indicate tears in which the contrast agent extends to the innermost, middle, and outermost sections, respectively, of the AF. Later, Grade 4 was added; the Grade 4 fissure has expanded into an arc- shaped tear outside of or in the innermost ring of the annulus (Figure 3).

Subsequently, Vanharanta[28] demonstrated the relationship between the expansion of the tear in the annulus and pain reproduction during discography.

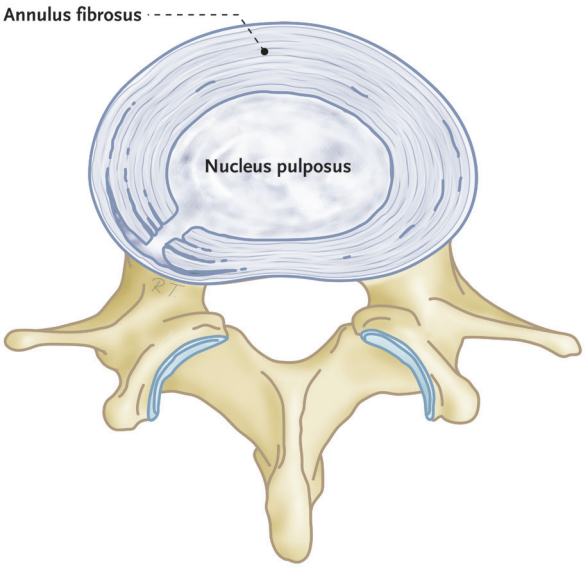

Figure 2. Discus intervertebralis with tears and fissures in the annulus fibrosus. Illustration: Rogier Trompert Medical Art. http://www.medical-art.eu.

Grades 0 and 1 are almost never painful. In Grade 3 annulus ruptures, more than 75% of the discographies are accompanied with exact reproduction of concordant pain. On the other hand, it has been shown that in pain reproduction during discography, 77% of the disci intervertebrales have an internal morphology with a Grade 3 rupture. This concordant pain is also present very intermittently in Grade 2 ruptures.

Chemical changes. There are two types of chemical changes that occur in the degenerative discus. First, a fracture in the vertebral endplate can lead to the introduction of inflammatory cytokines in the NP. This inflammation response changes the delicate nutrient balance in the nucleus, resulting in diminished oxygen diffusion, increase in local lactate concentration, and decrease in pH inside the discus.

In some cases, the cytokines themselves can be the source of pain, and outer annular rupture may facilitate the "leakage" of these inflammatory mediators to the adjacent epidural structures such as the ligamentum longitudinale posterius, dura, and ganglion spinale (dorsal root ganglion, DRG). The ingrowth of nociceptors into the deeper layers of the discus may sensitize the discus to normal mechanical loads. In addition, irritation of the nerve endings in the VE can produce pain. All or some of these mechanisms may cause a "chemically or mechanically" sensitized discus.[28]

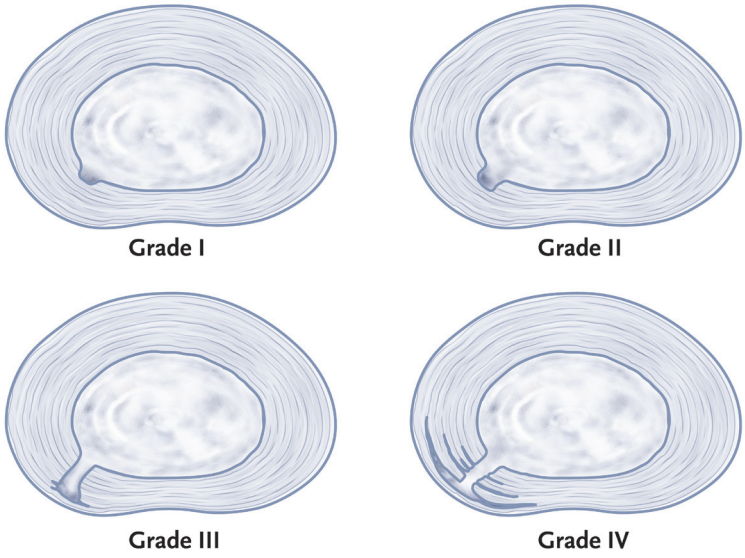

Figure 3. Gradation of the radial fissures visible on CT discography. Illustration: Rogier Trompert Medical Art. http://www.medical-art.eu.

Lumbar Discography

Definitions. Stimulation of a discus intervertebralis is a procedure that was developed for the purpose of confirming or refuting a clinical hypothesis of discogenic low back pain. The procedure is performed by inserting a needle in the NP of the target discus and injecting contrast agent (or another suitable medium) in order to test the sensitivity of the discus to gradually increasing distending pressures.

Discus stimulation is the more accurate name for a procedure that until now has often been described as (provocative) discography.

Discography is a procedure in which a contrast agent is introduced into the nucleus of a discus with the goal of describing the morphology of that discus.

Discography thus differs from disc stimulation—a procedure in which attention is focused on the reaction of the patient. Discus stimulation is usually followed by discography in order to verify the correct needle position or to elucidate the internal morphology of the discus. A combination of these definitions could be called provocative discography.

Patient selection. Suitable patients for this procedure are those with chronic low back pain, with or without pseudo-radicular referral, which lasts for longer than 3 months and which does not react to medication, transcutaneous electric nerve stimulation (TENS) and other conservative measures, and for which minimal invasive treatments of the facet joints and the sacroiliac joints do not prove to be effective or are not sufficiently effective. The implementation of the discography procedure is only advisable as a preparation for a possible interventional treatment aimed at reducing discogenic pain. An X-ray and an MRI of the lumbar spinal column must be performed not earlier than 6 months prior to the procedure.

Contraindications

Absolute
- absence of informed consent for discography (or other interventional treatments);
- local infection;
- pregnancy;
- local infection at injection site; and
- systemic infection

Relative
- allergy to contrast agent, local anesthetics, or antibiotics;

- known increased tendency to hemorrhage; and
- use of anticoagulants.

Procedure. Provocative discography is performed in the operating room under strict sterile conditions. Thirty minutes before the intervention, the patient is administered intravenous antibiotics (2 g cephazolin, i.v.). Many interventionalists also mix antibiotics within the intradiscally injected contrast at a concentration between 1 and 10 mg/mL (e.g., 3 mg/mL cephazolin). The administration of antibiotics for the prevention of a discitis is disputed.[29] In their review, Willems et al. indicate that the side effects of antibiotics (allergic reactions) are even greater than the potential benefits and advise against administering antibiotics.[29] Yet currently, international consensus exists to administer periprocedural antibiotics as part of the discography procedure. The most important condition for the prevention of a discitis is observance of strict sterile technique.

Position. In the operation room, the patient lies in the prone position on an X-ray permeable table.

Sterility. The skin of the low back and the gluteal region is thoroughly disinfected. The operator and the assistant must wash their hands according to the local protocol of the hospital and must wear protective clothing (surgical caps, surgical jackets and sterile gloves). After the injection point has been marked, the patient is covered with a sterile drape. The same must be done with the C-arm. Due to the limited rotation of the C-arm, it must be located on the side of the patient where the needle will be inserted.

Level determination. The levels to be examined are chosen based on a combination of patient history, physical examination, and additional examinations. The symptomatic level and the two adjacent levels are examined. Heretofore, the one or two adjacent disci intervertebrales serve as control levels, although recent evidence[30] showing a ~20% increase in long-term degenerative changes on the side of needle puncture may preclude needle puncture of MRI normal-appearing discs for the sole purpose of a control level. Typically, the least degenerated or more likely asymptomatic levels are studied first. The patient should be blinded to the discus level and should not be aware of the start of the discus stimulation. The patient should preferably be only be lightly sedated during the procedure, but those on copious narcotics should be given a judicious dose so that their pain sensitivity is not exaggerated. The patient must be awake and able to reliably report during the discus stimulation.

The C-arm is first positioned with the direction of the radiation beam parallel to the subchondral plate of the lower vertebral plate of the discus. In the discs above L5-S1, the C-arm is then rotated ipsilaterally until the lateral aspect of the processus articularis

overlies the axial middle of the discus to be punctured (Figure 4), and the discus height is at its maximum. In this projection, the needle can be inserted parallel to the direction of the radiation beam and brought into position (tunnel view). The target for the puncturing of the AF is the lateral-middle side of the discus, just lateral to the lateral edge of the processus articularis superior (Figure 5).

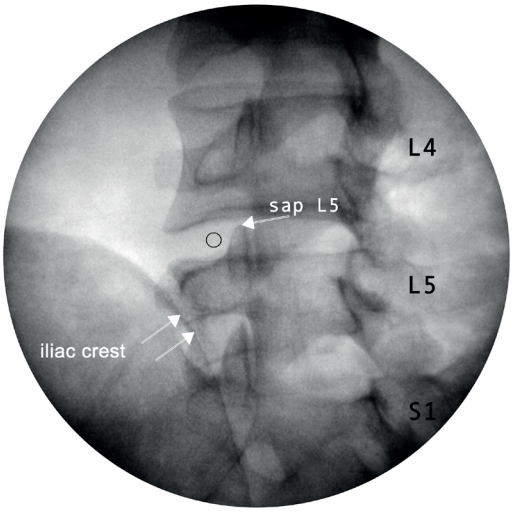

Figure 4. Starting point of the needle, assuming a maximal discus height, is such that the C-arm is rotated so that the facet column is between 1/3 and 1/2 of the corpus vertebrae. The injection point is then directly lateral to the processus articularis superior (superior articular process, sap).

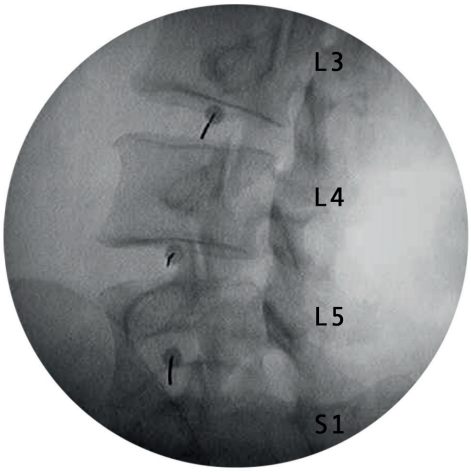

Figure 5. Needle position for an ideal discogram at the L3-L4, L4-L5, and L5-S1 levels.

At the L5-S1 level, the crista iliaca does not allow access to the discus using a down-the-beam approach. The fluoroscopy tube is rotated until the lateral edge of processus articularis superior of S1 is positioned approximately 25% over the posterior to anterior distance of the corpus vertebrae.

Needle positioning. A new needle is used for each discus to be examined. After anesthetizing the skin and the underlying tissue, a one-needle or a two-needle technique can be used to approach the discus. In a two-needle technique, a 20-G needle is advanced over the lateral edge of the processus articularis superior. A 25-G hollow needle is then inserted through this needle and into the AF until it reaches the middle of the nucleus. The two-needle technique may help reduce the incidence of discitis and allow entering the discus with needles of a small diameter (e.g., 27 G) which might help prevent the incidence of iatrogenic disc degeneration.[30]

The needle is carefully advanced to the needle-point end position. Beyond the processus articularis superior, the needle passes through the foramen intervertebrale in the vicinity of the ramus ventralis. In case of paresthesia, the needle must be repositioned. A strong resistance is felt as the needle passes through the annulus. The needle is pushed through the annulus to the center of the discus. The needle's progress is followed in various projections, first in AP and then in lateral projection (Figure 6). Ideally, after placement, the needle is situated in the middle of the disc's nucleus, as seen in the AP as well as in the lateral projection. Other examples are given in Figures 7 and 8.

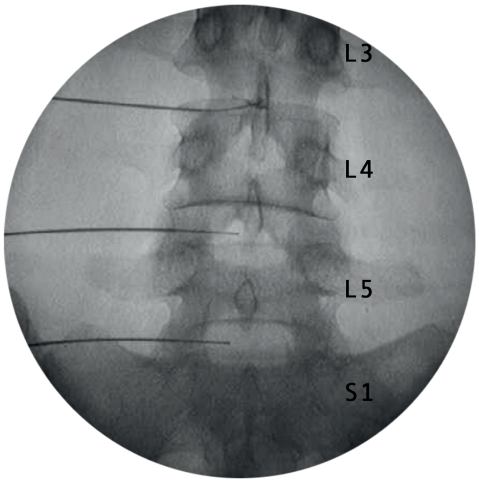

Figure 6. AP-position of the needles at discography in which the needles have been positioned in the middle of the nucleus pulposus

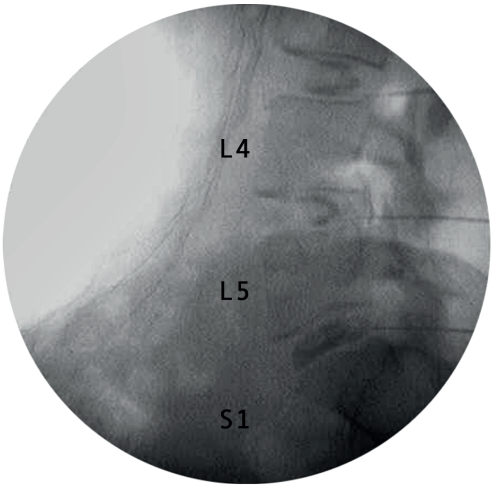

Figure 7. Discography at 3 levels where Grades 1 to 2 discs are visible at L3-L4 and L4-L5, and a discus with Grades 3 to 4 rupture is visible at level L5-S1

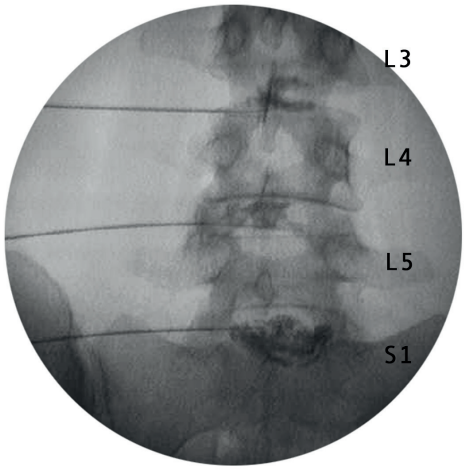

Figure 8. Discography at 3 levels: L3-L4, L4-L5 and L5-S1, all in anteroposterior view

Discus stimulation. After verification of the correct needle position, the stylet is removed from the needle and the needle is connected to a contrast agent delivery system which can measure the intradiscal pressure (manometry). The rate of infusion of the contrast agent should not exceed 0.05 mL/s.[31–33] This rate reflects a static flow that corresponds to the distension pressure in the discus intervertebralis. If a higher flow is used, false positive discographies can occur due to the resultant pressure peaks. Pain is often provoked by these pressure peaks due to vertebral end-plate compression and distention

of the adjacent facet joint. It is important that the discus expected to be most painful is stimulated last; the patient must not be able to see which discus is being stimulated. If the painful discus is stimulated first, it is possible that the echo of that pain lasts long enough to make adequate stimulation at other levels no longer possible. If these conditions have been met, the stimulation can be started.

The following parameters must be carefully monitored during the injection of the contrast solution: the opening pressure (OP), the pressure at which contrast is first visible in the discus; the provocation pressure, the pressure greater than the opening pressure at which complaints of pain arise; and the peak pressure or the final pressure at the end of the procedure. Ideally, pressure, volume, and provocation details are recorded at 0.5 mL increments, with additional notation made for the aforementioned events.

The procedure, per level, is continued until the following events:

- Concordant pain is reproduced at a level of 7 or greater (on a 0 to 10 numeric rating scale; NRS), and subsequent injected volume confirms the response.
- The volume infused reaches the 3.0 mL. (Up to 4 mL may be injected into a very degenerated discus when pressures remain less than 15 psi.).
- The pressure rises to 50 psi above opening pressure in discs with a Grade 3 annular tear.
- If contrast leaks through the outer annulus or through the endplates, one may not be able to pressurize the disc to a pressure sufficient to test the disc sensitivity. In these cases, the rapid manual injection may be acceptable, but must be noted and a negative response is a more defendable response.

Assessment criteria. The guidelines of the IASP (International Association for the Study of Pain), as well as those of the ISIS (International Spine Intervention Society), state that two levels must always be tested as controls when performing provocative discography (except if the target disc is that of L5-S1).[34–36] A disc is only considered to be provocative (positive) if concordant pain can be induced at the target level, and if the control levels were negative for provocation of pain.

Manometry: Overestimation of discogenic pain due to a false positive response to provocative discography is also possible. Asymptomatic discs, with over pressurization, may become painful because normally quiescent nociceptors and mechanoreceptors in the endplates and ligamenta longitudinales posteriores, and perhaps capsules of the facet joints, are stimulated. The diagnosis of discogenic pain can only be made if there is reproduction of concordant pain resulting from a pressure that does not produce pain in a normal disc or in an asymptomatic patient.

The concept and definition of a chemically sensitive discus was first described by Derby et al.[37] In 2004, O'Neill further described subgroups: discs with a pain threshold of 0 psi—these discs are described as chemically sensitive discs and [31] discs with a pain threshold of 1 psi or higher—these discs are considered to be pressure sensitive. Pain thresholds ≥ 50 psi above the opening pressure correlated with a 100% chance of a false positive discography, whereas pain thresholds between 25 and 50 psi above the opening pressure still lead to 50% false positive results. This chance of a false positive discus decreases to 14% in a pain-sensitive disc sensitive discus probably has a pain threshold of 1–9 psi above opening pressure or is considered a chemically sensitive discus (0 psi). The latter (chemically sensitive) discus intervertebralis is usually already extremely painful at the time of puncture. The classification of discs based on the pressure at which pain arises is illustrated in Table 2.

Morphologically, these discs are Grades 2 to 3 based on the Dallas Discogram Scale (Table 3). The inter- national (IASP and ISIS) guidelines are based on these operational criteria:

1. Absolute discogenic pain:
   - Stimulation of target discus reproduces concordant pain.
   - The intensity of this pain has a Numeric Rating Scale (NRS) score of at least 7 on an 11-point scale.
   - The pain is reproduced by a pressure of less than 15 psi above the opening pressure.
   - Stimulation of the two adjacent discs is not painful.
2. Highly probable discogenic pain:
   - Stimulation of target discus reproduces concordant pain.
   - The intensity of this pain has a NRS score of at least 7 on an 11-point scale.
   - The pain is reproduced by a pressure of less than 15 psi above the opening pressure.
   - Stimulation of one of the adjacent discs is not painful.

Table 2: Classification of discs on the basis of the pressure at which pain arises

• Discs that are painful at a pressure lower than 15 psi above opening pressure
• Discs that are painful between 15 and 50 psi above opening pressure
• Discs that are painful at greater than 50 psi above opening pressure
• Discs that are not painful in spite of the fact that the pressure is higher than 50 psi above opening pressure

Table 3: Assessment of the morphology of the disc using discography

Dallas discogram scale:	
Grade 0:	The contrast remains entirely in the nucleus pulposus.
Grades 1 through 3:	Indicate tears in which the contrast agent extends to the innermost, middle and outermost sections, respectively, of the annulus fibrosus.
Grade 4:	Here the Grade 3 fissure has expanded into an arc-shaped tear -outside of or in- the innermost ring of the annulus.

3. Discogenic pain:
   - Stimulation of target discus reproduces concordant pain.
   - The intensity of this pain has a NRS score of at least 7 on an 11-point numerical scale.
   - The pain is reproduced by a pressure of less than 50 psi above the opening pressure.
   - Stimulation of the two adjacent discs is not painful.
4. Possible discogenic pain:
   - Stimulation of target discus reproduces concordant pain.
   - The intensity of this pain has a NRS score of at least 7 on an 11-point numerical scale.
   - The pain is reproduced by a pressure of less than 50 psi above the opening pressure.
   - Stimulation of one of the adjacent discs is not painful, and stimulation of another discus is painful at a pressure greater than 50 psi above the opening pressure, and the pain is discordant.

Given that a strict selection process will improve the outcome of minimally invasive and surgical treatments, the goal must be to strive toward criteria 1 and 2 for the purpose of concluding that 1 and/or 2 discs are actually positive.

During discography the distribution of the contrast agent is monitored via lateral and AP radiographic examination.

Postoperative care. After the discography, the patient goes to the ward or to the recovery room. The patient may be discharged if the pain is under control and there are no signs of loss of neurological function. The patient may experience worsening of the pain symptoms in the first postoperative days and should be prescribed pain- relieving medication. The patient should be instructed to contact the doctor immediately if she/he experiences an increase in symptoms, loss of neurological function, and/or fever.

Differential diagnosis

The differential diagnosis is first and foremost directed at ruling out *red flags*, such as trauma and fractures, infection, tumors, and neurological complications. Thereafter, one strives to rule out visceral pain. Before making a decision about the interventional treatment plan, it is important to demonstrate that the discus intervertebralis is the cause of the (pseudo-) radicular pain.

Treatment options

Conservative management

There are no known studies that have demonstrated that long-term antinociceptive medication has any significant positive effect in patients with discogenic low back pain. Generally, medication such as NSAIDs and weak opioids are recommended for a limited time (maximum of three months).[38] A systematic review found no evidence for the added value of active exercise therapy in relation to inactive treatment (bed rest) and other conservative treatments such as traction, manipulation, hot packs, or corsets.[39,40]

Interventional management

In the last few years, various minimally invasive treatments have been advanced to treat discogenic pain, such as intradiscal injections, IDET (intradiscal electrothermal therapy), disctrode, biacuplasty, intradiscal radiofrequency (RF) thermocoagulation, and RF treatment of the ramus communicans. Several small-scale prospective and anatomical studies have been published recently concerning the possible role of nucleoplasty in chronic discogenic low back pain. In spite of the fact that these minimally invasive treatments may be an effective alternative to surgical treatments, they remain experimental. The definitive value of these treatments must be determined in the coming years with randomized, controlled studies.

Intradiscal Corticosteroid Injections

The goal of intradiscal corticosteroid injections is the suppression of the inflammation that is considered to be responsible for discogenic pain. The literature on this topic is limited to case reports that only yield positive results. However, positive and negative results are been found in prospective studies. Butterman published in 2004 a prospective study comparing patients with degenerative discus disease (DDD) and end-plate inflammatory changes on MRI (Modic Type-1) with a patient group having DDD and no end-plate

inflammatory changes. The group with Modic Type-1 changes had significantly better results after intradiscal steroid injection compared with the group without Modic Type-1 changes.[41]

In 1992, Simmons published a study in which 25 patients received 80 mg methylprednisolone intradiscally versus a control group to whom 1.5 mL bupivacaine (0.5%) was administered.[42] No significant difference was found between the two groups. Khot et al. published a comparable study of 12 patients in which, after positive discography, the patients were randomly divided into two groups.[43] In one group, intradiscal corticosteroids were administered, and in the control group, physiological saline solution was administered. The authors concluded that intradiscal corticosteroids do not improve clinical outcomes in patients with discogenic low back pain relative to placebo.[44] Intradiscal injections with other chemical substances are being investigated. Klein et al. published a pilot study in which a glucosamine and chondroitin sulfate solution combined with hypertonic dextrose and dimethyl sulfoxide (DMSO) were injected intradiscally.[45] It has been suggested that the injection of these substances synergistically promotes the hypermetabolic response of chondrocytes and retards the enzymatic degradation of cartilage. The authors reported positive results in the VAS score and in the "disability score". Derby et al. performed a comparable study in which he described effects analogous to those of IDET.[46] Given that this was only a pilot study, we must wait for RCTs to be able to make a judgment about the effect of these injections.

Intradiscal Electrothermal Therapy (IDET)

Saal and Saal published the first use of IDET for discogenic pain. The procedure consists of percutaneous insertion of a thermocoil into the discus under radiographic examination.[47] The catheter must be placed along the internal aspect of the posterior annulus. The distal portion of the catheter (5 cm) is heated for 16 min to 90°C. Experimental veterinary studies have demonstrated that this will result in temperatures exceeding 60°C in the posterior annulus and to a possible local denervation.

The first results were promising, with 50–70% of the patients experiencing significant pain reduction. Recent controlled studies are fueling much discussion about the actual effectiveness of this treatment.[48,49] Concerning this, it must be said that it is unclear whether the inclusion criteria of the patients was selective enough, and whether the discography was considered the most important method of selection in conformity with what has already been described in this chapter.

Pauza et al. performed a randomized, placebo-controlled prospective study of the effectiveness of IDET in the treatment of chronic discogenic low back pain.[50] His group

screened 1,360 patients with low back pain; 64 of these patients were selected for study after positive discography results. Thirty-seven patients were randomized to the IDET group, and 27 patients to the sham group; the IDET catheter was inserted into the sham group, but without application of the RF current. Patients in both groups indicated improvement. In the IDET group, the average improvement in pain score, disability, and depression scale was significantly higher. Approximately 40% of the IDET group patients had an improvement of more than 50% in their pain scores. The NNT (number needed to treat) to reach more than 75% pain reduction was 5. These results suggest that the results of the IDET treatment cannot be completely ascribed to the placebo effect. These results also correspond with the results of various small-scale prospective study populations, which allow one to conclude that IDET can be effective in chronic, discogenic low back pain in a population selected with strict criteria. Pauza used the following inclusion criteria: age between 18 and 65 years, back pain more severe than leg pain, duration of pain symptoms at least 6 months, no improvement after a minimum of 6 weeks of conservative treatment (including medication, physical therapy, rehabilitation), back pain worsens with sitting and standing and is lessened by lying down, a score lower than 20 on the Beck Depression Inventory, no surgical interventions in the last 3 months, and less than 20% loss of disc height in the lumbar spine. In discography, the symptomatic level is indicated by way of negative control levels. A relative contraindication was obesity.

In 2006, Appelby et al. published a systematic review of the literature, and concluded that there was sufficient evidence for the effectiveness and safety of the IDET procedure.[51] Contrary to Appelby's report is that of Freeman et al.[51] This group took a very critical look at the existing literature, and came to the conclusion that the evidence for the effectiveness of the IDET procedure was weak and had a scientifically insufficient foundation. To date, a positive RCT, a negative RCT, various positive prospective studies, and two negative studies have been published. Notably, the fact that no more than two discs are degenerative is important. The outcomes in the cases with more extensive discus degeneration have been shown to be significantly worse. A serious limitation among the available IDET studies is that the selection criteria do not concur: a critical factor for achieving useful results. New studies with internationally defined inclusion criteria are needed in order to arrive at definitive judgments about the clinical effectiveness of the IDET procedure. The mechanism by which IDET might act is not yet known. Two hypotheses have been proposed. The first hypothesis assumes that electrothermal therapy of the annulus produces local pain reduction by way of denervation of the nociceptors. The second mechanism proposed states that changes occur in the structure of the collagen fibers in the annulus due to heating; these changes improve the stability of the annulus. As of yet, there is little histological proof to support this hypothesis.
The following are described as complications: catheter breakage, nerve injury (cauda equina lesion), post- IDET spinal disc herniation, discitis, local infection, epidural abscess.

Biacuplasty

Intradiscal biacuplasty is the latest in a series of minimally invasive posterior annulus heating techniques. This technology works specifically by concentrating RF current between the ends of two straight probes. Relatively even heating over the larger area of the posterior annulus is achieved by internally cooling the electrodes.[52,53]

The procedure is completed under fluoroscopy, with the patient lying in the prone position. Two TransDiscal 18 G electrodes via introducers are placed bilaterally in the posterior annulus of the discus intervertebralis. The generator controls the delivery of RF energy by monitoring the temperature measured by a thermocouple at the tip of the probe. The temperature increases gradually over a period of 7–8 min to 50°C, with final heating at 50°C for another 7 min. It should be noted that although the temperature is set to 50°C on the RF generator, tissue temperature reaches 65°C due to ionic heating. During this time, the patient should be awake and able to communicate with the physician.

First, two pilot studies involving 8 and 15 patients demonstrated significant pain relief following the discus biacuplasty procedure at 3, 6, and 12 months.[54] In the European case series involving 8 patients, there was an average of about 50% pain reduction at 3 months, with overall good patient satisfaction. In the prospective pilot study involving 15 patients, Kapural et al. reported patient improvements in several pain assessment measures after undergoing discus biacuplasty procedure for discogenic pain.[54] Results from these pain assessment measures included a reduction in the median VAS pain score from 7 to 4 at 1 month, which remained at a level of 3 at 6 and 12 months follow-up, improvement in Oswestry index from 23.3 to 16.5 points at 1 month, which remained similarly improved after 12 months, and an increase in the SF-36 Bodily Pain score from 38 to 54 points.[54] Pilot studies and case series, even when designed as prospective trials, tend to exaggerate the positive outcomes. Therefore, we await results of sham controlled, prospective randomized studies before accepting or refuting this approach to the treatment of discogenic pain. Still, intradiscal biacuplasty may hold several advantages over previous techniques. There is minimal disruption to the native tissue architecture, and thus the biomechanics of the spine are likely unchanged. Additionally, the relative ease of electrode placement eliminates the need to thread a long-heating catheter (e.g., compared with IDET).

Intradiscal Radiofrequency (RF) Thermocoagulation

Intradiscal RF thermocoagulation is used for the treatment of discogenic pain. Barendse et al. performed a double-blind, randomized prospective study on 28 patients.[55] The discogenic pain diagnosis was made on the basis of the injection of a mixture of 2 mL lidocaine (2%) with contrast agent. Patients who indicated more than a 50% reduction in pain within 30 min were included and randomized into 2 groups. Patients in the RF group (n = 13) received an RF treatment of the discus intervertebralis lasting 70 s at 90°C in which the needle was placed in the center of the discus. Patients in the control group underwent the same procedure, except that no RF current was administered. Eight weeks after the treatment, there was no difference between the VAS scores of the two groups for pain and global perceived effect, or in the Oswestry Disability Index. The conclusion was that RF is ineffective for the treatment of discogenic pain. Two important remarks can be made about this study. First of all, the discography was not performed using a method that is currently accepted. It has subsequently become clear that discogenic pain is caused by nociceptors that are found in the outermost layer of the annulus. Heating the center of the nucleus will not necessarily lead to the destruction of nociceptors in the annulus.

Ercelen et al. performed another randomized prospective study with RF for discogenic pain using an improved selection and treatment method.[56] Ercelen's group selected 39 patients on the basis of a provocative discography. These patients were randomized into 2 groups. In the first group, the discus was heated for 360 s to 80°C; in the other group, for 120 s to 80°C. In this study, there were also no significant differences in pain reduction and functionality.

Recently a new intradiscal RF method has been introduced—discTRODE™ (Valleylab, Boulder, CO,U.S.A.). The DiscTrode is positioned along the posterior interface between the nucleus and the annulus. In an open trial, Erdine et al.[57] found improvement of symptoms as measured by the SF-36 and the VAS score in 10 of 15 patients (66.6%). Finch et al. reported a case- control study of 46 patients with mono-discopathy with an annular tear confirmed by means of a provocative discography.[58] Thirty-one patients underwent the disc treatment with heat via the DiscTrode, and 15 patients functioned as control group. In the control group, conservative treatment was continued. The VAS score was significantly reduced in the RF group, and this reduction persisted for 12 months. In the control group, the VAS score did not change. The authors concluded that heating the annulus, particularly at the level of the annular tear, can potentially be a good alternative for the treatment of discogenic pain. More recently, Kvarstein et al.[59] published a randomized controlled trial comparing intra-annular RF to sham treatment. The authors concluded that there was no beneficial effect of DiscTrode compared with the sham group. Another conclusion was the advice not to use the DiscTrode because of the high number of patients with increased

pain in the treatment group.[59] However, the study of Kvarstein et al. was criticized for its lack of power and the fact that the study was terminated early.[60] This technology proved to be ineffective in improving functional capacity and VAS scores when compared with IDET during the study where strict patient selection criteria were employed.[61]

Ramus Communicans Block

Discogenic low back pain could be considered to be deep somatic pain, if viewed from its neural origin. However, the innervation of the discus shows a multisegmental origin. As described above, the sensory nerve fibers reach the spinal cord via adjacent and more distant rami communicantes and ganglia spinalia (dorsal root ganglia, DRG's) (Figure 1). Based on the work of Groen et al., Ohtori's group recently demonstrated that in rats the low lumbar intervertebral discs are chiefly innervated by L1-L2 ganglia spinalia (DRG's) via the truncus sympathicus and the ramus communicans.[6,62] Fibers from the L3-L6 ganglia spinalia (DRG's) directly innervate the LLP via the nervi sinuvertebrales. Nakamura et al. looked at the afferent pathways that could be responsible for the discogenic low back pain by selectively blocking the L2 root in 33 patients.[9] On the basis of these findings, the authors concluded that the L2 segmental nerve could possibly be the most important afferent pathway for discogenic pain of the low lumbar discs, mainly by way of sympathetic afferent fibers of the nervi sinuvertebrales. Infiltration of the L2 root can then also be useful as a diagnostic procedure and as a therapy.

A block and destruction of the ramus communicans is also described as a treatment for discogenic low back pain or for pain in the vertebra itself.[63] Chandler et al. described the ramus communicans block as being an effective treatment for pain originating from a vertebral compression fracture.[64] Oh and Shim investigated the effectiveness of RF thermocoagulation of the ramus communicans in 49 patients.[7] These patients had chronic discogenic low back pain at 1 level, and had previously received no effect from an IDET treatment. Patients were randomized into an RF group and a control group. The control group received a lidocaine injection near the ramus communicans without RF. After 4 months, there was significant improvement in VAS scores and improvements in the Short Form (36) Health Survey (SF-36) in the RF group relative to the control group. The authors concluded that the RF thermocoagulation of the ramus communicans could be considered as one of the treatments for discogenic low back pain.

In spite of the promising initial results, further randomized studies of the effects of the ramus communicans block on discogenic pain are also needed in this case. A number of questions must still be answered. What is the definitive role of L1-L2 in discogenic low back pain; what is the role of the ramus communicans in this? Which patients react best to a ramus communicans block, and how long is this treatment effective?

Other interventional techniques.

Although this overview is not complete, the following techniques have been used frequently in the past. In chemonucleolysis, the enzyme chymopapain is injected into the discus intervertebralis; as a result, the NP is dissolved. This therapy has been almost completely abandoned due to problems related to dosage reliability, difficulties with the supply of chymopapain, and a number of serious complications. Otherwise, the treatment appears to be effective as demonstrated by various RCT's.[65]

Automated percutaneous lumbar nucleotomy (APLD) is a technique in which a section of the nucleus is mechanically removed percutaneously in order to effect decompression of the nucleus. However, the technique has been proven to be less effective in comparison with other treatments, and is therefore not advised.[65] A more modern variant of percutaneous nucleotomy using the Dekompressor™ (Stryker Corp., Kalamazoo, MI, U.S.A.) is still being used; it has a smaller diameter than the original APLD apparatus. There is no evidence present in the literature for this technique, and until otherwise shown, it can be considered to be the same as the classic APLD. Percutaneous laser disc- decompression (PLDD) is a treatment method that has been utilized on a large-scale world-wide since the beginning of the 1990s. Laser heat is used to bring about the evaporation of nuclear material. Unfortunately, until now, only case series have been reported.[65] Currently, the following techniques are applied most often worldwide: Nucleoplasty® (Arthrocare, Stockholm, Sweden), Ozone Discolysis, Targeted DISC Decompression, and the aforementioned Dekompressor™.

Percutaneous intradiscal treatments for disc herniation

As previously mentioned in the introduction, there is a clear overlap of the clinical signs of discogenic lumbago and the symptoms of spinal discus herniation. Discus herniation usually leads to a combination of discogenic lumbago and radicular leg pain. There seems to be evidence of a complex interaction between biochemical factors originating from the NP of the discus intervertebralis and mechanical factors (nerve root compression), which together cause the pain. Also, see the practice guideline on radicular pain.[66]

The goal of epidural injection of steroids in cases of herniated discus is primarily anti-inflammatory and therefore pain lessening. The goal of this treatment is rapid reduction in pain symptoms compared with a conservative treatment. The treatment must be considered conservative during the natural course of the acute lumbosacral radicular syndrome, which is the result of a discus herniation. In the long term, there are no differences in outcome in comparison with conservative treatment without epidural injection of steroids.

The differences between conservative treatment and operative discectomy are also not demonstrated in the long term. Operative discectomy is nonetheless utilized on a large scale. The reason for this is that the intervention can often lead to a more rapid reduction in symptom complaints when compared with a conservative treatment policy.[65] The disadvantages are the operative and anesthesiological risks and the risk of epidural adhesions, which are associated with the so-called postlaminectomy syndrome, or the failed back-surgery syndrome. Otherwise, the indications for operative discectomy are larger discus protrusions and extrusions that show signs of nerve root compression on MRI. Smaller, focal protrusions without nerve root compression appear to be less apt to spontaneously resorb and have a less favorable natural course; in other words, these small hernias often produce long-term pain symptoms with a slow spontaneous recovery.[67]

Over the years, the aforementioned considerations have led to various percutaneous, minimally invasive intradiscal techniques directed at the mechanical factor of discus herniation with the underlying idea of capitalizing on the advantages of operative therapy with as few of the disadvantages as possible. Most of these techniques—in contrast to the surgical discectomy— have the common goal of decompressing the nucleus so that there is a change in volume and an accompanying reduction in the pressure on the nerve and/or a lessening of the inflammatory reaction as a result. For these purposes, these techniques are usually only possible in the case of a so-called "contained" hernia.

Nucleoplasty.

The decompression method utilizes "coblation," in which a high-energy plasma field is generated with the help of a bipolar RF probe. This plasma field breaks molecular bonds. For this reason, the technique is also called plasma disc decompression (PDD). Tissue can be evaporated in this way at relatively low temperatures (40 to 70°C). However, the plasma field can only arise in conductive surroundings. In practice, this means that the treatment is not effective in a dehydrated discus ("black disc" on MRI). After a 16-G needle has been positioned in the nucleus, the probe is moved back and forth and rotated intradiscally. In this way, 6 or more tunnels are made in the nucleus, and the intradiscal pressure drops. Meanwhile, the treatment has been utilized on a large scale, and the complication level appears to be low and acceptable.[68–70]

Percutaneous Disc Decompression Using Dekompressor™

The percutaneous disc decompression (Dekompressor™) technology extracts nuclear discus material by an auger within a cannula that ends inside the nucleus. A significant change in intradiscal pressure should follow the reduction of nuclear volume within the closed hydraulic space. It is imperative that the annular wall should be intact in order

to retract the bulging section. Therefore, provocative discography may occasionally be needed to confirm the affected level and to rule out any annular disruption. In their case series, Alo and colleagues reported an 80% success rate with this technique.[71] Although there are no controlled studies published on Dekompressor efficacy, a European study reported also pain score improvements in the majority of patients treated with Dekompressor. This seems to suggest that patients with posterolateral foraminal discus protrusions can typically expect more pain relief than those with posteromedian ones.[72] There are no randomized, sham studies on percutaneous discectomy using Dekompressor device.

Ozone discolysis.

Ozone discolysis consists of the injection of a mixture of O_3 and O_2, usually both intradiscally, as well as epidurally. As a result, an oxidative dehydration takes place in the nucleus; this is comparable with chemonucleolysis by means of chymopapain. In addition, upregulation of the intracellular antioxidant scavenger system occurs due to oxidative stress; this results in an increase in the endogenous anti- inflammatory response.[73] In addition to various large case series with remarkably good results, two comparative studies have been published.[74,75] In Gallucci's study, intradiscal and transforaminal epidural corticosteroid injection is compared with intradiscal transforaminal epidural steroid injection with the addition of an O_3/O_2 mixture.[76] Bonnetti et al. had already published a comparative study examining transforaminal epidural injection of an O3/O2 mixture versus transforaminal epidural steroid injection.[77] In both studies, ozone resulted in a significantly better effect than corticosteroids. There are no significant complications of the technique described. Ozone discolysis can be utilized for "contained," as well as for "noncontained" spinal discus herniation. The extent to which the degree of discus degeneration has an influence on the clinical result is not yet clear. Although the technique is primarily meant for spinal discus herniation with prominent radicular pain, it is also utilized for discogenic lumbago associated with spinal discus herniation.

Targeted Disc Decompression (TDD).

This technique stems from the IDET technique for discogenic lumbago. In connection with the IDET technique, there have been some reports of unintentional shrinking of the size of discus protrusions as an effect of the technique. TDD makes use of just this property. The catheter used has approximately the same configuration as an IDET catheter; however, the active zone, where coagulation of discus tissue occurs, is markedly shorter. The goal is to position the active zone on the annulus-nucleus boundary at the point of the "contained" protrusion. Given that this technique is a thermocoagulation, the degree of hydration of

the nucleus is, in principle, not important. Although the technique is increasingly utilized and appears to provide good results, no literature has as yet been published about TDD.

Evidence for New Developments

The techniques described in new developments above are currently being investigated for effectiveness and complications. At this time, it does not appear to be possible to formulate an evidence rating and recommendations.

Complications of interventional management

Although all these procedures are associated with minimal tissue damage, a short recovery time, and low infection risk, various rare complications have been reported such as catheter breakage, nerve root injuries, post-IDET discus herniation, discitis, radicular pain, severe headache, cauda equina syndrome, and vertebral body osteonecrosis.[59] The most important complication of minimally invasive intradiscal procedures is discitis. The incidence is very low at 0.25% to 0.7%.[29,78] Any patient who complains about increased pain within 1 week after the procedure must be carefully examined. At the very minimum, this examination must include patient history, physical examination, and laboratory examination (infection parameters). If the infection parameters are elevated or abnormal, or in case of doubt, an MRI must be performed in order to rule out discitis.

Staphylococcus aureus is the major cause of discitis. The chance of discitis can be reduced by the routine prophylactic use of intravenous or intradiscal antibiotics. Sharma et al. reviewed the literature and described that the chance of discitis is reduced from 2.7% to 0.7% with the use of the "through the needle technique"; in this technique, the needle is advanced through the skin until the annulus is reached, and another thin needle (25 G) is then advanced through the first needle into the discus.[78] Willems published a 0.25% incidence of discitis in a series of 4,981 patients on which the "through the needle" technique was used and to whom no prophylactic antibiotic were administered.[29] They also concluded that the routine use of antibiotics is not necessary for this procedure. However, the international guidelines currently prescribe routine use of periprocedural prophylactic antibiotics.

Evidence for interventional management

A summary of the available evidence is given in Table 4.

Table 4: Evidence of interventional pain management of discogenic pain

Technique	Assessment
Intradiscal corticosteroid administration	2 B -
Radiofrequency treatment of the disc	2 B -
IDET (Intradiscal Electrothermal Therapy)	2 B ±
Biacuplasty	0
Disctrode	0
RF ramus communicans	2 B ±

Recommendations

Intradiscal corticosteroid injections and RF treatment of the discus are not advised for patients with discogenic low back pain. The current body of evidence does not provide sufficient proof to recommend intradiscal treatments, such as IDET and Biacuplasty for chronic, non-specific low back complaints originating from the discus intervertebralis. We are also of the opinion that at this time the only place for intradiscal treatments for chronic low back pain is in a research setting. RF treatment of the ramus communicans is recommended.

Clinical practice algorithm

Figure 9 illustrates the practice algorithm for the management of low back pain of discogenic origin.

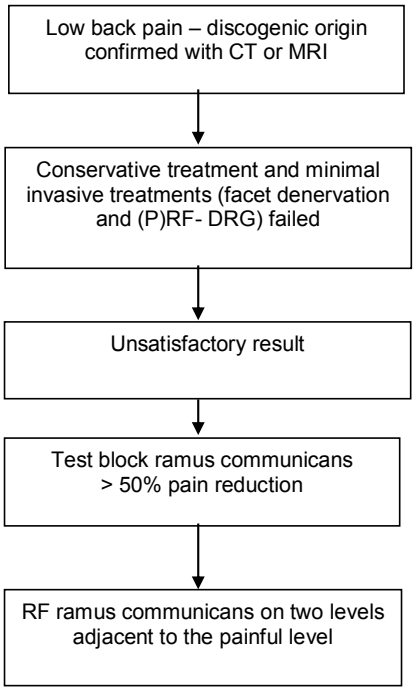

Figure 9: Practice algorithm for the interventional treatment of discogenic pain

Techniques

IDET

The procedure takes place under sterile OR conditions on a patient lying in the prone position with the aid of radiographic examination. While administering prophylactic antibiotics, a 17 G needle is inserted posterolaterally into the discus, generally on the side with the least complaints. Thereafter, a 30 cm-long catheter with a flexible tip, 5 cm of which can be heated, is advanced through the needle. This tip is advanced circumferentially through the NP until it covers the entire posterior section of the annulus. After placement of the tip has been checked radiographically, the tip of the catheter is heated for 18 min to 90°C according to a standard protocol. This temperature is reached after 14 min and is then maintained for 4 min at this level. Then the needle and the catheter are removed, and the patient can be discharged after the recovery period. If during the procedure, the patient complains of leg pain, it is possible that a spinal nerve is being irritated. In this case, the heating process should be immediately terminated. After the procedure, the patient must follow a strict 12-week long rehabilitation protocol. In patients with a large

tear in the annulus, it may appear to be impossible to maneuver the catheter into the correct position.

Ramus Communicans

Diagnostic block. The C-arm is positioned in such away that the direction of the radiation beam in the transverse plane is approximately 20° oblique such that the facet joints are projected away and the vertebral column is clearly visible. For the angle in the sagittal plane, the C-arm is rotated on its axis. As a result, the processus transversus changes location relative to the corpus vertebrae. The direction of the radiation beam must be such that the axis of the processus transversus lies slightly above the middle of the corpus vertebrae. Usually, an SMK-C15 cannula (Radionics, Burlington,MA, U.S.A.) is used for this procedure. An injection point is marked just caudally to the processus transversus, and somewhat medially to the lateral edge of the corpus vertebrae. After local anesthetization of the skin, the needle is advanced using a tunnel view, for which the general rules of this technique must be observed; in other words, corrections to the direction of the needle must be made while the needle is in the superficial layers, and the depth of the needle must be checked regularly on the lateral projection. Do not try to make contact with the processus transversus. The needle is advanced until contact is made with the corpus vertebrae. On the lateral projection, the point of the needle lies somewhat ventral to the posterior side of the corpus vertebrae. Contrast agent (0.5 mL) is then injected. On the anteroposterior projection, this usually results in a very compact shadow; on the lateral projection, the contrast agent spreads anteriorly over the corpus vertebrae. In case of intravascular dispersal, a minimal change in position is usually sufficient. Finally, 1 mL lidocaine (2%) is injected.

RF treatment. An SMK-C15 cannula with a 2 mm active point is used. Fluoroscopy and the insertion of the needle conform completely with the technique described for the diagnostic block. When the needle has been correctly positioned, stimulation at 50 Hz causes sensations in the back at a voltage of < 1.5 V.Thereafter, 2 Hz stimulation is applied. Contractions of the leg muscles may not be allowed to occur at below twice the value of the sensory threshold. If these conditions are not met, then the needle is moved slightly laterally and anteriorly until a safe position has been achieved. A RF treatment is made for 60 s at 80°C.

The L5 level. This level deserves special mention since the anatomical relationships can require an adapted technique. This can be the result of a high crista iliaca or of a broad processus transversus. In these cases, the L5 segmental nerve exits the foramen intervertebrale more horizontally than the other lumbar nerves do. While adjusting the C-arm axially, it is best to project the processus transversus as high as possible. By doing

so, a safe needle position can often be found for this level. Nevertheless, the intervention at this level is not possible in all cases.

Summary

Lumbar discography, provocative discography, and disc manometry are all examinations whose goal is to determine whether a discus intervertebralis is the cause of patient's pain symptoms. In spite of the unceasing stream of contradictory literature, provocative discography remains the gold standard for the determination of the diagnosis of discogenic pain. For the purpose of improving the results of minimally invasive intradiscal treatments, it is important to use a strict selection process to select discography patient's and to perform discography with manometry. It must be noted that the studies performed up to now have not included patients selected in the correct manner generally, and in particular by not adequately performing discography. This has certainly not had a positive influence on the results. For the treatment of discogenic pain, a RF treatment of the ramus communicans can be recommended.

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CHAPTER 2b

2b

“Evidence-based interventional pain medicine according to clinical diagnoses”: Update 2018. Discogenic pain

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Abstract

The numerous publications since the latest literature search of the previous guideline justified an update. The literature was retrieved by an independent 3rd party, who also assessed the quality of the evidence according to the GRADE methodology. The current guideline focused on the evidence for minimal invasive treatment options for several indications including chronic discogenic low back pain.

Recommendations

Description	Strength of recommendation	Level of evidence
Intradiscal methylene blue injection could be used in a carefully selected patient group with chronic discogenic low back pain. *	Weak	Moderate

Description	Strength of recommendation	Level of evidence
Intradiscal corticosteroid injections could **not** be used for the treatment of discogenic pain.*	Weak against	Low

Description	Strength of recommendation	Level of evidence
Conventional intradiscal radiofrequency treatment could **not** be used for the treatment of discogenic pain. *	Weak against	Low

Description	Strength of recommendation	Level of evidence
Intradiscal electrothermal therapy could be used for the treatment of chronic low back pain of discogenic origin. *	weak	low

Description	Strength of recommendation	Level of evidence
Radiofrequency treatment of the ramus communicans could **not** be considered for the treatment of low back pain of discogenic origin.	Very weak, against	Very low

Description	Strength of recommendation	Level of evidence
Intradiscal pulsed radiofrequency treatment could be considered for the treatment of low back pain of discogenic origin in selected patients.*	Very weak	Very low

Description	Strength of recommendation	Level of evidence
The treatment of low back pain of discogenic origin with intradiscal biacuplasty should be used in a highly selected group of patients. *	Moderate	Moderate

* refers to the risk of accelerated disc degeneration, disc herniation, loss of disc height and signal and the development of reactive endplate changes after punction of the intervertebral disc.
Additionally, the risk of discitis cannot be neglected

Introduction

The chapter discogenic pain is part of the series "Evidence-based interventional pain medicine according to clinical diagnoses: Update 2018". It is an update of chapter 2a.[1] For the update an independent 3rd party: specialized in systematic reviews was asked in 2015 to perform the literature search and summarize relevant evidence using Cochrane and GRADE methodology to inform guidelines on interventional pain management. The guideline committee reviewed the information and made a last update on March 1st, 2018. The information from new studies and additional observational studies was used to estimate other factors such as side effects and complications, invasiveness, costs and ethical factors, which influence the ultimate recommendations.

Clinical question

What is the place for minimal interventional pain treatments in the management algorithm for CD-LBP?

Researched treatment options

For patients with CD-LBP pain we studied the following treatments:

1: intradiscal methylene blue injection
2: intradiscal corticosteroid administration
3: RF treatment of the discus intervertebralis
4: biacuplasty
5: intradiscal electrothermal therapy (IDET)
6: RF of the ramus communicans
7: pulsed RF treatment of the discus intervertebralis
8: disctrode

Any comparators including sham, no treatment or other active treatment techniques were eligible. Inclusion was not restricted based on outcome.

Methods

For the search strategy and the methodology, we refer to the introduction.

Note *

A prospective, match cohort study of disc degeneration progression over 10 years with and without baseline discography showed that even small gauge needle insertion and limited pressurization for discography resulted in accelerated disc degeneration, disc herniation, loss of disc height and signal and the development of reactive endplate changes compared to match controls.[2]

An in vitro study on the effect of cortisone, lidocaine, and iopamidal on nucleus pulposus cells, showed that all three substances decreased the cell viability, cell count and proliferation.[3]

The risk for infection by bacteria introduced through the hollow needle placed in the intervertebral disc has been described. The resulting discitis is classified as potentially catastrophic. Infection within the disc space is a well-recognized complication of diagnostic discography.

The most common organisms identified are S. aureus and S. epidermidis. Strict sterile conditions should be observed when performing intra-discal procedures. Moreover it is recommended to use the double needle or "through the needle" technique.[1] The 1999 CDC Guideline for Prevention of Surgical Site Infection supports the use of routine antimicrobial prophylaxis during discography and other intradiscal treatment techniques.[4, 5] A study in a consecutive patient group who received discography with the double needle technique, but no prophylactic antibiotics showed that at 3 month follow-up there was no discitis in the 200 patients followed. A systematic review showed that discitis occurred in 0.25% of the patients or 0.094% of the discs.[6]

There is much debate about the prognostic and added value of performing a discography for patients with suspected CD-LBP.

In the absence of other evidence based prognostic indicators discography remains the golden standard in diagnosing CD-LBP for minimal invasive pain treatments.

Therefore , intradiscal procedures should only be performed in specialized centers, using prophylactic antibiotics and the "double needle" or "needle in needle" technique.

Results of literature search

Two systematic reviews were published between 2010 and 2015 on the described interventional pain management techniques for the treatment of CD-LBP.[7, 8] These were only used to check the reference lists.

Ten RCTs met the inclusion criteria for discogenic pain.[9-18]

Methylene blue injection

Literature overview

The use of methylene blue was not described in the previous guideline.[1]
One randomized controlled trial of methylene blue in 72 patients[15] found statistically significant reductions in pain and disability when compared to placebo at 6, 12 and 24 months. Adverse events were assessed and for 24 months follow up no patients had symptoms of nerve root injury or back pain exacerbation. No disc space infection and nerve root stab injury were found in either group. This was a high-quality trial according to the Cochrane risk of bias. All patients had failed conservative treatment over a period of at least six months and discogenic pain was confirmed using discography.

Conclusion

Quality of the evidence	Description
Moderate	There is evidence of moderate quality indicating that methylene blue injection into the intervertebral disc results in better pain relief than placebo injection at 6, 12 and 24 months. *Peng B et al 2010.*

Consideration

There are two additional prospective trials. The first[19] followed prospectively 20 patients whith discogenic pain refractory to conservative treatment who received intradiscal methylene blue injection. Fifty five percent of the patients had a successful outcome (pain

reduction and improved mobility) at 3 months. This effect seemed to wean off during time with only 20% of the patients having maintained effect at 12 months.

The second study was a prospective multicenter clinical series.[20] Sixteen consecutive patients were enrolled. Six months after the injection 40% had a 30% pain reduction. In patients who responded the physical function improved. No procedural complications were observed.

Bogduk mentioned in his editorial accompanying this study, that there remains skepticism about the results of the randomized controlled trial.[21]

Although the intradiscal injection of methylene blue seems to produce a clinically relevant effect, no complications are reported there is a risk for infection and disc degeneration in the short term.

The moderate level of evidence is based on one study. Moreover, the risk of early disc degeneration of this procedure is unknown. For that reason, the strength of recommendation has been downgraded.

Recommendations

Description	Strength of recommendation	Level of evidence
Intradiscal methylene blue injection could be used in a carefully selected patient group with chronic discogenic low back pain. *	Weak	Moderate

Intradiscal corticosteroid injection

Literature overview

The negative recommendation for intradiscal corticosteroid injections was based on case series with variable results and 3 controlled trials.[12, 22, 23] In one study patients with degenerative disc disease and end-plate inflammatory changes on MRI (Modic type-I) had a better outcome than patients without endplate inflammation.[22] Comparison of injection of methylprednisolone with injection of local anesthetic showed no difference between groups.[23] Another study compared intradiscal corticosteroid with intradiscal saline injection, no difference in outcome was noted.[12]

The current review found an additional RCT.[11] Patients were divided into two groups according to the degree of Modic changes (I and II) of the endplates and the degeneration of the disc. Patients in both groups were randomly assigned to one of the 3 groups, receiving saline, betamethasone, and betamethasone + peptide (a Chinese herbal medicine). In patients with Modic type-I changes saline did not produce improvement at 3 and 6 months, in the two active groups a significant improvement in pain and mobility was observed. No differences were noted between the patients with Modic type-I and patients with Modic type-II changes.

Conclusion

Quality of the evidence	Description
Low	There is evidence of low quality that intradiscal corticosteroid injection has **no** better effect than intradiscal saline injection. *Khot A. et al. 2004; Buttermann GR et al. 2004; Simmons JW et al. 1992.*

Quality of the evidence	Description
Low	There is evidence of low quality that intradiscal betamethasone reduces pain and improves function in patients with discogenic pain and Modic type-I or -II changes. *Cao P et al. 2011.*

Consideration

There is conflicting evidence on the clinical effect of intradiscal corticosteroid injection. We found two negative and 1 positive RCT's. An editorial from Carragee accompanying the Cao study[24] formulates several remarks. First, the reported 5-point pain intensity improvement is unparalleled in the treatment of chronic low back pain. Second, there was absolutely no improvement in the saline injection group. Third, the outcome is strikingly uniform in each group, despite the small numbers. Fourth, the duration of apparent effect is at least 6 months which is not corresponding with the pharmacological duration of action of the agents used.

Moreover, the fact that patients with Modic type-I changes respond as well as those with type-II Modic changes, does not support the hypothesis of steroid to reduce the inflammation, which is not present in patients with type-II Modic changes.
These observations justify criticisms about the results.
Intradiscal injection always include the risk for infection, and early disc degeneration.

Recommendation

Description	Strength of recommendation	Level of evidence
Intradiscal corticosteroid injections could **not** be used for the treatment of discogenic pain.*	Weak against	Low

Radiofrequency treatment of the discus intervertebralis

Literature overview

In the previous guideline RF treatment of the discus intervertebralis had a negative recommendation. This recommendation was based on two RCT's in relation to RF treatment of the intervertebral disc. Ercelen and colleagues[10] compared different treatment durations. Barendse and colleagues[9] compared percutaneous intradiscal radiofrequency treatment (PIRFT) with sham procedure in 28 patients. Outcomes presented were evaluated at eight weeks and found PIRFT to be ineffective in reducing CD-LBP. In terms of adverse events, the authors made a statement that 'there were no complications during or after the procedures. Thirty-nine patient's with positive provocative discographies were found to be eligible for the study. In the first group, treatment was performed for 120 seconds, and in the second group for 360 seconds, both at 80°C. At 1 week, 2 weeks and 1-month visual analogue scale were significantly decreased compared to the pre-treatment value in both groups. Those values returned to baseline at 6 months in both groups.
No new information was found since the previous guideline.

Conclusion

Quality of the evidence	Description
Low	There is evidence of low quality that radiofrequency treatment of the discus intervertebralis is **not** effective in the treatment of chronic discogenic low back pain. *Barendse et al. 2001; Ercelen et al. 2003.*

Considerations

Radiofrequency treatment of the discus intervertebralis seems to have no clinically relevant effect. The risks of this procedure are high.

Recommendations

Description	Strength of recommendation	Level of evidence
Conventional intradiscal radiofrequency treatment could **not** be used for the treatment of discogenic pain. *	Weak against	Low

Intradiscal electrothermal therapy (IDET)

Literature overview

In the previous guideline it was recommended to perform IDET for CD-LBP, preferably study related. This recommendation was based on two studies that evaluated IDET in relation to a sham procedure in a total of 121 patients with discogenic back pain. These studies both assessed outcomes at six months but had divergent findings. Pauza and colleagues[14] found statistically significant improvements in VAS pain and ODI scores between IDET and sham procedures. Freeman and colleagues[17] found no statistically differences between groups in ODI and in outcomes related to treatment success at six months. A meta-analysis of the ODI outcomes at six months was considered but differences in populations (severity of disease) and in the sham procedures precluded this. In terms of adverse events, Pauza[14] stated that no patient had any adverse events attributable to their treatment. One person in the IDET group died (stated as being 'unrelated causes'). Freeman[17] found no serious adverse events in either arm of the study. Transient radiculopathy (<6 weeks) was reported in four IDET and one placebo patients. Both trials were of reasonably high

quality according to the Cochrane Risk of Bias tool although there were some concerns in Freeman's trial that outcome data might be incomplete. The two small, contradictory studies render the evidence moderate for pain and low for disability. Further trials on the utility of this procedure are warranted.

Conclusion

Quality of the evidence	Description
Moderate	There is evidence of moderate quality that intradiscal electrothermal therapy reduces pain (visual analogue scale) for 6 months. *Pauza et al. 2004; Freeman et al. 2005.*

Quality of the evidence	Description
Low	There is evidence of low quality that intradiscal electrothermal therapy improves disability (Oswestry Disability Index) for 6 months. *Pauza et al. 2004; Freeman et al. 2005.*

Considerations

Since the publication of the two RCTs discussed above a prospective trial with 24 month follow-up showed a maintained improvement compared to the baseline value.[25] Predictors of 24-month clinical success included discographic concordance ($p < 0.0001$), a high-intensity zone on MR imaging ($p = 0.0003$), low Pfirrmann grade ($p = 0.0002$), and more extensive anulus coverage ($p < 0.0001$).

Recommendation

Description	Strength of recommendation	Level of evidence
Intradiscal electrothermal therapy could be used for the treatment of chronic low back pain of discogenic origin. *	weak	low

Radiofrequency treatment of the ramus communicans

Literature overview

In the previous guideline RF of the ramus communicans in the treatment of CDLBP was recommended. This recommendation was based on one trial of RF of the ramus communicans in 49 patients[18] that found significant improvements in pain and function according to ODI at four months when compared to a sham procedure. Adverse events were assessed, and none were found to be serious.

The search in 2015 did not yield new evidence.

Conclusion

Quality of the evidence	Description
Very low	There is evidence of very low quality that at 4 months there is a significant improvement in pain and function for radiofrequency treatment of the ramus communicans versus a sham procedure. *Oh WS et al. 2004.*

Considerations

The trial of Oh and Shim[11] had a number of methodological limitations including a lack of information on randomization and allocation procedures and a lack of blinding. In addition, to be eligible for the trial, patients needed to have failed to improve after an IDET procedure and to have >50 % pain relief after diagnostic ramus communicans block. A 2016 publication found no difference between RF ramus communicans and sham intervention.[26]
Although there is no consensus in selecting patients with presumed CD-LBP, in this study patients were selected by means of a test block of the communicating ramus. No MRI or other diagnostic tools were used to select patients and "affected levels".

Recommendation

Description	Strength of recommendation	Level of evidence
Radiofrequency treatment of the ramus communicans could **not** be considered for the treatment of low back pain of discogenic origin.	Very weak against	Very low

Pulsed radiofrequency treatment of the discus intervertebralis

Literature overview

In the previous guideline PRF of the intervertebral disc for the treatment of CD-LBP was not discussed. We did not identify any RCTs using PRF discus. Existing evidence is based on observational studies which are subject to a greater degree of bias than RCTs. In an uncontrolled prospective cohort study, pulsed radiofrequency in the nucleus was studied in 76 patients with discogenic pain confirmed by magnetic resonance imaging and provocative discography.[27] Pain intensity was measured using the numerical rating scale (NRS). At three-month follow-up, 38% of the patients had >50% pain reduction, at 12 months the effect is maintained in 29%. Patients with unsatisfactory pain relief three months after the intervention could receive additional treatment. Overall, 56% of all patients had > 50% pain reduction one year after first treatment.

Conclusion

Quality of the evidence	Description
Very low	There is evidence of very low quality that at 3 and 12 months there is a significant improvement in pain intensity (numeric rating scale) after a pulsed radiofrequency treatment in the nucleus of the discus. *Rohof O. 2012.*

Considerations

There are only observational trials on the intradiscal PRF treatment, based on these studies the clinical relevance is unclear.

Recommendation

Description	Strength of recommendation	Level of evidence
Intradiscal pulsed radiofrequency treatment could be considered for the treatment of low back pain of discogenic origin in selected patients. *	Very weak	Very low

Cooled radiofrequency intradiscal (Biacuplasty)

Literature review

In the previous guideline biacuplasty for the treatment of CD-LBP was not recommended. This recommendation was based on 2 pilot studies with 8 and 15 patients. In the first study[28] patients showed a mean pain reduction of 50% 3 months after the intervention. The second study[29] compared two prospectively matched controlled groups. One group treated with biacuplasty and one group treated with RF annuloplasty. One year after the intervention pain reduction was significantly better in the biacuplasty group.

In the current search one RCT of biacuplasty for discogenic low back pain in 64 patients (56 patients analyzed for pain outcomes) was identified.[16] Improvements in pain relief and disability were statistically significantly better at six months for the biacuplasty group compared to the sham group. The authors stated that no procedure-related complications were found in 29 active biacuplasty procedures or in 30 sham procedures. This trial was rated high quality according to the Cochrane Risk of Bias tool with the only potential for bias arising through a lack of clarity of reporting of all outcome data.

Conclusion

Quality of the evidence	Description
Moderate	There is evidence of moderate quality that at 6 months there is a statistically significant improvement in pain and disability in the intradiscal cooled radiofrequency (biacuplasty) group versus a sham group. *Kapural et al. 2013.*

Considerations

An additional randomized controlled trial was published in 2015[30] Patients were randomized to receive biacuplasty or sham. At 6 months the treatment was unblinded, patients in the biacuplasty group were followed for the next 6 months up to 12 months after the intervention. Patients from the sham group were offered active treatment upon unblinding. Twenty two out of 27 of the initial biacuplasty group were followed for 12 months and showed significant clinical improvements. Twenty four of the 30 patients initially treated with sham intervention crossed over to biacuplasty at 6 months. 20 out of 24 completed 6 months follow-up. Improvements in physical function and pain did not differ statistically from those of patients originally randomized to biacuplasty treatment.

Since the termination of the literature search an additional randomized controlled trial was published.[31]

A total of 63 subjects with lumbar discogenic pain diagnosed via provocation discography were randomized to intradiscal biacuplasty (IDB) + conventional medical management (CMM) (n = 29) or CMM-alone (n = 34). At 6 months, patients in the CMM-alone group were eligible for crossover if desired. In the IDB cohort, the mean VAS score reduction exceeded that in the CMM cohort (-2.4 vs. -0.56; P = 0.02), and the proportion of treatment responders was substantially greater (50% vs. 18%)

The effect of biacuplasty seems to be clinically relevant.

Recommendation

Description	Strength of recommendation	Level of evidence
The treatment of low back pain of discogenic origin with the intradiscal cooled radiofrequency (biacuplasty) should be used.*	Moderate	Moderate

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CHAPTER 3

No Transfer of Pressure to Adjacent Discs During Human Low-Pressure Controlled Discography: A Prospective Clinical Study

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Abstract

Background

A substantial part of low back pain (LBP) originates from degeneration of the intervertebral disc. To confirm the diagnosis of discogenic pain, provocation discography seems the best available tool. However, provocation discography is also considered to be a controversial and subjective test because the patient's personal pain response is the most crucial for the result of the test. Recently, an in vivo porcine study and a study in nine human subjects showed passing of pressure to the adjacent discs during discography. This could mean that the concordant pain the patient describes originates from an adjacent disc. The object of this study is to assess if during human lumbar pressure-controlled provocation discography there is pressure transmission to adjacent discs.

Methods

Consecutive patients between age 18 and 65 years with intractable low back pain and at least 50% preserved height of the suspected painful disc were included. Exclusion criteria were prior lumbar surgery of the suspected level, use of anticoagulants, pregnancy, local infection, and iodine allergy. An arterial blood pressure monitoring system simultaneously assessed the pressure in the adjacent discs while low-speed flow, pressure-controlled discography was performed.

Results

In 50 patients with a positive discography, the average intradiscal peak pressure was 15.1 psi (SD = 11.1). In 48 procedures, no pressure rise in the adjacent discs was found. A small pressure rise (1.1 psi) in the adjacent disc during discography was recorded in two patients.

Conclusions

Pressure rise in adjacent discs does not seem to occur during low-speed flow pressure-controlled lumbar provocation discography. False-positive pain reactions caused by potentially painful adjacent discs are therefore unlikely during pressure-controlled discography.

Key Words

Diagnostic Tests; Intervertebral Disc; Low Back Pain; Humans, Discography; Pressure

Introduction

Low back pain (LBP) is a major cause of disability in modern society, with lifetime prevalence of up to 80%, that results in high medical and economic costs.[1] In most patients, a period of acute LBP will resolve spontaneously without any intervention. However, a substantial subgroup of patients experiences sustained back pain.[2, 3] Although the exact cause of chronic LBP remains uncertain in the majority of patients, the most common pathway is believed to be degenerative lumbar disc disease.[4, 5] The intervertebral disc consists of a central gel-like structure called the nucleus pulposus (NP), which is surrounded by lamellar layers of collagen type I, the annulus fibrosus. The proteoglycans in the nucleus pulposus attract water, thus creating a hydrostatic pressure that allows motion while resisting load in the spine. Degenerative disc changes can already occur in the second life decade, with a breakdown of proteoglycans,[6] resulting in a loss of disc hydration.[7] In progressed degeneration, loss of disc height and annular fissures that extend from the NP to the outer innervated annulus can be observed.[8] It is believed that these annular fissures cause inflammation [9, 10] and, with neovascularization and neoinnervation via biochemically sensitized nociceptive nerve fibers, are the origin of so-called discogenic pain.[11-13]

Provocation discography is an invasive diagnostic test that is commonly used in clinical practice to determine whether a degenerative disc, as observed on plain radiographs or MRI, could be the primary cause of a patient's pain syndrome. By intradiscal injection of contrast dye, the pressure in the disc will increase,[14] which is believed to distend the torn annulus and excite nociceptors, thus causing pain.[15]

However, provocation discography is also a controversial test. On the one hand, there is evidence that discography could serve as a predictor of favorable outcome for surgery, although this evidence is conflicting.[16, 17] The reported diagnostic accuracy is regarded as moderate (according to GRADE)[18] for discogenic low back pain.[19-22] There is evidence that discography might accelerate disc degeneration.[23, 24] This means that careful consideration of risks and benefits should take place before disc injections are performed.

For pain interventions, and even more so for pain intervention research projects regarding discogenic pain patients, it is important to use the best diagnostic tool available to establish the diagnosis of lumbar discogenic pain and to assess the best target point for the pain intervention. Signs and symptoms and additional tests like magnetic resonance imaging (MRI) and radiography are not conclusive in identifying the source of discogenic pain.[25, 26] Despite contradictory reports in literature[12, 27, 28] provocation discography is considered by many pain physicians to be the gold standard[29] to affirm the diagnosis of discogenic pain and to assess the best target point for minimal invasive pain interventions.

For standardization and reproducibility of discography, precise control of intradiscal pressure during injection of contrast fluid is essential because the degree of the patient's reported pain will depend on the magnitude of the provocation stimulus.[14] Recently, it was reported that during in vivo porcine discography there is a substantial pressure transmission to adjacent discs.[30] This study was repeated in nine human subjects, and similar results were reported.[31] This result would imply that concordant pain as experienced by the patient during injection could originate from a pressure increase in an adjacent potentially painful disc (APPD). If so, this would constitute a specificity problem in clinical discography and in interventional pain medicine, and this could potentially lead to the treatment of the wrong disk. However, the abovementioned Hebelka study in nine human subjects was performed with maximum intradiscal pressures up to 80 psi. Several discs showed a pressure of higher than 50 psi above opening pressure, whereas in current pain practice pressure- controlled discography should be performed with pressures of 50 psi or lower above opening pressure (a.o.p.).[12, 32] Our study did not exceed 50 psi peak pressure, mean was 31.1 psi (SD 10.5), and this is considerably lower compared with the Hebelka study.

Therefore, the objective of this study was to assess whether in human subjects with discogenic pain intradiscal pressure in adjacent levels is increased when pressure-controlled provocation lumbar discography is performed according to clinical practice assessing the control disc first with maximum intradiscal pressures of 50 psi a.o.p.

Methods

Patient Selection

Eligible for this study were patients (between age 18 and 65 years) with axial low back pain, presumably originating from the lumbar disc(s), who had received conservative treatment for at least six months and had a negative result on medial branch block(s) of the lumbar facet joints, and with degenerative findings, that is, reduced disc height and Pfirrmann grading 2 to 4[33] on recent (less than six months) plain radiographs and MRI of the lumbar spine. The height of a suspect disc should be at least 50% as compared with adjacent control levels.[34] Only patients with presumed discogenic pain emanating from L3-L4, L4-L5, and L5-S1 were included in this study. Exclusion criteria were radicular symptoms, disc height lower than 50%, local infection, pregnancy, allergy to iodinated contrast agents, known increased tendency to hemorrhage or use of anticoagulants, patients with evidence of vertebral compression fractures, segmental instability, and scoliosis, and prior lumbar surgery of the suspect level. Eligible patients provided informed consent for this study and were scheduled for pressure-controlled provocation discography. This study

was approved by the Institutional Review Board of the Rijnstate Hospital in Arnhem, the Netherlands (No. 855-070512).

Discography protocol

In an outpatient operating room under anesthetic monitoring and sterile conditions, controlled provocation discography (CPD) was performed. All discographies were performed by JWK, a specialized pain physician with over 15 years of experience in pain interventions.[35, 36] All patients received prophylactic antibiotics 2 g Cephazoline i.v. 30 minutes before the procedure. By using a double needle technique (Neurotherm Discography Kit) and fluoroscopy, a 22 g x 3.5" introducer needle was introduced to the rim of the disc, and subsequently an inner 25 g x 6.0" Chiba needle was inserted through the introducer needle to enter the nucleus pulposus in the center of the intervertebral disc.[36, 37] The double needle technique is considered to reduce the incidence of post discography discitis because in this way skin tissue is not introduced into the disc, and additionally, by inserting needles of a very small diameter, the risk of iatrogenic disc degeneration will be diminished.[23, 38] Next, the discography needle was connected to a pressure-controlled discography device (CDS) (NeuroTherm, Wilmington, MA, USA). The CDS was calibrated for needle length (20 cm), needle gauge (25 g), contrast dye (Iohexol-Omnipaque 300; GE Healthcare, Princeton, NJ, USA), and fluid velocity. Under continuous fluoroscopic control, Iohexol, a low-osmolar, nonionic iodinated contrast agent, was injected into nucleus pulposus of the disc.

The controlled injection velocities were 0.02 mL/s and 0.05 mL/s, respectively, representing a low and high injection velocity, in order to study the potential influence of injection speed on recorded intradiscal pressures.[14] Thus, 25 of the patients were injected with low velocity (0.02 mL/s), and the other 25 patients with high velocity (0.05 mL/s).

Patient's pain was noted as rated on a numeric rating scale (NRS; 0–10). The moment the contrast dye first entered the nucleus pulposus as visualized on fluoroscopy, pressure was recorded as the opening pressure (OP). Maximum pressure above OP was recorded as peak pressure (PP). The CDS took care that the maximum accepted pressure was 50 psi a.o.p.[12] and the maximum volume of injection was 3 mL. The moment the patient experienced pain, pain pressure and volume level were recorded.

According to the IASP/ISIS criteria[39], the operational criteria for discogenic pain during discography are defined as 1) stimulation of target disc reproduces pain concordant to the usually felt severe pain, 2) the intensity of this pain has a numeric rating scale score of at least 7 on a scale from 0 to 10, or 70% of the maximum spontaneous pain, 3) the pain is reproduces by a pressure of less than 50 psi above opening pressure[32], and 4)

stimulation of at least one of the adjacent discs is not painful. Apart from the IASP criteria, we maintained the criterion that the provoked, and concordant, pain during discography should be more than the baseline pain.

The degree of degeneration of the tested disc was classified according to the Modified Dallas Discogram Score.[34]

Adjacent disc pressure assessment

Per usual clinical practice during provocation discography, the discs adjacent to the suspect disc(s) were first assessed for discogenic pain. For assessment of the intradiscal pressure, the discography needle(s) were placed in the adjacent level(s) and were connected to an arterial blood pressure monitoring system (Codan critical care) flushed with saline (Figure 1). Before connection, calibration, establishment of the zero value, and leveling to the right atrium took place.[40] During discography, a trained nurse practitioner recorded the changes in pressure, registered in mmHg (1 psi 51.7149326 mmHg), that were visible on the anesthesia monitor (anesthesia system: Drager Zeus).

This procedure was first tested to assess if the pressure rise with the CDS would correlate with the pressure rise with the other system by placing two needles in one disc. One needle was then connected to the CDS, and the other needle was connected to the arterial pressure monitoring system. During the provocation discography, a corresponding pressure rise could be seen between the two systems.

During the procedure in 50 patients, the suspect disc(s) and one or two adjacent discs were assessed. (Figure 2.) If the L4-L5 disc was suspect, provocation discography was performed at L4-L5, and the levels L3-L4 and L5- S1 were adjacent disc pressure tested. In case L5-S1 was suspect, levels L4-L5 (CDP) and L5-S1 (PD) were assessed. After the CDP test procedure was performed, discography of the adjacent levels followed to verify whether these were symptomatic.

Discography Parameters

The opening pressure is the pressure above baseline (zero) when the first contrast dye appears in the disc. Peak pressure is the maximum pressure above opening pressure; it is either the moment the patient reports concordant pain with an intensity of 7 or higher out of 10 on 11-box NRS or it is the pressure that is reached after injection of the maximum volume of contrast dye (3 mL) in a nonpositive discogram.[39] The build-up intradiscal pressure is defined as pressure increase (PI), that is, the difference between opening pressure and peak pressure.

Statistics

Descriptive statistics were used to record findings of the tests in the target discs and in the adjacent discs. Relations between parameters found during provocation discography and the degree of disc degeneration, injection velocities, and positive discographies were analyzed by one-tailed Spearman's rho.

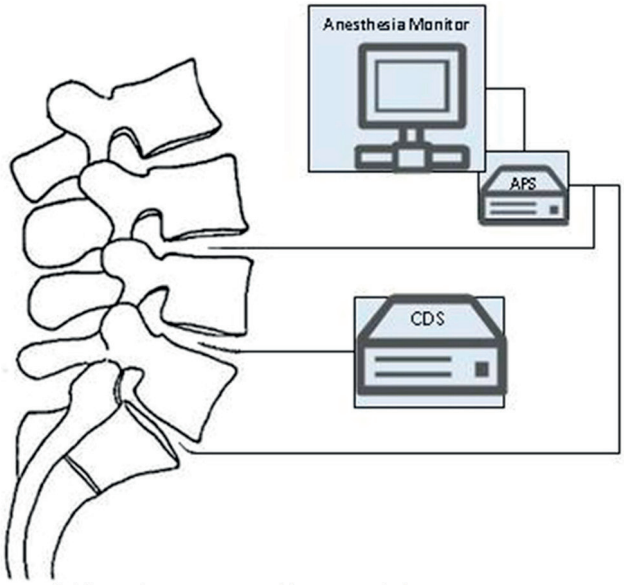

Figure 1: Schematic diagram of intradiscal pressure monitoring. APS = arterial pressure monitoring system; CDS = controlled discography system.

Results

From June 2011 to May 2012, 182 consecutive patients were assessed for eligibility, and 50 patients who fulfilled the inclusion criteria were asked to participate in this study. Due to the strict inclusion criteria of sufficient disc height, all disc centers could be reached by the needles, so all discography procedures were technically successful. The demographic and clinical features of the 50 included patients are listed in Table 1. Average age was 44 years, 32 patients were male, and 18 patients were female.

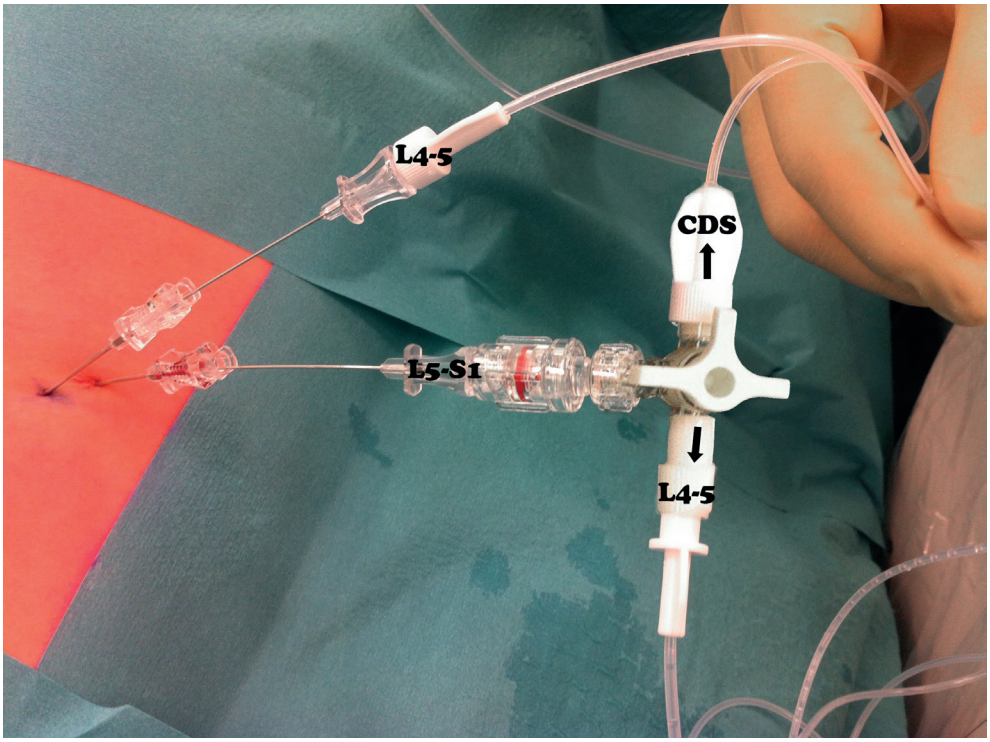

Figure 2: Test procedure: One needle was attached to the CDS device, and the other needle to the arterial pressure monitoring system.

Adjacent Disc Pressure Assessment

Figure 3 shows the typical curve registered during provocation discography. With the start of instillation of contrast dye in the disc through the CDS machine, there is build-up of pressure until the first contrast dye appears in the disc (OP). At this moment, there is a short drop of pressure seen, which will start building up again after a few seconds. This pressure build-up continues until pain intensity of 7 or higher out of 10 on NRS is achieved, peak pressure is reached, or the maximum volume (3 mL) to be instilled is reached.

We found in two out of 50 patients a pressure rise in the adjacent disc(s) (Table 1). This pressure rise was in patient number 7 in adjacent discs 20 mm HG (0.35 psi) and, in patient number 33, 60 mmHg (1.1 psi). The findings in these two patients were not related to higher opening pressure, peak pressure, pain provocation pressure, or more severe disc degeneration.

Discography Parameters

In all patients, the mean intradiscal pressure increase during provocation discography was 16.8 psi (SD = 10.4). In patients with a positive discography, PI was 15.1 psi (SD = 11.1), and in patients with a negative discography PI was 18.3 psi (SD = 9.9).

To assess potential correlations between degeneration and discography parameters, the Modified Dallas grading was dichotomized between less degenerated discs (grade 1 and 2) and more severe degeneration (grade 3 to 5).[41]

Intradiscal pressure increase was shown to be related to the degree of disc degeneration. In patients with low-grade degenerated discs (i.e., Modified Dallas 1 and 2), the build-up intradiscal pressure (PI) was on average higher (Spearman's correlation coefficient –0.32, $P = 0.01$) (see Figure 4). There was no correlation between OP, PP, or instilled volume until peak pressure and degree of disc degeneration; Spearman's correlation coefficient showed, respectively, –0.044 ($P = 0.77$), –0.251,($P = 0.08$), and 0.07 ($P = 0.30$).

Table 1: Lists of all patient (N=50) who underwent a discography and Adjacent Disc Pressure assessment.

Patient's Characteristics			Pressure Test			Disc Pressure Adjacent Disc(s) in mmhg			Pressure in Psi			Modified Dallas Criteria			CPL
N	Age, y	Gender	Velocity in Seconds	ML	Discography Level	L3-4 mmhg	L4-5 mmhg	L5-1 mmhg	Opening Pressure	PP	PI	L3–L4	L4-L5	L5-S1	
1	43	F	0.05	1.38	L4-L5	0		0	19	20	1	1	4	5	L4-L5
2	51	M	0.05	3	L4-L5	0		0	14	34	20	2	2	3	NEG
3	39	M	0.05	3	L5-S1	NA	0		9	37	28	-	3	5	L5-S1
4	22	V	0.05	3	L4-L5	0		0	22	30	8	1	3	4	L4-L5
5	40	V	0.05	3	L4-L5	0		0	44	50	6	3	5	-	L4-L5
6	54	M	0.05	3	L4-L5	not done		0	4	16	12	-	1	1	NEG
7	34	M	0.05	3	L4-L5	20		20	12	22	10	4	4	SL	NEG
8	37	V	0.05	3	L4-L5	0		not done	10	20	10	4	3	DH<30%	NEG
9	51	M	0.05	3	L4-L5	0		0	6	40	34	5	1	3	L5-S1
10	47	V	0.05	1.5	L4-L5	0		0	19	50	31	1	1	5	NEG
11	56	M	0.05	1.8	L4-L5	0		0	37	50	13	3	5	2	L5-S1
12	56	V	0.05	3	L4-L5	0		0	15	43	28	DH<50%	4	1	NEG
13	52	V	0.05	3	L4-L5	0		not done	4	23	19	4	4	DH<50%	NEG
14	43	V	0.05	2.4	L4-L5	not done		0	8	20	12	DH<50%	4	1	L4-L5
15	50	V	0.05	2.7	L5-S1	not done	0		15	50	35	-	2	4	L5-S1
16	25	V	0.05	2.3	L4-L5	0		0	43	50	7	1	5	5	NEG
17	19	V	0.05	1.9	L4-L5	0		0	15	50	35	2	1	2	NEG
18	64	M	0.05	2.2	L4-L5	0		0	11	50	39	2	1	4	NEG
19	61	M	0.05	3	L4-L5	0		0	12	47	35	-	5	5	NEG
20	59	V	0.05	3	L4-L5	0		0	4	17	13	5	5	5	NEG

Continued

Patient's Characteristics			Pressure Test						Pressure in Psi			Modified Dallas Criteria			CPL
						Disc Pressure Adjacent Disc(s) in mmhg									
N	Age, y	Gender	Velocity in Seconds	ML	Discography Level	L3-4 mmhg	L4-5 mmhg	L5-1 mmhg	Opening Pressure	PP	PI	L3–L4	L4-L5	L5-S1	
21	44	M	0.05	3	L4-L5	0		0	12	38	26	3	3	2	NEG
22	20	M	0.05	1.5	L4-L5	0		0	8	28	20	4	4	2	L3-L4 / L4-L5
23	33	M	0.05	3	L4-L5	0		0	25	35	10	-	4	3	NEG
24	39	M	0.05	3	L4-L5	0		0	11	19	8	2	2	4	L5-S1
25	58	M	0.05	2.6	L4-L5	0		0	10	20	10	5	1	5	L4-L5
26	42	M	0.02	3	L4-L5	0		0	15	30	15	2	4	2	L4-L5
27	33	M	0.02	3	L4-L5	0		0	6	14	8	5	3	5	NEG
28	45	V	0.02	3	L4-L5	0		0	32	41	9	2	3	4	L3-L4
29	39	M	0.02	1.5	L4-L5	0		0	5	8	3	5	5	5	L4-L5
30	43	V	0.02	1.3	L4-L5	0		0	16	50	34	4	3	4	L3-L4 / L5/S1
31	26	V	0.02	2.8	L5-S1	not done	0		6	26	20	-	1	3	L5-S1
32	45	M	0.02	2.9	L4-L5	not done		0	26	50	24	DH<50%	1	1	NEG
33	52	M	0.02	3	L4-L5	60		60	19	27	8	3	5	5	NEG
34	35	M	0.02	3	L4-L5	0		0	6	16	10	2	4	4	NEG
35	46	M	0.02	3	L4-L5	0		0	12	29	17	2	4	4	L4-L5
36	58	M	0.02	3	L4-L5	not done		0	35	45	10	DH<50%	1	4	NEG
37	31	M	0.02	3	L4-L5	0		0	32	41	9	2	3	4	L3-L4
38	58	M	0.02	3	L4-L5	0		0	19	50	31	1	1	2	L5-S1
39	61	M	0.02	3	L4-L5	0		0	12	15	3	1	3	1	NEG
40	55	M	0.02	3	L4-L5	0		0	6	32	26	2	4	4	NEG

Continued

Patient's Characteristics			Pressure Test												
						Disc Pressure Adjacent Disc(s) in mmhg			Pressure in Psi			Modified Dallas Criteria			CPL
N	Age, y	Gender	Velocity in Seconds	ML	Discography Level	L3-4 mmhg	L4-5 mmhg	L5-1 mmhg	Opening Pressure	PP	PI	L3–L4	L4-L5	L5-S1	
41	46	M	0.02	2.7	L4-L5	0		0	9	28	19	4	4	4	NEG
42	57	M	0.02	3	L4-L5	0		0	1	24	23	1	2	1	NEG
43	33	V	0.02	3	L4-L5	0		not done	3	15	12	3	3	DH<50%	L3-L4 / L4-L5
44	58	M	0.02	3	L4-L5	0		not done	4	19	15	3	3	DH<50%	NEG
45	64	V	0.02	2.9	L4-L5	0		0	10	10	0	3	5	4	L4-L5 / L5-S1
46	43	M	0.02	3	L4-L5	0		not done	5	31	26	4	5	DH<50%	NEG
47	30	M	0.02	3	L4-L5	0		0	4	22	18	4	5	4	NEG
48	38	M	0.02	3	L4-L5	0		not done	19	28	9	2	5	DH<50%	NEG
49	50	M	0.02	3	L4-L5	0		0	12	33	21	5	5	5	L3-L4 / L4-L5
50	33	V	0.02	2	L4-L5	not done		0	11	12	1	DH<50%	3	1	L4-L5

Two groups are shown: high velocity (0.05 mL/s) and low velocity (0.02 mL/s). Maximum instilled volume was 3 mL; infusion was stopped when peak pressure exceeded 50 psi above opening pressure. Discography level depicts the level that is provoked. The pressures and pressure differences measured in the adjacent discs are recorded. Pressures measured were opening pressure (OP), peak pressure (PP), and pressure increase (the difference between OP and PP) ADP ¼ adjacent disc pressure; CPL ¼ concordant pain level; DH ¼ disc height; NA ¼ not available because of reduced disc height > 50%; NEG ¼ negative discography; OP ¼ opening pressure; PI ¼ pressure increase; PP ¼ peak pressure; psi ¼ pound for square inch (1 psi ¼ 51.7149326 mmHg); SL ¼ surgery level.

Psi = Pound for square inch (1 Psi = 51.7149326 mmHg); CPL= Concordant Pain Level; Veloc in Sec.= Velocity in seconds; ML =Milliliter; ADP= Adjacent Discs Pressures; OP= Opening Pressure; PP= Peak Pressure; PI= Pressure Increase; NEG= Negative Discography; SL= Surgery Level; DH=Disc Height; NA= not available because of reduced disc height>50%

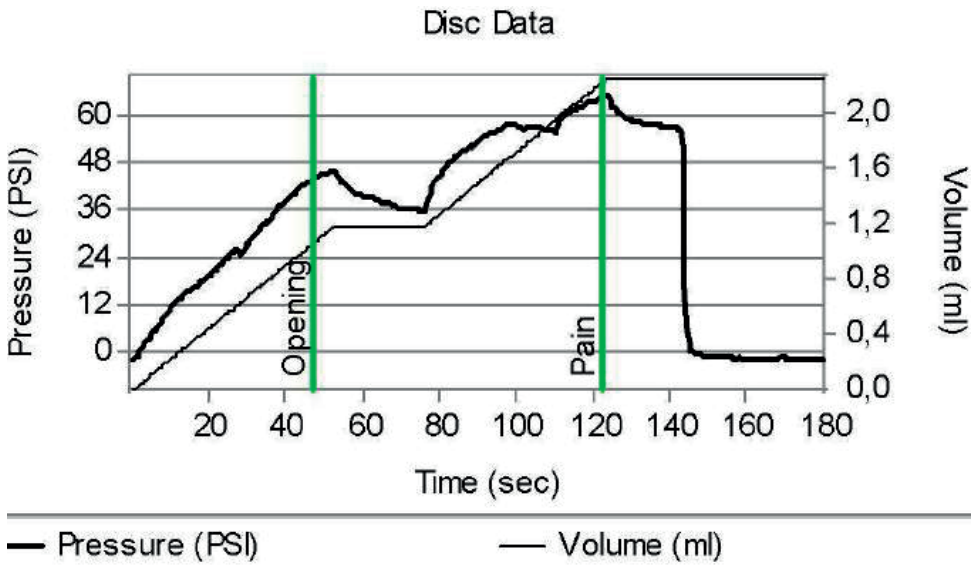

Figure 3: Relative pressure volume curve. The pressure rises after the start of the discography parallel with the volume of contrast dye. The opening pressure (OP), depicted by the first vertical line, captures the moment the first contrast dye appears in the disc (visible on fluoroscopy). Shortly after the OP, there is a short drop in the pressure because of the fact that the contrast dye can now flow throughout the disc. After this initial drop, pressure builds up again until the maximum pressure allowed is reached (50 psi above opening pressure), the maximum volume instilled (3 mL of contrast dye), or pain provoked pressure is reached. The pain provocation level is depicted by the second vertical line. At this point, the procedure is stopped, no more fluid is instilled, and the pressure drops gradually.

Peak pressure during discography was significantly *(P* = 0.04) correlated to the injection speed: At low velocity (0.02 mL/s), the mean PP was 27.8 (SD = 12.8), and at high velocity (0.05 mL/s) the mean PP was 34.4 (SD = 13.0). PI and OP showed no significant correlation to velocity (*P* = 0.12 and *P* = 0.15, respectively). There was no correlation between injection speed and the amount of positive or negative discographies (*P* = 0.4). However, the maximum level (PP) of 50 psi was reached in 28% of discographies performed with an injection speed of 0.05/s and only in 12% of cases that were assessed with 0.02/s (*P* = 0.08).

Discussion

The main finding of the present study was that in human in vivo provocation lumbar discography using a pressure-controlled low-speed technique, the intradiscal pressure at adjacent levels is not elevated. This makes the probability of a false-positive discogram because of pain in an adjacent level as caused by transmission of increased pressure in human subjects unlikely.

Hebelka et al.[30] performed discography using high-speed injection (0.07 mL/s) and low-speed injection (0.03 mL/s) in 36 lumbar discs of nine adolescent pigs under general anesthesia. During contrast injection in one of the discs at pressures up to 8 bar (116 psi), intradiscal pressure was measured in the two adjacent discs using a fiber-optic pressure transducer. Thus, transmitted pressure could be recorded both in noninjected discs and in discs that had been prefilled with contrast. They showed that in these porcine discs, with this set up, during contrast injection, there was an intradiscal pressure rise in the adjacent discs with a mean value of 16% (3.2–37%) over baseline pressure (2–13 psi). These results were confirmed[42] in a study of in vivo discography in a porcine model of degenerate discs in which an average pressure increase of 11% (mean 3.2 psi, range 1.7– 8.2, SD 1.8) above baseline in most adjacent discs during the procedure was found. A study in nine human subjects showed similar results.[31] However, in this human study, the authors used maximum pressures of 80 or lower psi absolute pressure, resulting in several discs with much higher-pressure build-up than advised in guidelines (max 50 psi above opening pressure).[39]

The present study was undertaken to verify whether an identical rise in pressure at the adjacent level is present in provocation discography in human subjects using the advised maximum PP of 50 psi a.o.p. Our results for relatively high-speed injection (0.05 mL/s), as well as for low-speed injection (0.02 mL/s), showed no pressure rise in the adjacent discs. The pressure in the adjacent discs was measured in mmHg. There were two patients with a pressure rise of 20 and 60 mmHg, respectively, which is equal to 0.25 and 1.1 psi. As the lowest pain pressure was above 8 psi, we considered this pressure rise of 1.1 psi clinically not relevant and concluded that it is not likely that provocation discography in human subjects with pressure-controlled high- and low-speed injection induces a pressure rise in the adjacent discs.

These results differ substantially from the aforementioned findings in porcine discs, where discography induced pressure increase in adjacent discs.[31, 42]

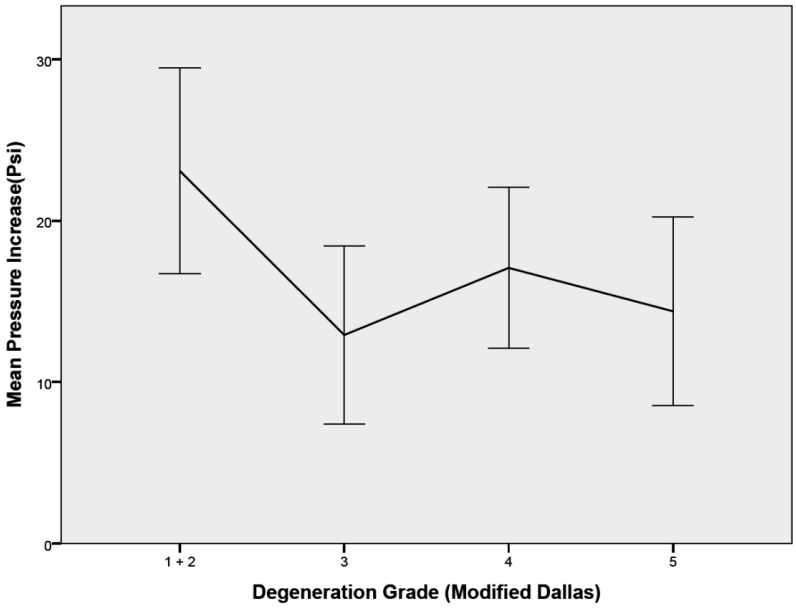

Figure 4: Disc degeneration graded by the Modified Dallas scale (1–5) vs mean intradiscal pressure increase (PI) during discography. Less degenerated discs (Modified Dallas scale 1 and 2) show higher build-up pressure increase.

Possible reasons for the conflicting findings could be that in those studies the pigs were under general anesthesia, intubated, and placed on a respirator. Respiration machines and general anesthesia are known to influence intradiscal pressure[43, 44]: respiration machines by their impact on the venous system, and general anesthesia due to muscle relaxation.

Another possible explanation of the fact that no pressure rise was found in adjacent discs in our study of human subjects could be the difference in accepted pressures during discography between the aforementioned studies and our study. The average and peak pressures measured in the porcine study of Hebelka et al.[30] were much higher than the pressures induced in our study; pressures in the porcine disc test were measured of up to 129 psi, whereas in our study peak pressures higher than 50 psi a.o.p. were not accepted as we adhered to the International Spine Intervention Society (ISIS) and the International Association for the Study of Pain (IASP) criteria.[39] Moreover, those high pressures would probably be too painful for awake human subjects. An explanation for the difference in our findings with the abovementioned human study[31] could be that, in contrast to our study, adjacent pressure differences were measured in prefilled (suspect) discs. This could make the adjacent (suspect) disc more sensitive to further rise in pressure.

In the current setting for adjacent disc pressure measurements, we only use reference discs that are not used for discography and therefore are not prefilled.

Correlations between disc degeneration and provocation discography parameters were additionally evaluated in this study. Less degenerated discs showed on average a higher build-up pressure during provocation discography. This finding is in line with a study of Panjabi et al., who also found that intrinsic disc pressure decreases with increased disc degeneration.[41]

Lumbar provocation discography is considered by many clinicians as the gold standard to determine discogenic low back pain and is mainly used in pain management to define the indication and precise location for minimally invasive treatment.[45, 46] The test itself is controversial because of its variable diagnostic accuracy, with substantial false-positive rates in asymptomatic subjects. Furthermore, the reliability of this test depends on the patient's subjective pain response as well as on the experience and technical expertise of the physician performing the procedure.[46]

Manual injections are not standardized and generally cause high intradiscal pressure peaks, which has been suggested as a possible reason for the high number of false-positive findings.[32] The introduction of pressure-controlled discography has been reported to reduce the rate of false-positive discs down to only 0.06 when using low pressure criteria (i.e., less than 15 psi above the opening pressure when the injected contrast dye first overcomes the internal osmotic disc pressure as visualized on fluoroscopy).[22, 47] Automated discography devices equipped with syringe pumps that control injection speed of contrast fluid, and simultaneously display a dynamic peak pressure, could be helpful in further reducing false positives in lumbar discography.

This study found a positive correlation between injection speed and peak pressure. It has been reported that high injection speed, high viscosity, a small diameter of the needle, and the use of a long needle all increase recorded dynamic pressure in the disc.[14, 48] An in vitro evaluation of injection speed, sensor location, and tube length demonstrated that discography can better be performed with low injection speed (<0.01 mL/s), to minimize overpressure, using an extra syringeal sensor.[37]

To minimize differences among physicians performing provocation discography and to reduce false-positive findings, standardization of injection speed, viscosity of the injected material, and diameter and length of the needle is recommended. Therefore, discography has developed in recent years from a manually performed test into a completely standardized low-speed, pressure-controlled technique[14] by using an automated discography system (CDS) that calibrates for needle gauge, needle length, and contrast

dye and has a controlled injection speed with exact registration of opening pressure and peak pressure, not allowing pressures of more than 50 psi above opening pressure (ISIS/IASP criteria).[39] Over the last years, the injection speed has been reduced more and more: Fluid injection of 0.01 mL/s reduces the difference between post syringeal pressure and intradiscal pressure to a minimum.[37] In this way, the specificity of discography improves.[49] However, due to limitations of the CDS device, for this study 0.02 mL/s was used as low-velocity assessment.

A limitation of the current study is the fact that during discography the baseline intradiscal pressures of the adjacent discs were not assessed. The intradiscal pressure in adjacent discs was measured indirectly by the Codan pressure monitoring system, which uses baseline zero leveling. However, changes in pressure, even the smallest, if present, are very well detected by this technique.[40]

One of the strengths of this study is that it was performed in real low back pain patients, thus reflecting daily clinical practice, and that it can be repeated in virtually any clinical discography setting. Another strength is the number of procedures, 50 suspect discs with adjacent control discs, performed by one experienced discographer using low-speed, pressure-controlled discography.

Conclusions

In the present low back pain study population, low-pressure provocation discography did not induce a pressure rise in adjacent discs in patients with discogenic low back pain. Therefore, it is not likely that specificity of low-pressure provocation lumbar discography is limited by a pressure transfer phenomenon to adjacent discs in humans when discography is performed according to the guidelines. Furthermore, this study showed that PPs reached during discography were significantly lower, with a low injection speed of 0.02 mL/s compared with a higher velocity of 0.05 mL/s.

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CHAPTER 4

Efficacy, Safety, and Predictors of Intradiscal Methylene Blue Injection for Discogenic Low Back Pain: Results of a Multicenter Prospective Clinical Series

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Abstract

Study Design
Prospective clinical study of intradiscal methylene blue injection for the treatment of lumbar discogenic pain.

Objective
The objective of this study was to collect information about efficacy, safety, and acceptability of the intervention, gain and burden of outcome measures, and sample size assumptions for a potential following randomized controlled trial (RCT). If the pilot study demonstrates that this treatment is potentially effective and safe, and the methods and procedures used in this study are feasible, an RCT follows.

Summary of Background Data
Low back pain (LBP) is a highly common problem with a lifetime prevalence of more than 70%. A substantial part of chronic LBP is attributable to degenerative changes in the intervertebral disc. A recently published RCT assessing the treatment intradiscal injection of methylene blue for chronic discogenic LBP, showed exceptionally good results.

Methods
Patients were selected on clinical criteria, magnetic resonance imaging, and a positive provocative discogram. The primary outcome measure was mean pain reduction at 6 months.

Results
Fifteen consecutive patients with chronic lumbar discogenic pain enrolled in a multicenter prospective case series in two interventional pain treatment centers in the Netherlands. Six months after the intervention, 40% of the patients claimed at least 30% pain relief. In patients who responded, physical function improved, and medication use diminished. We observed no procedural complications or adverse events. Predictors for success were Pfirrmann grading of 2 or less and higher quality of life mental component scores.

Conclusions
Our findings of 40% positive respondents, and no complications, give reason to set up a randomized, double-blind, placebo-controlled, trial.

Key Words
chronic pain, intervertebral disc, low back pain, methylene blue, refractory pain

Introduction

Low back pain (LBP) has a lifetime prevalence of 70%. Although LBP often resolves spontaneously, it has a high rate of recurrence. Approximately 60% of patients who consult their general practitioner with a recent onset LBP still suffer pain after 1 year.[1] Chronic LBP often leads to a low quality of life due to pain, disability and loss of work productivity. Moreover, chronic LBP is accompanied by high health care costs for society.[2, 3] Approximately 40% of chronic LBP has been reported to be of discogenic origin.[4, 5]

Previous studies[6, 7] suggest that discogenic LBP is caused by internal disc disruption and is closely related with vascularized granulation tissue containing nociceptive nerves, extending from the outer layer of the annulus fibrosis into the nucleus pulposus.[7, 8] Sensitization of these nerve endings in the outer annulus by various inflammatory mechanisms may lead to chronic discogenic LBP. Assuming that these ingrown nerve endings play an important factor in mediating discogenic LBP, many attempts have been made to prove that reduction of inflammation and/or ablation of intradiscal nociceptors would be beneficial for patients with discogenic LBP.[9-15] Despite some promising results of these methods, the ideal interventional treatment of discogenic LBP has still to be found.

Since Methylene blue was first synthesized in 1876, it has been used in many different ways such as a tissue dye during various treatments and for diagnostic purposes.[16] Due to its neurolytic effect, methylene blue was first injected into the intervertebral disc in 2007.[17] A positive prospective study followed by a randomized controlled trial (RCT), published in 2010,[18] both showed statistical and clinically meaningful reduction in pain and disability in patients with discogenic LBP. A decrease in pain was measured by a Numeric Rating Scale (NRS) from 0 to 100. At least 20 points were seen in 89% of the patients, of which 19% reported no further pain and 28% reported dramatic improvement of symptoms. In the editorial that accompanied the publication, it was stated that 1 positive RCT should not amount to endorsement, and the author encouraged other centers to reproduce these results.[19] The current study aimed to duplicate the original prospective case series.[17] The effects of intradiscal methylene blue injection treatment were explored in a well-selected group of 15 patients with objectified discogenic LBP for at least 6 months. It was agreed that if at least 5 of 15 patients would show a clinically relevant reduction in pain of at least 30%,[20, 21] and both procedure and treatment would have no complications or serious side effects, a placebo controlled randomized clinical trial would follow this pilot study.

Materials and methods

This prospective clinical series is conducted in a regional interventional pain center and in a university interventional pain center in the Netherlands. Trial registration number is NTR 2547. The study was approved by the European Union Drug Regulating Authorities Clinical Trials (EudraCT) registration numbers 2010-022025-15, and the medical ethics committee (METC) of the Maastricht University Medical Centre (ref: 10-2-055). Written informed consent was obtained from all subjects included in the study.

The goal of this study was information collection about efficacy and safety of the intervention, complications and side effects, recruitment strategies, acceptability of intervention, gain, burden of outcome measures, and sample size assumptions. The study committee stated that if this pilot study indicates that this treatment is effective, a placebo controlled RCT would follow. Effectiveness was achieved if at least 30% patients responded, and no major complications and side effects occurred. Patients were responder patients if the mean pain relief was clinically important,[21] ie, at least 30% pain reduction at 6 months follow-up.

Patient Selection

In the period March 2011 to September 2012, 174 consecutive patients with chronic LBP without radiculopathy were selected for eligibility. Eligibility criteria were: (1) axial LBP and impaired function of at least 6 months duration; (2) non-responsiveness to conservative treatment for at least 6 months; (3) The suspected discs has at least 50% disc height compared to a control disc.[22] (4) Pain provocation by low pressure discography < 50 PSI (pounds per square inch above opening pressure) at the affected level(s), without pain reproduction or with discordant pain at adjacent unaffected control levels; (5) age between 18 and 65 years; and (6) mean pain intensity of 5 or higher, measured by a pain diary with NRS 3 times a day for 4 consecutive days.[23]

Exclusion criteria were: (1) severe disc degeneration at the affected level evidenced by > 50% of disc height loss on plain anteroposterior and lateral radiographs; (2) CT or MRI of the lumbar spine shows extruded or sequestrated nucleus pulposus tissue at the affected levels; (3) mean pain NRS below 5; (4) previous lumbar back surgery at the affected level(s); (5) intradiscal procedures previously performed at the affected level(s); (6) BMI > 35; (7) pregnancy; and (8) provocative discography with pressures exceeding 50PSI above opening pressure.[24, 25]

Lumbar Pressure-controlled Provocative Discography

Consecutive eligible patients who for at least 6 months were treated conservatively, and who had facet blocks without pain reduction, received a provocative discography to confirm LBP of discogenic origin.

Intradiscal Methylene Blue Injection

After antibiotic prophylaxis (2 grams Cephazolin i.v.), a needle (with double needle technique) was placed in the symptomatic disc. Anteroposterior and lateral plane fluoroscopy confirms needle position. A mixture of 1 mL methylene blue 10%, and 1 mL lidocaine 2% was then injected, with pressure control, into the disc. Patients were all day-care surgery submitted and after treatment and kept under bed rest observation for at least 2 hours.

Objectives

All primary and secondary outcome parameters were assessed at baseline, at 6 weeks, 3 months, and at 6 months after the intervention. Main outcome measure was the mean pain change at 6 months after the intervention. Mean pain was measured by a pain diary with NRS 3 times a day for 4 consecutive days at baseline and at the follow-up time points.[23] Furthermore, Patients Global Impression of Change (PGIC)[26] measured by a 7-point Likert Scale, and number of adverse and serious adverse events were reported.[26, 27]

Secondary study parameters were disability measured by the Oswestry Disability Index,[28] and Quality of life measured by the SF-36 and EuroQol.

A tertiary objective was a retrospective comparison of Magnetic Resonance imaging (MRI)[29-32] and provocative discography[26] findings with success or failure of treatment. Magnetic resonance imaging (MRI) was performed at baseline and was repeated 1 year after treatment. Both the MRI findings (baseline and follow-up) were evaluated, blinded for success of outcome, individually by 3 authors (JK, PW, HS). Differences in MRI evaluation were discussed in a consensus meeting with all authors to derive general agreement. Because the analyses were performed on a relatively small group of patients, the Pfirrmann and Modified Dallas grading were dichotomized. Literature states that, for the Pfirrmann grading, interobserver agreement is highest between grade II and III.[32] Therefore Pfirrmann grade findings were dichotomized (≤ or > grade II). Furthermore, other baseline values of possible predictors were registered (ie, demographics and baseline patient characteristics).

Statistical Methods

A linear mixed model analysis for longitudinal data establishes differences in pain score changes over time. The changes in outcome between baseline and 6 months were compared between responder patients and non-responders. Differences were tested with the Mann–Whitney test for nonparametric data. Furthermore, binary logistic regression explored possible predictors for success or failure of the procedure.

Results

Participant Flow

One hundred and forty-seven patients with chronic LBP were eligible for screening and 56 reacted positive on facet blocks. After discography, 15 patients enrolled in the pilot study (Figure 1). Of the 15 patients included in the study, 12 patients completed the study protocol with follow-up data of 6 weeks, 3 months, and 6 months. The 2 two patients of the pilot were dissatisfied with the short-term result and only filled in the follow-up data of 6 weeks after the intervention. In reaction to these events, patients received more information about expectations of the short time results. With this routine established, only one patient was lost to follow-up at the 6-month assessment.

Recruitment and Follow-up

Patients were recruited from March 2011 until September 2012. Patients received a pain diary and a questionnaires booklet at baseline and at standardized follow-up moments of 6 weeks, and 3 and 6 months.

Baseline Data

Table 1 shows baseline demographics and clinical characteristics of the study group. Ten female and 5 male patients were treated. The mean duration of LBP was 5.6 years, mean pain at baseline was NRS 6.7, and quality of life was on average rated rather low between 32 and 54. Five patients used opioids at baseline. Mean age was 40.8 (22 to 57).

Outcome

Pain and Patient Global Impression of Change. Linear mixed model analysis for pain at 6 months (Figure 2) shows that mean predicted pain reduction at 6 months is 2 points (6.4 to 0.08 x weeks). The result of responder analyses is depicted in Figure 3. Pain treatment at

6 months was successful in 40% of patients, with at least 30% pain reduction in 6 patients (more than 50% in 5 patients). Table 2 shows that the mean pain reduction at 6 months in responding patients is 7.1 (11-box NRS score 0 to10) resulting in a mean NRS pain score of 2.4. In contrast, the non-responders mean pain score was 6.8 at 6 months. The Patient Global Impression of Change was very much improved in 5 and much improved in 1 responder patient. One nonresponding patient rated the change as minimally improved, the other 5 patients as not improved.

At 3 months follow-up, 7 patients (47%) responded with at least 30% pain reduction to the treatment (Mean NRS pain change -3.4, SD 1.6).

Table 1: Baseline Characteristics and Demographics

Variables		**Value *N* (total =15)**
Sex		
Male		5
Female		10
Discopathy Level:		
L3-L4		1
L4-L5		5
L5-S1		9
	Mean(SD)	**Min-Max**
Age (Years)	40.8 (10.5)	22-57
Body Mass Index	24.4 (3.8)	15-31
Duration of LBP (Years)	5.6 (5.1)	1-20
Mean Pain (NRS)	6.7 (1.4)	4-9
Quality of Life		
Physical Component Score	32.1 (7.5)	22.5-44.1
Mental Components Score	48.0 (11.9)	29.4-66.4
EuroQol VAS	54.2 (22.6)	15-90
Disability	**%(SD)**	
Oswestry	59.7(10.9)	44-82
Prior Analgesic use		**N(%)**
Non-NSAID		3(20)
NSAID		3(20)
OPIOIDS		5(33)

NRS= Numeric Rating Score VAS=Visual Analogue Scale

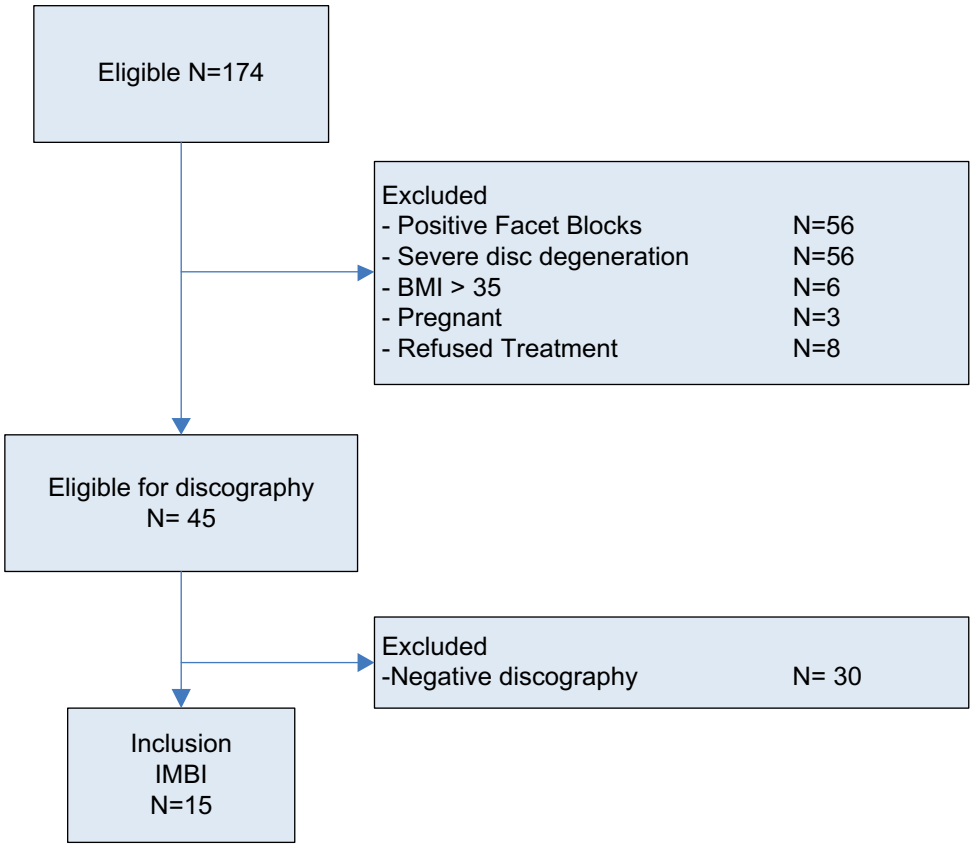

Figure 1. Flowchart of study participants.

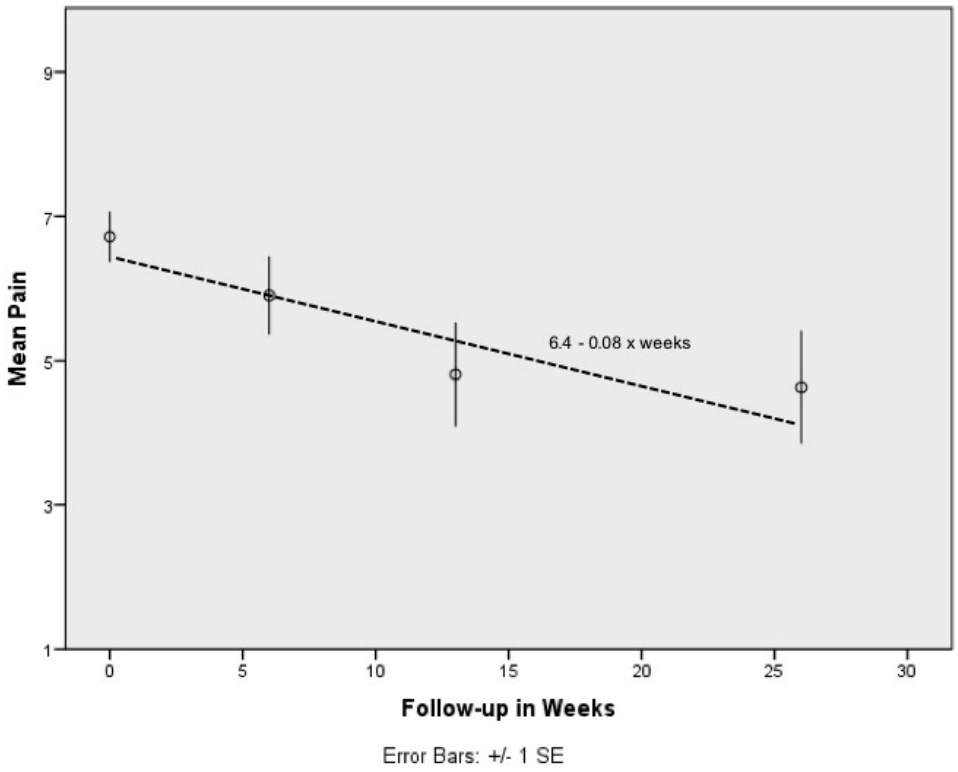

Figure 2. Mean pain over time. The points and vertical lines represent mean pain (NRS) with standard errors, at each measured time point. Linear regression line (dashed line) calculated with linear mixed model analysis.

Function and Quality of Life.

Two main quality of life outcome scores were calculated from the SF-36: the Mental Components Summary (MCS) and the Physical Components Summary (PCS).[33] Decreasing values for the Oswestry, EuroQol-VAS, PCS, and MCS scores of the SF 36 are related to patient deterioration (increase in pain and disability, decrease in quality of life). Responding patients improved their physical function with 17.3% on average, measured with the Oswestry Disability Index (Table 2). The PCS of the SF- 36 also showed progress (ie, 10 points improvement. The MCS and Euroqol VAS showed no improvement

Analgesic Use.

Overall, use of NSAIDs and opioids was reduced at 6 months. Of the responder patients, the 2 patients who used an opioid for their pain ceased the use of opioids during the follow-up. In the non-responder group, 2 patients still used opioids at 6 months.

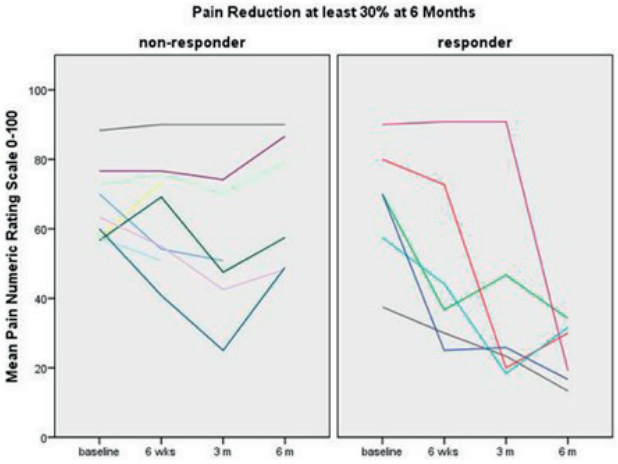

Figure 3: Result of responder analysis of pain reduction over time. Each line depicts a patient.

Adverse Events and Complications.
No adverse events were reported. Most patients suffered a transient increase in axial LBP for 1 to 2 weeks after treatment. Some patients reported a transient (1 to 2 weeks) painful feeling of pressure in the injected spine area.

Magnetic Resonance Imaging (MRI) and Provocative Discography Findings.
At baseline, the MRI of 8 (53%) patients showed a Pfirrmann grading of more than II.[32-34] In 5 MRIs Modic signs were detected,[35] high intensity zones in 6. Twelve-month follow-up MRI findings showed no signs of rapidly progressed disc degeneration. There was no noticeable change in the presence of Modic signs, high intensity zones, or Pfirrmann grading.[16, 30]

Table 2: Results of Responder Analyses

Outcome Variables	Responders	Non Responders	P-value*
	N=6	***N=6 Completers***	
Pain	***CS(Mean)***	***CS(Mean)***	
Mean Pain (NRS) 6 Months	-7.1 (2.4)	0.1 (6.8)	**0.002**
Quality of Life			
Mean Physical Component Score	10 (44.2)	-4.0 (26.8)	**0.002**
Mean Mental Components Score	-1 (55.5)	3.5 (48.2)	0.818
EuroQol (VAS)	3 (65.3)	-10 (43.0)	0.126
Disability			
Oswestry (%disability)	17.3 (38)	-6.3 (67.6)	**0.002**
Analgesic use (N)			
Non-NSAID (Baseline use)	-2 (2)	+1(0)	
NSAID (Baseline use)	-1 (1)	-1 (1)	
OPIOIDS (Baseline use)	0 (2)	-1 (3)	
PGIC			
Very Much Improved	5	0	
Much Improved	1	0	
Minimally Improved	0	1	
Not improved	0	8	

*Mann-Whitney U Test
Change Scores after six Months of Non-Responders versus Responders
CS= Change Scores NRS= Numeric Rating Score VAS=Visual Analogue Scale

Prediction for Success or Failure

Binary logistic regression analyses assessed if success or failure is predictable by baseline variables (Table 3). The quality of life main component, MCS, appears to be a predictor for success or failure. It indicates that patients who score higher at baseline are more likely positive responding to intradiscal methylene blue injection treatment. The Pfirrmann grading was also an independent factor for failure (P = 0.02); 7 of the 8 patients with a Pfirrmann Grade of more than grade II were nonresponsive to treatment. Patients with a Pfirrmann grade of 2 or less were better responders (P = 0.04). Seven patients had relatively well-maintained discs (Pfirrmann Grade 2 or less); 5 of these 7 responded well.

Discussion

This prospective case series of 15 patients showed that intradiscal methylene blue injection treatment is successful in 40% of well-selected discogenic LBP patients. Success definition was pain relief of at least 30% at 6 months. Patients who responded well also improved in function and quality of life and diminished their medication use. No complications or serious side effects were noted.

Since the publication of the original RCT in which methylene blue is described as a highly successful remedy for discogenic pain 2 two prospective studies have been published.[36, 37] First, in a study of 8 patients, no clinical effect was found. Second, in a study of 20 patients, only 20% of patients showed long-term pain reduction.[37] A possible explanation for the discrepancies in results between our study and the 2 aforementioned prospective studies could be that our selection criteria were more stringent. For instance, in our study, the treatment algorithm dictates that patients should have had facet blocks without sufficient pain reduction before intradiscal methylene blue injection treatment is considered. Pain, mainly produced by facet arthritis is in our patient-series therefore, excluded.

The presumed and accepted working mechanism of this treatment is denervation of the small nociceptive fibers that grow into a diseased disc's annulus fibrosis. The other working mechanism of intradiscal methylene blue could be that it alleviates inflammatory processes that may lead to fibrosis.[16, 38] Methylene blue is also a direct inhibitor of nitric oxide (NO) synthesis. Nitric oxide plays an important role in the inflammatory process of disc degeneration and therefore, in discogenic pain. [16, 38] A recent study that describes the positive effect of antibiotics on lumbar discogenic pain, shows that inflammatory and low-grade infectious processes could be involved in discogenic pain.[39] In that respect, Modic type 1 changes could be an indication for chronic spondylodiscitis in discogenic LBP.[29, 30, 39]

In our study, we duplicated the prospective study of 2007.[17] In order to select exclusively patients with discogenic pain, we performed provocative discography with pressure and velocity control using a Controlled Disc Stimulation (CDS) system. Despite our efforts, we could not duplicate the exceptionally good result of the aforementioned study and found only 40% of patients responding to this treatment. Nevertheless, the 40% of responding patients had good pain relief and improved in physical function and quality of life.

It is important to know the effect of injection(s) with methylene blue on disc tissue. Therefore, MRI's were repeated 1 year after treatment. Findings after 1 year of treatment indicate that in the patients assessed, there is no indication of rapidly degeneration of the intervertebral disc. To establish possible positive effects of methylene blue on intradiscal inflammation processes, MRI scans before and after treatment were also judged on the

presence of Modic signs.[16] There was no change in the presence of Modic signs in these patients. Since only 5 patients had Modic signs a baseline, this result could be due to the small numbers assessed. Therefore, this assessment of 1-year follow-up MRI findings shall be repeated in the subsequent RCT.

The MCS appeared to be a predictive factor for success or failure, indicating that patients who score higher at baseline at this quality of life main component have a better chance of success after intradiscal methylene blue injection treatment. Although this result seems to be coherent to everyday clinical practice, we must point out that predictor analysis in such a small number of patients can only be classified as indicative. The results of the ensuing RCT will probably be more conclusive. The predictor analysis also shows that a Pfirrmann grade of 2 or less before the treatment could be a predictor for success. This matches the finding in a recent study in which patients with Pfirrmann grade ≤ 2 responded favorably on Intradiscal Electro Thermal therapy (IDET).[40] The presumed working mechanism of IDET therapy is similar to Intradiscal methylene blue injection insofar as the target points for treatment are the nerve endings in annular tears.

Table 3: Results of Binary Logistic Analyses

Baseline Predictor Variable	Baseline Value of Responder	Baseline Value of Nonresponder	P-value
Gender			
Male *(N)*	1	4	***0.28***
Female *(N)*	5	5	
	Mean (SD)	**Mean (SD)**	
SF 36 QOL Mean(SD)			
MCS			
PCS	55.6(3.2)	42.9(13)	0.07
EuroQol (VAS)	34.1(8.8)	30.7(6.6)	0.37
Disease duration	54.2 (20.4)	54.2 (25.2)	0.99
(months)	48(34)	80(73)	0.34
	N (% ^{r})	N (% ^{nr})	
MRI			
Modic signs	1 (17)	4 (44)	0.29
HIZ	3 (50)	3 (33)	0.52
Pfirrmann Grade > 2	1 (12.5)	7 (87.5)	0.02
Provocative discography			0.27
Modified Dallas Scale > 2	3 (22)	3 (50)	

HIZ, high intensity zone, % $^{(n)r}$ = % within (non)responder; MCS, Mental Components Summary; PCS, Physical Components Summary

For lumbar discogenic pain patients, for whom to date there is no alternative pain remedy, intradiscal methylene blue injection could be a treatment option. It seems unlikely that the results (40% of treated patients had at least 30% pain reduction) are a product of placebo response only. Furthermore, only 15 patients were recruited and followed-up, this sample size is too small to come to firm conclusions. Therefore, a randomized double-blind placebo-controlled trial will follow this study to establish whether these results are reproducible in a larger discogenic back pain population and to determine the size of a possible placebo effect under controlled conditions. This RCT will be performed in 4 specialized interventional pain centers in the Netherlands. Based on the former published RCT, adapted by the results from this prospective study, the sample size assumption for the following RCT is 80 patients, 40 will be randomized in the treatment group and 40 patients in the control group. In this RCT, the randomized treatment group will receive an intradiscal injection with 1 mL Methylene blue, 0.5 mL Lidocaine, and 0.5 mL Iohexol contrast dye (Iohexol-Omnipaque 300; GE Healthcare, Princeton, NJ, USA); the control group will be injected with 1 mL NaCl 0.9%, 0.5 mL Lidocaine and 0.5 mL Iohexol. Interim analysis with the data of the 6 months assessment of 50 patients is preplanned to correct for sample size assumptions.

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CHAPTER 5

A Multicenter Randomized Controlled Trial on the Efficacy of Intradiscal Methylene Blue Injection for Chronic Discogenic Low Back Pain: the IMBI Study

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Abstract

A study published in PAIN in 2010 showed remarkable effects of intradiscal methylene blue (MB) injections compared with placebo on pain intensity in patients with chronic discogenic low back pain (CD-LBP). Both groups received lidocaine hydrochloride injections for pain associated with the procedure. We replicated the design of the previously published study and performed a multicenter, double-blind, randomized, placebo-controlled trial to assess whether the extraordinary effects of MB on pain intensity could be confirmed. The primary outcomes were treatment success defined as at least 30% reduction in pain intensity and the Patient's Global Impression of Change 6 months after the intervention. We included 84 patients with CD-LBP of which 14 (35%) in the MB plus lidocaine group showed treatment success compared with 11 (26.8%) in the control group who received placebo plus lidocaine (P = 0.426). Twenty-seven percent of all participants treated with MB stated that their overall health improved much or very much (Patient's Global Impression of Change), vs 25.6% in the placebo group (P = 0.958). We were unable to confirm that intradiscal MB injections are better capable of significantly reducing pain in patients with CD-LBP 6 months after treatment compared with placebo. We observed that over one-quarter of patients receiving only lidocaine injections reported treatment success, which is in contrast with the previously published study. Our results do not support the recommendation of using intradiscal MB injections for patients with CD-LBP.

Keywords

Low back pain, Discogenic, Randomized controlled trial, Methylene blue, Lidocaine

Introduction

In 2010, Peng et al.[1] published a very large clinical effect of intradiscal methylene blue (MB) injections compared with placebo on pain intensity in patients with chronic discogenic low back pain (CD-LBP). In their study, they reported that the average pain intensity in the MB group dropped from 72.33 at baseline to 24.94 on a 0- to 100-point Numeric Rating Scale (NRS) score compared with a decrease of 67.28 to 63.51 in the placebo group 6 months after the intervention.[1] The effect of MB was observed over a study period of 24 months. Their results are much debated,[2-4] and the authors as well as the accompanied editorial concluded that the effect of MB was indeed remarkable and urged others to replicate their results.[2] A few small studies tried to, but to date without convincing evidence.[5-7] In a clinical series of 15 patients, we observed that 40% of patients who received MB showed a clinical meaningful decrease in pain 1 year after treatment, but we did not include a control group.[8]

The importance of confirming their results is exemplified by the sheer impact of LBP on society: more than 70% of the population in industrialized countries will experience LBP at least once in their lifetime,[9] and it brings about a substantial financial burden.[4-7, 10-13] In many cases, health care professionals are unable to identify a specific nociceptive cause of LBP.[14] Various research studies indicate that a part of chronic LBP may be attributed to degeneration of the intervertebral disk or CD-LBP.[8, 9, 15-18]

The leading cause of CD-LBP is internal disk disruption that is hypothesized to be related to vascularized granulation tissue containing nociceptive nerves, extending from the outer layer of the annulus fibrosis into the nucleus pulposus.[15, 19-21] Under the assumption that these ingrown nerve endings in the outer annulus play an important factor in CD-LBP, many attempts have been made to prove that reduction of inflammation and/or ablation of the nociceptive nerves in the outer annulus could be beneficial for patients with CD-LBP.[22]

Methylene blue is known to have a neurolytic effect and has been used for the treatment of various painful conditions and idiopathic pruritus ani.[23-25] Methylene blue also has an anti-inflammatory effect, including the inhibition of free radical generation, deactivation of xanthine oxidase, and inhibition of the production of nitric oxide.[26] The anti-inflammatory effect on postoperative LBP has been studied in patients who underwent open lumbar discectomy.[27] Methylene blue significantly reduced postoperative LBP and radicular pain as well as improved functional results. Peng et al. described one of the first applications of MB in patients with CD-LBP.[1, 22] The objective of this multicenter, double-blind, randomized placebo-controlled trial was to assess the efficacy of intradiscal MB injection on pain intensity compared with placebo in patients with CD-LBP, and to assess whether the previously published effect could be confirmed.

Methods

This study was reported in accordance with the Consolidated Standards f Reporting Trials (CONSORT) statement. This parallel-group multicenter, double-blind, randomized placebo-controlled trial was performed in 4 interventional pain centers in the Netherlands (ie, Rijnstate Arnhem, Catharina Eindhoven, Rijnland Leiderdorp, and Maastricht University Medical Centre). The study was approved by the Medical Ethics Committee of the Maastricht University Medical Centre and was registered in the Dutch Trial Registry (NTR number 2547). We replicated the study protocol of Peng et al. to be able to recreate the conditions of their study as best as possible. A side-by-side comparison of the methods of both studies is shown in supplementary Table 1 (a supplement at the end of this manuscript) A thorough description of our study protocol has been published previously.[17]

Patients

Patients with chronic lumbar axial pain referred to one of the participating hospitals between July 2013 and February 2017 were asked to participate in the study if they met the eligibility criteria. Patients were considered eligible if they had a history consistent with lumbar discogenic pain, suffered from LBP for at least 6 months, reported poor response to conservative treatment such as physical therapy and medication for at least 6 weeks before their intake, were between 18 and 66 years of age, had a neurological examination without motor deficit, reported pain intensity of at least 5 on an 11-point NRS in a seated position, and had a magnetic resonance imaging in the past 12 months to rule out severe disk degeneration, defined as more than 50% loss of disk height at the affected level.[17] Patients were excluded if discogenic pain was confirmed on more than 2 levels, if they had extruded or sequestered herniated nucleus pulposus, had undergone previous lumbar surgery or invasive intradiscal procedures on suspected levels, had grade 1 to 5 spondylolisthesis, had a body mass index of 35 or more, were pregnant, received coagulopathy or oral anticoagulant therapy (except low-dose acetylsalicylic acid) in conditions that do not allow for a temporary discontinuation, or had an infection. All eligible patients received a facet blockade to rule out facet pain.[28-30] If the facet blockade was negative, patients were scheduled to receive a provocation discography.

Provocative discography is an imaging-guided procedure used to confirm or rule out a clinical hypothesis of discogenic LBP.[31, 32] During the procedure, which was conducted according to ISIS/ IASP guidelines, a needle was inserted in the nucleus pulposus of the

presumed symptomatic level and at least one adjacent level, and injected with a contrast agent to test the sensitivity of the disk by gradually increasing distending pressure (pressure-controlled discography). A small amount of patients were sedated during the needle insertion at their request. During the actual procedure, all patients were fully awake and not aware which disk level was provoked. Pain provocation had to be present in the disk(s) at pressures of less than 50 PSI above opening pressure, pain severity of 7 points on a 0- to 10-point NRS, or at least 70% reproduction of worst spontaneous pain.[33-35] During the procedure, annular tears were classified (grade I-IV) according to the modified Dallas classification.[36] All patients who fulfilled the eligibility criteria were asked to provide informed consent.

Interventions

All intradiscal procedures were performed in an operating room under strict sterile procedures by their pain physician. Before the procedure, the patient was administered intravenous antibiotics.[37] After antibiotic prophylaxis of 2-g cephazolin intravenously, a needle (with the double-needle technique) was placed in the symptomatic disk(s). Anteroposterior and lateral plane fluoroscopy was used to confirm needle position. The intradiscal injections were performed with a pressure- and velocity-controlled system (0.02 mL/ second).[38] In the MB group, a mixture of 1-mL MB (10 mg/mL), 0.5-mL lidocaine hydrochloride 2%, and 0.5-mL contrast dye (Iohexol Omnipaque 300) was injected into the disk. In the placebo group, a mixture of 1-mL isotonic saline, 0.5 mL of lidocaine hydrochloride 2%, and 0.5-mL contrast dye (Iohexol Omnipaque 300) was used. Patients were all submitted to the outpatient surgery unit after treatment and kept under bed rest observation for at least 2 hours.

Outcomes

Both primary and secondary outcome measures were assessed at baseline, at 6 weeks, and at 3, 6, 12, and 24 months after the intervention (see Fig. 1 for the study flowchart). During the follow-up moments after treatment, patients were seen by a physician or research nurse, blinded for the treatment. Before each visit, patients were asked to fill out a pain diary and several online questionnaires.

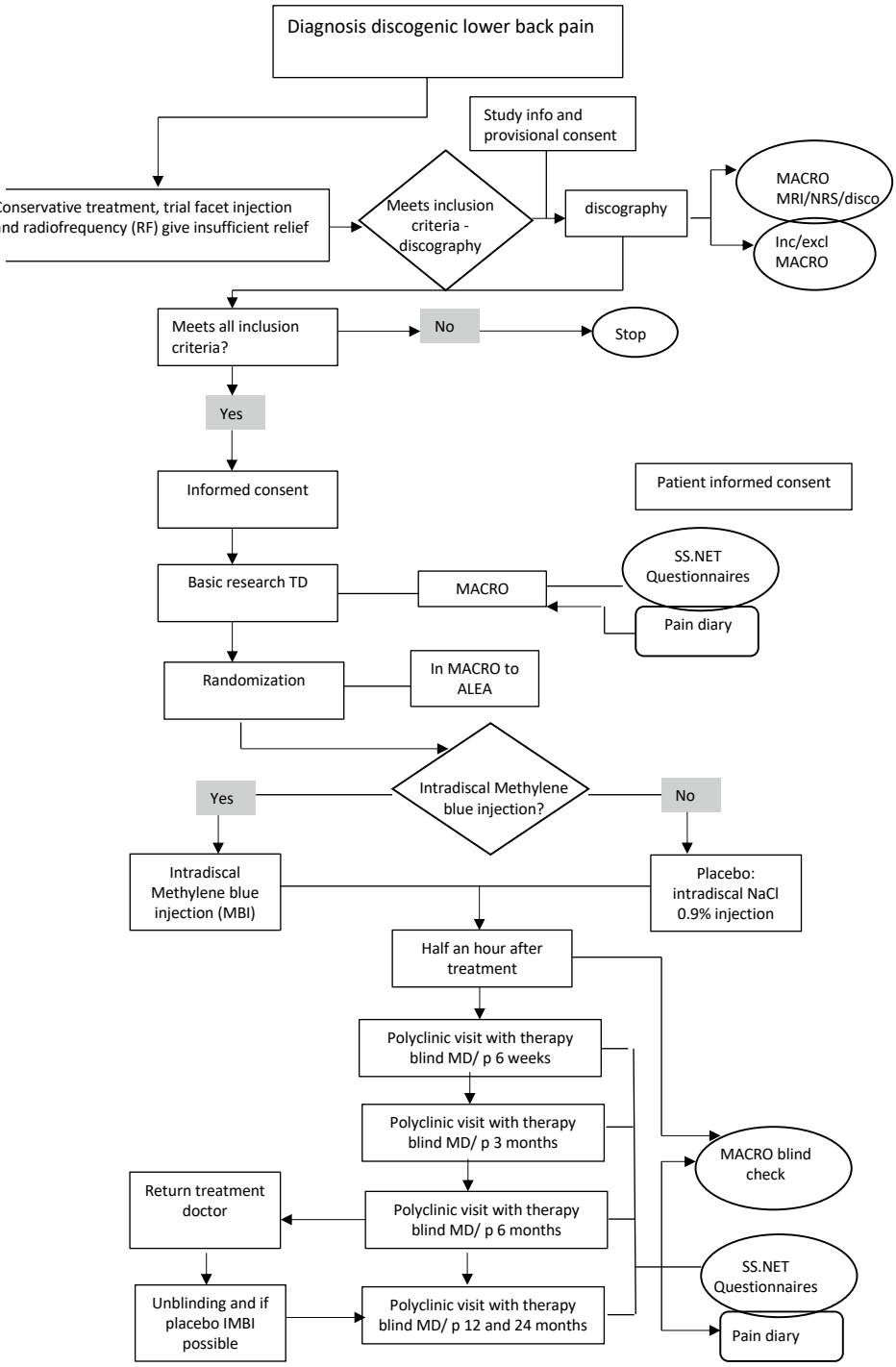

Figure 1: Flowchart of RCT IMBI. MRI, magnetic resonance imaging, NRS, Numeric Rating Scale; RCT, randomized controlled trial

The primary outcome measures were treatment success and the effect as perceived by the patient. Treatment success was defined as a pain reduction of at least 30% compared with baseline. Pain was quantified as the average of 3 measures per day for a total of 4 days using a 0- to 10-point NRS.[39, 40] The effect as perceived by the patients was measured using the Patients' Global Impression of Change (PGIC),[39] measured on a 7-point Likert scale. The PGIC was dichotomized into improved or not improved by combining the answer categories "improved" and "much improved," compared with all other answer categories "minimally improved," "no change," "minimally worse," "much worse," and "very much worse." The primary endpoint was 6 months after the intervention.

Secondary outcome measures were the use of analgesics, disability, quality of life (QoL), and pain characteristics. Patients were asked about their use of analgesics when completing their pain dairies. The patients were asked for 4 consecutive days to fill out the name, dosage, frequency, and times taken, of all medications they used. Disability was measured using the Oswestry Low Back Pain Disability Index (ODI), a 10-item questionnaire with 6 answer categories per item.[41] The total score represents the percentage of disability to manage in everyday life.[41] The RAND-36 and the EuroQol-5 Dimension (EQ-5D) were used to measure QoL.[42] Furthermore, the EQ-5D contains a Visual Analogue Scale (VAS) asking patients to grade their perceived health on a scale from 0 (worst possible health status) to 100 (best possible health status).[42] The McGill Pain Questionnaire was used to assess the sensory, affective, and cognitive dimensions of a patient's pain experience.[39, 43, 44]

Sample size

The sample size was based on obtaining 80% power to detect a clinically meaningful difference in the proportion of patients reporting treatment success. To be conservative, we estimated the success rate in the control group to be 20%. Given the minor invasive nature of the procedure, an additional 30% patients or more reporting treatment success in the MB treatment group was regarded as a clinically meaningful difference between the groups. A total of 36 patients would be needed for each group, when keeping the type-I error rate at 5%. To account for a potential loss to follow-up of 10%, the sample size was adjusted upwards to include 40 patients per group. A sample of this size would also ensure ample power (>80%) to detect differences of as small as 1 point on the NRS between groups, assuming a SD of 1.5 (pooled SD of the 6-month measurement in the study by Peng et al.).

Randomization and blinding

After inclusion by their treating physician or a research nurse, patients were randomized using stratified block randomization with random permuted block sizes. Patients were

allocated in a 1:1 ratio to the intervention or the control group, using the dedicated randomization software (ALEA version 2.2, CTCM/ ALEA). The randomization was stratified by study center, sex, disk level (L3/L4-L4/L5 vs L5/S1) and dichotomized modified Dallas criteria (grade I and II vs grade III and IV). After randomization, an email containing the treatment allocation was automatically sent to the treating physician. Patients and the researcher or research nurse who performed patient visits after treatment were blinded to the treatment allocation. To verify the blinding process, all patients were asked directly after the intervention to state which treatment they believed they had received: MB treatment, placebo treatment, or not sure what treatment. This question was repeated at the 6-week follow-up.

Statistical analyses

Patient characteristics were summarized using mean and SD or count and percentage. In case of severe skewness of continuous variables, we used the median and the first and third quartiles. Missing data were imputed using stochastic regression imputation to prevent a loss of statistical power and to decrease the probability of biased treatment effects compared with using only complete cases.

The difference in the proportion of treatment success and in the proportion of improvement on the PGIC between the MB and the placebo group was assessed using the Pearson x^2 test. Secondary outcome measures were tested between groups using the Student *t* test and Pearson x^2 test, depending on the measurement level of the outcome (continuous or dichotomous). All analyses were performed according to the intention-to-treat principle. As a sensitivity analysis, we performed a per-protocol analysis on the primary outcomes. All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

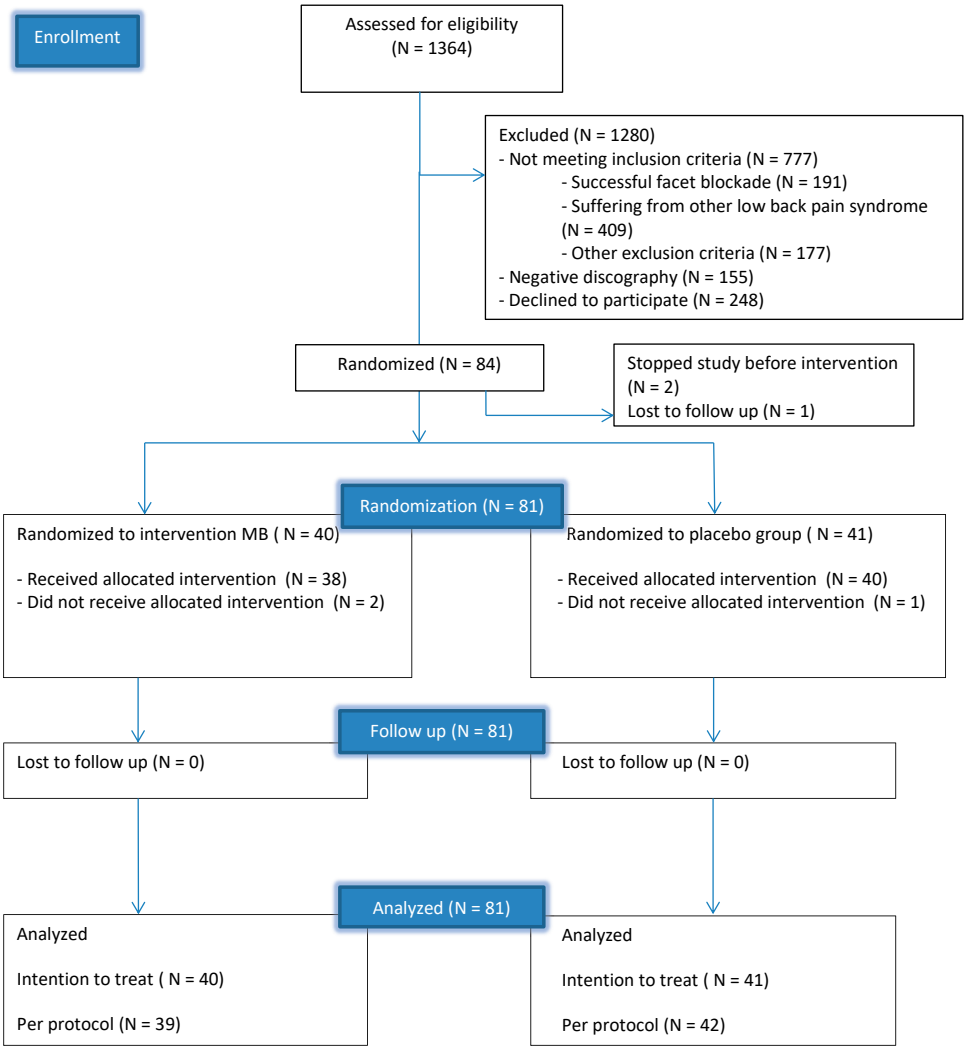

Figure 2: Flowchart of study participants. MB, methylene blue

Results

Participant flow

Patients were recruited from July 2013 up to January 2017. A total of 1364 patients with chronic LBP were eligible for screening (Fig. 2). Patients were excluded from participation because of successful facet blockade (n = 191), suffering from a pain syndrome different from CD-LBP (n = 409), not fulfilling other inclusion and exclusion criteria (n = 177), refusing to participate in the study (n = 248), negative discography (n = 155), and other reasons (n = 100). Of the 84 patients enrolled in the study, 81 patients completed the study protocol with follow-up data of 6 weeks, 3 months, and 6 months after the intervention. Two of the 3 patients who did not complete the protocol stopped participating voluntarily before the intervention was given and did not contribute any outcome measures. The remaining patient was lost to follow-up due to sickness of the research nurse in one of the participating centers. Because of lack of data, these 3 patients could not be imputed and did not contribute to the analysis. Three participants did not receive the correct treatment according to the randomization scheme. In 2 cases, the error was made due to incorrect medication distribution at the pharmacy. In the third situation, the error was made due to inaccurate verification of patient number vs randomization number.

Baseline data

Table 1 provides an overview of the baseline patient characteristics stratified by treatment allocation. In total, 81 patients were randomized into one of the treatment arms: 40 patients in the intervention group and 41 patients in the placebo group. Each treatment group consisted of 29 women. The mean age in the MB group was 41.2 years (22-59) vs 42.6 years in the placebo group (21-65). In both treatment groups, the mean pain at baseline was NRS 6.6. Fifteen patients in the MB group used opioids compared with 14 patients in the placebo group. The patients in the MB group rated their physical QoL (measured with the SF- 36 questionnaire) on average at 49.8, whereas the placebo group scored 46.9. The mental QoL (SF-36) was 66.1 (MB group) vs 63.9 (placebo group). In addition, Table 1 shows aggregated baseline characteristics of the study by Peng et al. There was a notable difference in the proportion of women included in this study compared with theirs.

Primary outcomes

In total, 25 patients (30.9%) had a pain reduction of at least 30% compared with baseline, which was regarded as treatment success. At 6 months, 14 (35%) patients in the MB group showed treatment success compared with 11 (26.8%) in the placebo group ($P = 0.426$). Table 2 shows the results of both groups for treatment success and perceived treatment

effect at 6 weeks, 3 months, and 6 months. Twenty-five percent of participants allocated to the MB group stated that their overall health improved much or very much (PGIC), compared with 24.4% in the placebo group ($P = 0.958$). Nine patients in the MB group (22.5%) and 8 (19.5%) patients in the placebo group had a pain reduction of at least 30% compared with baseline and stated that their overall health improved much or very much on the PGIC.

We observed that 6 months after treatment, the NRS score in the MB group was reduced on average with 1.4 points compared with baseline to a mean of 5.2 (Table 3). In the placebo group, the average score dropped 1.2 points, reducing the mean NRS score to 5.4 (*P* value for difference between groups = 0.671).

The per-protocol analysis showed no change in the amount of patients with treatment success 6 months after treatment. Although the mean NRS score in the MB group was slightly lower in the per-protocol analysis compared with intention-to- treat analysis (5.0 vs 5.2), the difference in pain scores between the 2 treatment groups remained statistically insignificant ($P = 0.536$). The results from the per-protocol analysis showed no change in conclusion with respect to the PGIC: 27.8% of the participants treated with MB stated that their overall health improved much or very much (PGIC), vs 25.0% in the placebo group ($P = 0.749$).

Table 1. Baseline characteristics stratified by treatment allocation, including summary measures of the study by Peng et al.

Characteristics	MB (N = 40)	Placebo (N = 41)	Peng et al. (N = 72)†
Women, No (%)	29 (72.5)	29 (70.7)	31 (43.1)
Age, mean (SD)	41.2 (9.6)	42.6 (10.2)	41.7 (13.3)
Pain NRS, mean (SD)	6.6 (1.4)	6.6 (1.6)	69.8 (12.0)‡
Body Mass Index, mean (SD)	25.8 (3.4)	24.9 (3.8)	NA
Duration LBP (years), mean (SD)	10.2 (8.8)	8.5 (7.1)	3.4 (1.7)
Level of painful disc, No (%)			
- L3-L4	1 (2.5)	4 (9.8)	1 (1.4)
- L4-L5	18 (45.0)	19 (46.3)	26 (36.1)
- L5-S1	14 (35.0)	15 (36.6)	32 (44.4)
- L3-L4, L4-L5	0 (0.0)	0 (0.0)	2 (2.8)
- L3-L4, L5-S1	1 (2.5)	0 (0.0)	3 (4.2)
- L4-L5, L5-S1	6 (15.0)	3 (7.3)	8 (11.1)
Analgesic use, No (%)			NA
- No medication	14 (25.0)	16 (29.6)	
- PCM	13 (23.2)	13 (24.1)	
- NSAID	14 (25.0)	11 (20.4)	
- Weak opioids and anti- neuropathic	11 (19.6)	9 (16.7)	
- Strong opioids	4 (7.1)	5 (9.3)	
Quality of life, mean (SD)			NA
Mental component score	49.8 (17.3)	46.9 (19.0)	
Physical component score	66.1 (16.5)	63.9 (23.0)	
EuroQol VAS, mean (SD)	52.9 (16.5)	51.8 (18.8)	NA
Oswestry Disability Index, mean (SD)	44.5 (14.1)	42.8 (15.9)	49.0 (6.0)

NRS, Numeric Rating Score (0-10); LBP, Low Back Pain; VAS, Visual Analogue Scale (0-100); NA, not available
†Aggregated data of both treatment groups
‡Measured on a 0-100 point NRS

Secondary outcomes

Mobility and quality of life

The SF-36 questionnaire was used to calculate the mental components summary and the physical components summary (Table 4). In both groups, we observed an improvement in the participant's physical function, and we did not find evidence of a difference between groups (P = 0.969). This also applied to the EuroQol VAS and the ODI. The mean score for both treatment groups on mental components summary showed a slight, statistically insignificant, deterioration.

Table 2: Treatment success based on NRS and treatment effect at 6 weeks, 3 months, and 6 months.

	MB (N = 40)	Placebo (N = 41)	*P*- value
Treatment success based on NRS, No (%)			
6 weeks	6 (15.0)	7 (17.1)	0.799
3 months	10 (25.0)	10 (24.4)	0.949
6 months	14 (35.0)	11 (26.8)	0.426
Treatment success based on patients global impression of change, No (%)			
6 weeks	5 (12.5)	6 (14.6)	0.821
3 months	8 (20.0)	11 (26.8)	0.554
6 months	10 (25.0)	10 (24.4)	0.892

NRS, Numeric Rating Scale (0-10)

Table 3. Change scores pain at 6 weeks, 3 months and 6 months post intervention.

	MB (N = 40)	Placebo (N = 41)	Difference (95% CI)	*P*- value
Pain NRS, mean (SD)				
Baseline	6.6 (1.4)	6.6 (1.6)		
6 weeks	-0.9 (1.8)	-0.5 (1.4)	0.4 (-0.3, 1.2)	0.206
3 months	-1.2 (2.3)	-0.7 (1.7)	0.5 (-0.4, 1.3)	0.295
6 months	-1.4 (2.3)	-1.2 (2.4)	0.2 (-0.8, 1.2)	0.671

NRS, Numeric Rating Scale (0-10); CI: confidence interval

Analgesic use

The number of participants who did not use any form of pain medication increased between baseline and 6 months in both groups (Table 4). The number of participants using opioids (both weak and strong) was the same in both treatment groups. Six weeks after the intervention, there was a statistically significant difference in paracetamol use between the MB group and the placebo group (17 in the MB group vs 4, $P = 0.040$). However, the difference decreased over time. A statistically significant difference between groups was found in the use of weak opioids and antineuropathic medication at the 3 months after the intervention. In the MB group, 17 patients used one or multiple analgesics categorized as weak opioids or antineuropathic, vs 8 in the placebo group ($P = 0.048$). The difference between treatment groups did not extend to the primary endpoint of 6 months.

Adverse events and complications

Fifteen transient adverse events (AEs) were reported in the 6 months after the intervention, including transient increase of pain (N = 4), dizziness (N = 1), radiating pain (N = 3), infection (urine tract infection) (N = 1), and tiredness (N = 1). Towards the primary endpoint of 6 months, 2 serious AEs (SAEs) were reported which both occurred in the MB group. One SAE was due to elective surgery not related to the invention, whereas the other SAE involved hospitalization due to illness (laryngitis) ($P = 0.494$). Analysis showed no statistical difference between the amount of AEs in each treatment group at 6 weeks ($P = 0.204$), 3 months ($P = 0.465$), or 6 months ($P = 0.363$).

Table 4. Mean change in Quality of Life, Disability and VAS score and overall analgesic use at 6 weeks, 3 months and 6 months post intervention.

	MB (N = 40)	Placebo (N = 41)		MB (N = 40)	Placebo (N = 41)		MB (N = 40)	Placebo (N = 41)	
	6 weeks	**6 weeks**	***P*-value**	**3 months**	**3 months**	***P*-value**	**6 months**	**6 months**	***P*-value**
Quality of Life, mean (SD)									
PCS	5.9 (19.6)	8.7 (20.5)	.535	9.3 (21.9)	9.2 (15.4)	.976	11.1 (22.4)	10.9 (18.7)	.969
MCS	3.3 (15.5)	4.0 (12.1)	.811	6.5 (17.3)	4.3 (13.5)	.520	-1.9 (10.3)	-1.5 (7.8)	.926
EuroQol VAS	3.1 (21.4)	4.2 (20.7)	.732	6.7 (21.3)	3.8 (22.3)	.482	7.7 (23.9)	5.6 (23.2)	.739
Oswestry Disability Index	-8.0 (17.1)	-1.7 (9.8)	.046	-8.8 (18.4)	-3.6 (9.9)	.123	-7.8 (16.9)	-5.5 (10.5)	.459
Analgesic use, No									
-No medication	18	25	.150	15	20	.306	18	20	.733
-PCM	11	4	**.040**	10	11	.851	11	12	.860
-NSAID	9	7	.540	14	9	.193	9	8	.741
-Weak opioids and anti-neuropathic	13	9	.107	17	8	**.048**	12	10	.570
-Strong opioids	1	5	.201	2	6	.264	3	4	1.000

PCS, Physical Components Summary; MCS, Mental Components Summary; VAS, Visual Analogue Scale (0-100)

Blinding

Most participants stated directly after the intervention that they did not know wich treatment they received (75% vs 73.2% in the MB group and placebo group, respectively). This also applies 6 weeks after the intervention. A small amount of participants thought that they had received MB or placebo. Statistical analysis showed that there was no difference in proportion between the treatment groups directly after the treatment ($P = 0.328$) or 6 weeks after the intervention ($P = 0.461$).

Discussion

Although we replicated the study protocol by Peng et al. as much as possible, we were unable to reproduce anything near their effect size. Patients on average showed clinically meaningful improvement over time, but our study showed only a small but statistically and clinically insignificant effect of the MB over the placebo group on both pain and QoL in patients with CD-LBP.

In their study, Peng et al. included 72 male patients evenly distributed over the intervention group (MB injections) and control group (isotonic saline injections). They reported that the average NRS score dropped 47.39 points on a 0- to 100-point NRS score compared with 3.77 in the placebo group 6 months after the intervention.[1] The mean ODI score in the MB group was 48.47 at baseline and 16.00 at 6 months. In the placebo group, the ODI scores were 49.37 at baseline and 48.40 at 6 months after the intervention, thus showed hardly any improvement.[1] In their study, the difference in NRS and ODI scores between the 2 treatment groups was both clinically and statistically highly significant in favor of intradiscal injection with MB.

We observed substantial differences in results in both the intervention group and the placebo group compared with the study of Peng et al. The average response in the MB group of our study was much lower than theirs. We observed an average decrease of only 1.4 on a 0- to 10-point NRS. In addition, the control group in their study showed only a very small decrease in pain intensity over time. The control group in our study showed an average decrease in the NRS at 6 months of 1.2 points on a 0- to 10-point NRS, and over one-quarter reported treatment success. Hence, patients in the placebo group in our study reacted almost similar to the treatment as participants in the MB group. We observed similar effects on the ODI. Both groups showed clinically meaningful decrease at 6 months compared with baseline, both between-group differences were small and insignificant. As a result, between-group differences were much lower than anticipated.

The lack of substantial between-group differences may to some degree be caused by patients in both groups improving due to the natural course of their complaints but might also be partly attributable to the analgesic and anti-inflammatory effects of lidocaine.[45-48] As such, the effect of lidocaine may have obfuscated the effect of MB to some extent. However, owing to the design of our study, we cannot draw any conclusions on the effect of lidocaine alone or lidocaine in combination with MB in these patients. We have no explanation why patients in the control group of the study by Peng at al. did not show clinically meaningful response in the control group, although they also received intradiscal lidocaine injections, and why the results of this study differ to such an extent. Patients of both studies did not differ substantially from each other, besides the ratio of men to women that were included, nor were there any substantial differences in study design and treatment strategy.

During the past few years, several other research groups studied the effect of MB on CD-LBP, albeit in mostly small studies. Gupta et al. studied 8 patients in India with CD-LBP who were treated with MB injections in a retrospective case series.
Four patients reported clinically meaningful effect. However, the duration of pain relief varied strongly among the subjects: one patient reported 80% pain reduction for the duration of 6 weeks, one patient had 100% pain reduction for 2 weeks, one patient reported 100% pain reduction for 5 months, and one patient reported a 100% pain reduction for 1 year.[5] An observational study in China by Zhang et al. involved 33 patients diagnosed with CD-LBP treated with MB injections who were assessed at 1, 3, 6, and 12 months after the intervention. At the 6-month follow-up, the mean NRS score in the MB group dropped from 6.5 to 3.7. The ODI decreased from 56.1 at baseline to 27.1 at 6 months. Approximately 63% of all participants in the Zhang study were specified as therapy success 6 months after the intervention.[7] Kim et al. performed a prospective study in South Korea in which 20 patients with CD-LBP were followed for a year after treatment with MB injections. One month after the intervention, the NRS score dropped from 5.1 to 2.9. However, 6 months after the intervention, the average NRS score increased to 4.2, and 12 months after the intervention, the NRS score was 4.5. At this point, there was no statistically significant difference between baseline score and 12 months after the intervention score.[6] In a multicenter, prospective clinical case series involving 15 patients, our study group observed that 6 months after injection with MB, 40% of the participants with CD-LBP had a drop in the NRS score of at least 30%.[8]

A finding of our study is the limited applicability of intradiscal MB injections. Peng et al. assessed 132 patients to include and were able to randomize 76 patients of them. In our study, we assessed 1365 patients with chronic LBP for eligibility, but only 84 patients were eventually included into the study. These numbers lead us to believe that solely Chronic-LBP originating from the intervertebral disk is a rare phenomenon. We assume

that the cause of CD-LBP is multifactorial in the majority of all patients suffering from LBP, as most patients with CD-LBP suffer from a degenerative disease of the lumbar spine.[14, 18]

In conclusion, we were unable to confirm that intradiscal MB injections are better capable to reduce pain for patients with CD-LBP 6 months after treatment compared with intradiscal injections with isotonic saline hydrochloride. The expected differences in outcome between the 2 treatment groups were smaller than anticipated because the patients in the placebo group responded better to the treatment than expected. Our results do not support the recommendation of using intradiscal MB injection as a treatment therapy of choice for patients with CD-LBP. Nevertheless, it is important to note that 6 months after treatment, 35.0% of the patients in the MB treatment group and 27.0% in the lidocaine group experienced clinically relevant pain relief. We recommend further research to study the exact mechanism of CD-LBP and to define the specific characteristics of patients with CD-LBP to determine whether intradiscal injections (with MB or lidocaine 1%) may be a treatment option. At present, we do not recommend the use of intradiscal MB injections for CD-LBP.

Supplementary Table 1. Side-by-side comparison of the methods of the study of Peng et al. and the IMBI study

Study Characteristic	Peng et al.	IMBI study
Design	multicentre, randomized, double blind, placebo-controlled	multicentre, randomized, double blind, placebo-controlled
Intervention	1 mL of 1% MB followed by 1 mL of 2% lidocaine hydrochloride	1 mL (10mg/mL) MB followed by 0.5 mL of 2% lidocaine hydrochloride and 0.5 mL contrast dye
Control	1 mL of isotonic saline followed by 1 mL of 2% lidocaine hydrochloride	1 mL of isotonic saline followed by 0.5 mL of 2% lidocaine hydrochloride and 0.5 mL contrast dye
Inclusion criteria	chronic low back pain, evidence of lumbar disc degeneration, normal or slight decrease of disc height, treated conservatively without sufficient response for > 6 months, positive discography	chronic low back pain, history consistent with lumbar discogenic pain, up to 50% of loss of disc height, treated conservatively without sufficient response, positive discography
Exclusion criteria	radiculopathy, lumbar disc herniation, spinal instability, lumbar canal stenosis, spondylolysis, spondylolisthesis, disc degeneration with endplate Modic changes, neurologic disease, inflammatory arthritis, tumor, infection, presence of depression or taking antidepressants or anxiolytic drugs for the treatment of depression, previous lumbar surgery	discogenic pain on >2 levels, lumbar disc herniation, grade 1 to 5 spondylolisthesis, infection, previous lumbar surgery or invasive intradiscal procedure, BMI >35, pregnant, received coagulopathy or oral anticoagulant therapy (except low-dose acetylsalicyclic acid) in conditions that do not allow for a temporary discontinue, positive facet blockade
Outcome variables	pain (NRS), disability (ODI), patient satisfaction, use of analgesics, complications	pain (NRS), disability (ODI), perceived effect (PGIC), use of analgesics, quality of life (RAND-36 and EQ-5D), pain characteristics (MPQ), adverse events, complications

MB: methylene blue, NRS: numeric rating scale, ODI: Oswestry Disability Index, PGIC: Patient Global Impression of Change, MPQ: McGill Pain Questionnaire

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CHAPTER 6

Prospective Cohort Analysis of DRG Stimulation for Failed Back Surgery Syndrome Pain Following Lumbar Discectomy

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Abstract

Introduction

Surgical lumbar discectomy is a commonly performed routine spinal procedure that is usually undertaken to alleviate lumbar radicular symptoms caused by a herniated intervertebral disc. Surgical lumbar discectomy can also lead to chronic postsurgical leg and/or back pain (failed back surgery syndrome [FBSS]), a condition that can be refractory to conventional medical management. Early clinical results on the use of dorsal root ganglion (DRG) stimulation for FBSS have supported the use of this treatment alternative.

Methods

A multicenter, single-arm, observational cohort study enrolled patients who had chronic pain following surgical lumbar discectomy, had failed conservative treatments, and reported pain intensity of at least 6 out of 10 in the primary region of pain. Data were collected on pain, quality of life, disability, and mood at baseline and through 12 months.

Results

Thirteen patients underwent a trial of DRG stimulation; 11 (84.6%; 95% confidence interval = 57.8% to 95.7%) had good outcomes and underwent permanent device placement. Pain was reduced from a score of 8.64 (±0.92) at baseline to 2.40 (±2.38; n = 9) after 12 months of treatment, a 72.05% average reduction ($P < 0.001$). Similar improvements were observed across the secondary clinical measures, and safety data were in line with published rates.

Discussion

These results suggest that DRG stimulation induces pain relief in subjects diagnosed with FBSS. These reductions in pain were also associated with improvements in quality of life and disability. Additional prospective studies are warranted to further investigate this potential application of DRG stimulation, as well as to optimize patient selection, lead placement, and programming strategies.

Key Words

failed back surgery syndrome, dorsal root ganglia, stimulation, neuromodulation, spinal cord stimulation, back, pain, neuropathic

Introduction

Surgical lumbar discectomy is believed to be the most commonly performed routine spinal procedure; it is usually used to alleviate lumbar radicular symptoms caused by a herniated intervertebral disc.[1] It has also been reported to be a surgical intervention that can lead to chronic postsurgical leg and/or back pain (failed back surgery syndrome [FBSS]).[2] Recent estimates suggest that approximately 10 new cases of FBSS, of all causes, develop per 100,000 population every year,[3] and that 10% to 40% of patients who undergo lumbar spinal surgeries will develop FBSS.[4] For FBSS pain specifically induced by lumbar discectomy procedures, the reasons for this may be recurrent disc pathology, scarring and fibrosis, spinal instability, infection, stenosis, facet joint hypertrophy, or other etiologies.[5] Surgical revision rates in FBSS due to lumbar discectomy range from 5% to 33%; a retrospective analysis of 182 such revisions indicated that, although 80% of patients reported short term pain relief, these results were sustained in only 22%, with poorer outcomes associated with multiple revisions.[6] Patients with FBSS experience a significant decline in their quality of life, psychological outlook, and work productivity.[7] For example, in a randomized controlled trial of 100 subjects with post-discectomy FBSS who had failed conventional treatments to the point of considering an implanted neurostimulator, baseline quality-of-life index scores were approximately 0.15[8] on the EuroQol-5D (EQ-5D); a health-related quality of life questionnaire scoring from 0 [death] to 1 [perfect health]; for comparison, the average EQ-5D rating across the general population in the United Kingdom is 0.856.[9]

FBSS is often refractory to pharmacological or other minimally invasive treatments,[10] and can require an extended intervention algorithm potentially requiring years to identify an adequate treatment[3] Neuromodulation, typically spinal cord stimulation (SCS), may be offered as a more sustainable option for improving function and pain symptoms, when all other conservative and minimally invasive pain treatments have failed. Good evidence exists for the value of SCS in the treatment of FBSS.[11-16] In recent years, dorsal root ganglion (DRG) stimulation emerged as a viable treatment option for neuromodulation, based on early clinical results that included patients with FBSS.[17-19] Today it is a proven technique for several indications.[20] These results suggest that DRG stimulation may be a good option for patients with FBSS. A recent report showed effective relief of chronic low back pain associated with FBSS with DRG stimulation; the average reduction in pain relief across 12 patients was 45.5% after 12 months of treatment.[21] Thus, more comprehensive study of the value of DRG stimulation for FBSS may be warranted.

This report describes a prospective study in a homogenous subpopulation of FBSS patients with chronic pain following a surgical lumbar discectomy. Twelve months of treatment with DRG stimulation was observed.

Methods

This was a prospective, single-arm, multicenter, post-market, observational study with oversight of local ethics committees. Adults were included if they reported having pain following a surgical lumbar discectomy procedure. The primary region of pain was required to have intensity of at least 6 on a standard 0-to-10 numeric pain rating scale (NPRS) and to have persisted for a minimum of 6 months despite conservative treatments. Unstable pain patterns, recent corticosteroid or radiofrequency treatment at the target stimulation site, or current or planned pregnancy were exclusionary. All subjects gave written informed consent before study procedures commenced.

At baseline, before trial device implantation, subjects provided data on pain (NPRS and Brief Pain Inventory [BPI]), quality of life (EQ-5D), disability (Oswestry Disability Index [ODI]), and mood (Profile of Mood States [POMS]). These measures were repeated after receiving the permanent implant, following 1, 3, 6, and 12 months of treatment. Safety data were captured throughout the study.

Descriptive statistics, including mean, standard deviation (SD), and percentages, were generated. A repeated-measures analysis of variance (RMANOVA) was performed, with Tukey's post hoc pairwise comparisons, to compare differences from baseline. All tests were performed with an $a = 0.05$

Results

A total of 25 subjects were admitted to the study on the basis of meeting the inclusion and exclusion criteria, and 13 continued on to a neurostimulator trial. The 12 patients who failed screening had extensive intraforaminal fibrosis, determined from an MRI, and it was determined that these patients were not ideal candidates or DRG stimulation. All 13 patients who passed the screening criteria had a trial evaluation of DRG stimulation (intraoperative or for up to 30 days using an external stimulator). In most cases, implanters found that lead placement was straightforward. Of these, 11 (4.6%; 95% confidence interval [CI] = 57.8% to 97%; 7 women and 4 men; average age 51 years [range 26 to 70 years]) experienced better than 50% pain relief during the 14-day trial and proceeded with a permanent implant. Nine subjects were followed for 12 months; 2 subjects discontinued the study due to insufficient pain relief after the 6-month study visit (Figure 1). Some subjects did not complete the full set of study questionnaires on every visit.

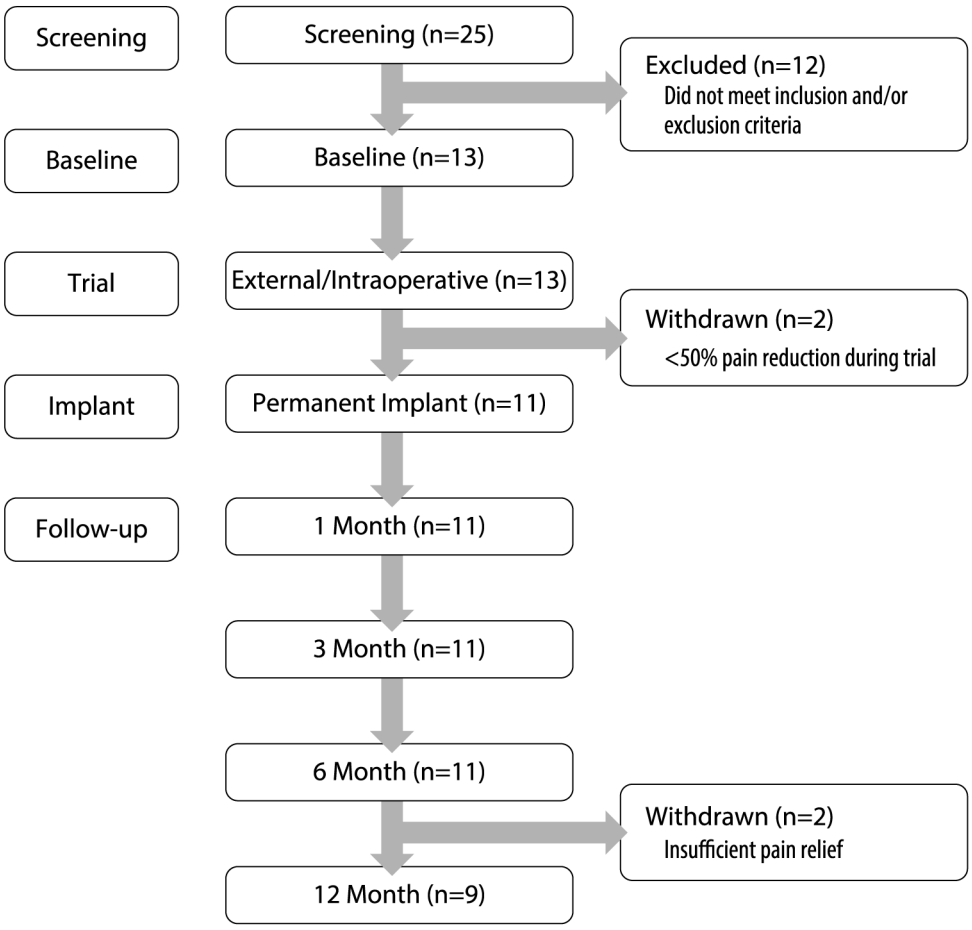

Figure 1. Diagram of subject disposition through this study.

Appropriate implantation levels were identified by observing pain–paresthesia overlap, particularly in the legs. Good coverage of the low back region was typically achieved with L2 stimulation, in accordance with a published report.[21] The majority of leads, for leg pain, were placed at L4–L5. Subjects received permanent implants with 1 to 3 leads; the majority of leads were placed at L2 (Table 1). During the trial, stimulation reduced pain in the primary painful area from a score of 8.64 (±0.92) at baseline to 1.60 (±2.61) at the end of the trial period; this was an average reduction of 81.67%. Pain scores were 1.99 (±2.19) at 1 month, 2.68 (±2.75) at 3 months, 2.06 (±3.00) at 6 months, and 2.40 (±2.38) after 12 months of treatment, a pain reduction of 72.05% (Figure 2). Pain ratings at all follow-up time points were statistically significantly lower than those at baseline ($P < 0.001$). After 12 months of treatment, 6 of the 9 (66.7%; 95% CI 35.4% to 87.9%) had better than 50% pain

relief, and 4 of the 9 (44.4%; 95% CI 18.9% to 73.3%), all of whom had lower back pain as their primary complaint, reported 100% pain relief (Figure 3).

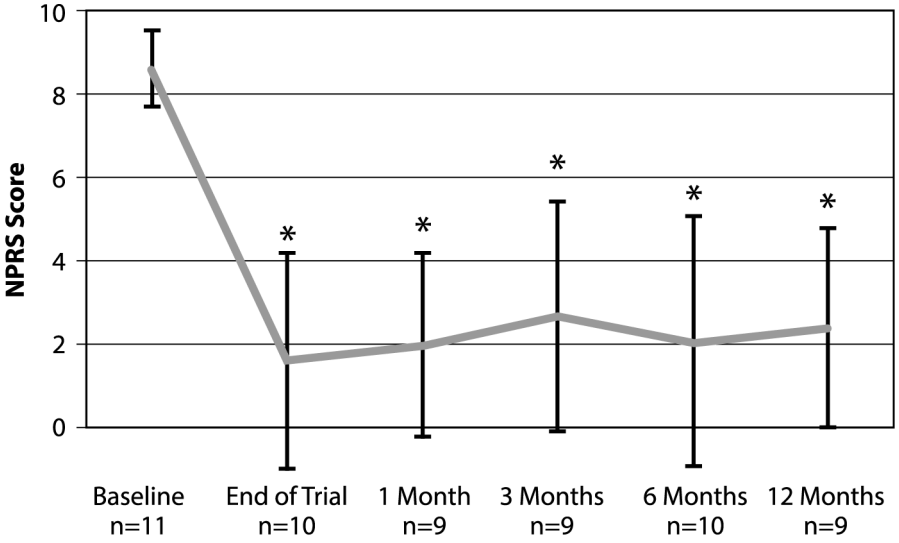

Figure 2. Pain ratings on the numeric pain rating scale (NPRS) in the primary area of pain were significantly reduced by dorsal root ganglion stimulation at the end of the trial period and at post-implantation follow-ups through 12 months. Values represent means ± SD; * indicates a statistically significant difference from baseline.

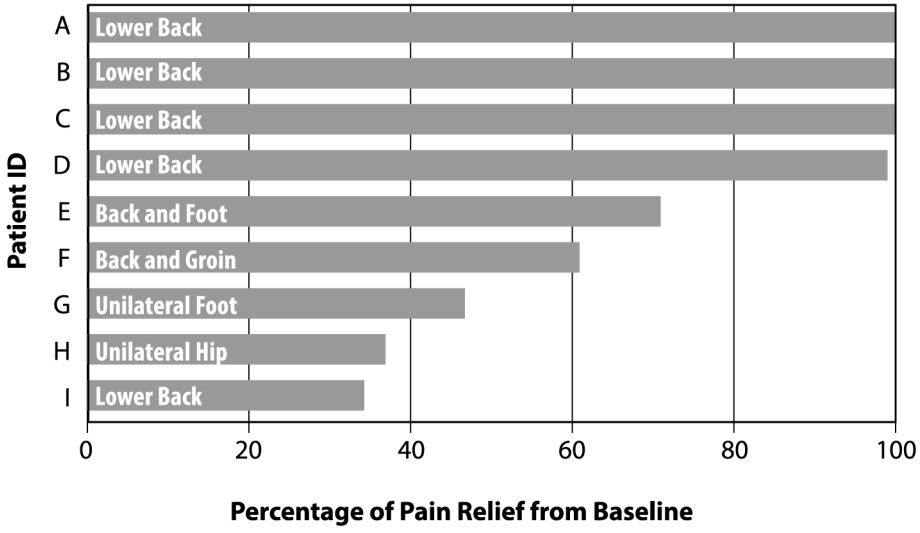

Figure 3. Percentage of pain relief for each patient at the 12-month follow-up; the location of primary pain is noted.

Table 1: Lead Placements

Total number of leads: 20	
Left side: 12	**Right side: 8**
L1: 0	
L2: 14	
L3: 0	
L4: 3	
L5: 3	

Similarly, assessment with the BPI indicated that pain severity was reduced with treatment, from a score of 7.16 (±1.14) at baseline to 3.53 (±2.22) at 1 month, 3.40 (±2.98) at 3 months, 3.20 (±2.85) at 6 months, and 2.78 (±2.35) after 12 months of treatment (a reduction of 61.20%). BPI pain severity scores at all follow-up time points were statistically significantly lower than those at baseline ($P < 0.001$). The interference of pain with activities and life roles was also reduced by DRG stimulation, from a score of 5.48 (±1.20) at baseline to 2.30 (±1.64) at 1 month, 2.69 (±2.62) at 3 months, 2.27 (±2.40) at 6 months, and 2.44 (±2.25) after 12 months of treatment. This was a reduction of 55.40%. BPI pain interference scores at all follow-up time points were statistically significantly lower than those at baseline ($P < 0.01$; Figure 4).

Concomitant improvements were also reported in secondary clinical outcomes. Quality of life improved during the study, with EQ-5D index scores increasing from 0.34 (±0.25) to 0.80 (±0.07) at 1 month, 0.71 (±0.25) at 3 months, 0.78 (±0.23) at 6 months, and (±0.82) after 12 months of treatment (Figure 5). Index scores at all follow-up time points were statistically significantly improved relative to those at baseline ($P < 0.001$).

Disability was reduced with DRG stimulation. ODI scores decreased from 46.14 (±10.33) at baseline to 31.14 (±16.78) at 1 month, 28.40 (±17.83) at 3 months, 24.20 (±19.56) at 6 months, and 19.21 (±10.92) after 12 months of treatment (Figure 6). Disability ratings at all follow-up time points were statistically significantly improved relative to those at baseline ($P < 0.05$).

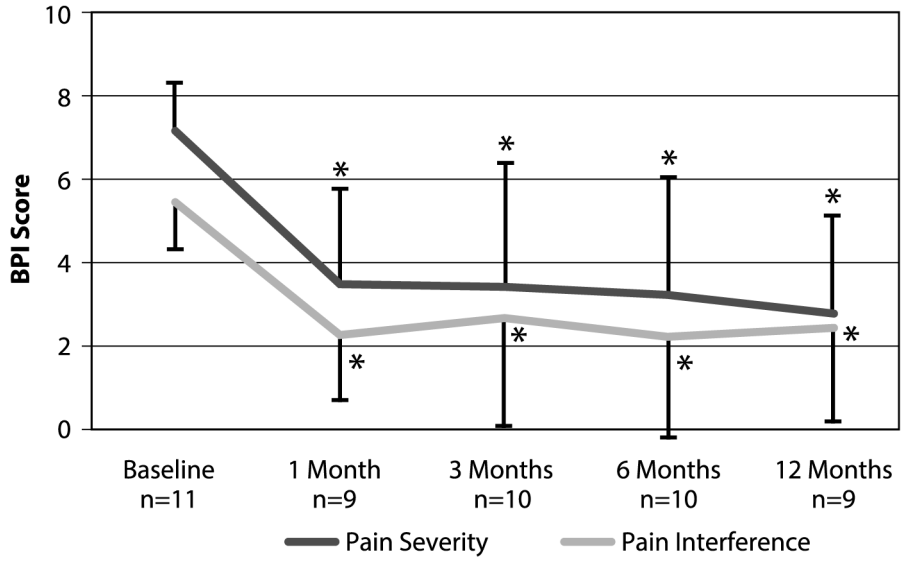

Figure 4. Pain severity and interference, assessed with the Brief Pain Inventory (BPI), both decreased with dorsal root ganglion stimulation. Values represent means ± SD; * indicates a statistically significant difference from baseline.

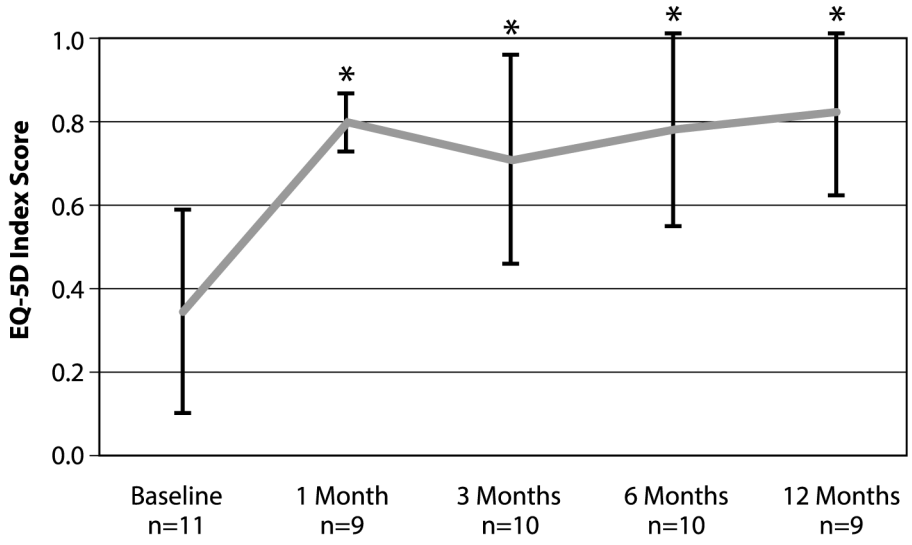

Figure 5. Overall quality-of-life ratings (EuroQol-5D [EQ-5D] index scores) improved with dorsal root ganglion stimulation. Values represent means ± SD; * indicates a statistically significant difference from baseline.

Mood improved with DRG stimulation. POMS scores decreased from 19.18 (±19.58) at baseline to -1.89 (±8.88) at 1 month, -3.89 (±9.88) at 3 months, -1.80 (±11.44) at 6 months, and -0.11 (±11.24 after 12 months of treatment (Figure 7). Mood disturbance ratings at

all follow-up time points were statistically significantly decreased relative to those at baseline ($P < 0.05$).

Six non serious device-related adverse events were reported by 6 subjects. One subject experienced increased pain after the trial implant procedure, which was determined to be due to mechanical irritation of the L5 DRG. A permanent implant was not performed. One subject fell due to weakness in one leg immediately after the trial implant procedure. This resolved after temporarily turning the system off, and the subject resumed study participation after 2 weeks. One subject perceived a buzzing sound in one ear and believed it to be related to the implantable pulse generator (IPG); because it was not experienced as a negative effect, no action was taken. One subject experienced pain at the IPG site, which resolved after surgical revision. One subject complained of loss of stimulation and increased pain approximately 6 months after implantation. Additional leads were placed during a revision procedure, but the system was ultimately explanted, and the subject was withdrawn from the study. Finally, 1 subject had a wound infection at the IPG site, which resolved with antibiotics. Additionally, 1 subject had the device temporarily deactivated for an emergency surgery; although serious, this was unrelated to the device or the study. The subject resumed participation in the study after recovery.

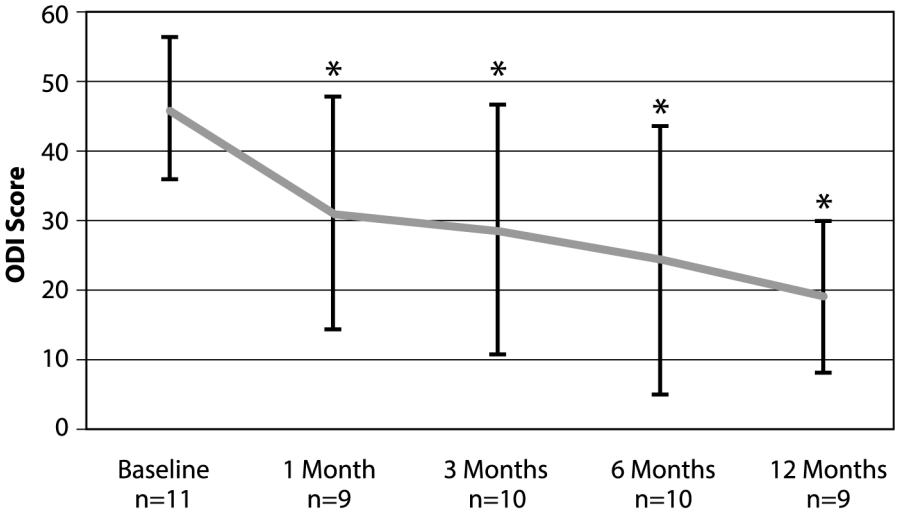

Figure 6. Oswestry Disability Index (ODI) scores of disability decreased with dorsal root ganglion stimulation. Values represent means ± SD; * indicates a statistically significant difference from baseline.

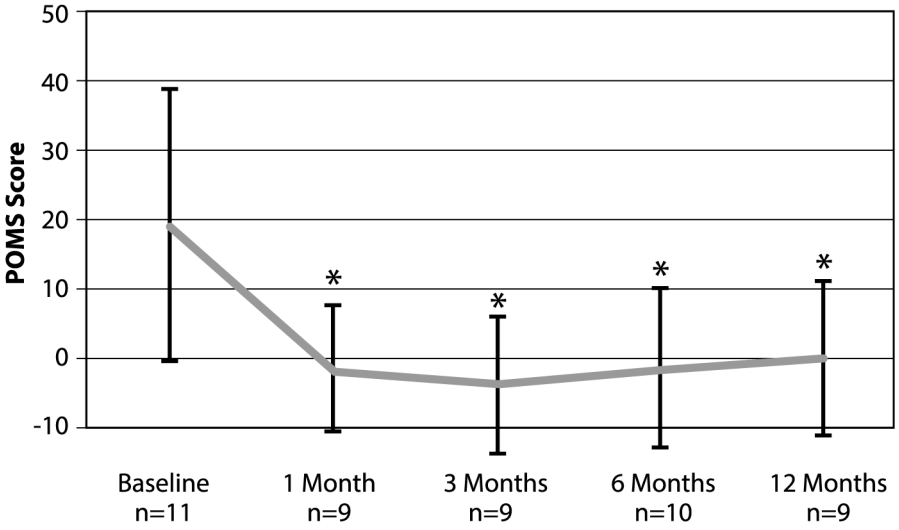

Figure 7. Profile of Mood States (POMS) scores indicating total mood disturbance decreased with dorsal root ganglion stimulation. Values represent means ± SD; * indicates a statistically significant difference from baseline.

Discussion

DRG stimulation resulted in a positive control of FBSS pain for 11 out of 13 patients who underwent a trial. Of the 9 subjects with evaluable pain data who were observed through 12 months, the average pain relief was 76.78%, and half of the patients had complete or near-complete relief of pain. This, along with improvements in pain interference, quality of life, disability, and mood, is indicative of an overall positive outcome across multiple domains. The observed complications were similar to those reported in other studies with DRG stimulation[18, 19] and occurred at a frequency similar to that in a large recent randomized clinical trial.[20] None of the complications were serious, and all were resolved satisfactorily. Together, this suggests DRG stimulation as a possible treatment option for FBSS pain following surgical discectomy.

FBSS is a challenging pain indication with various treatment options. For example, a recent review identified 8 different treatment modalities for FBSS, ranging from noninvasive to surgical,[22] and a large prospective study of FBSS patients described an iterative 6-step treatment algorithm requiring up to a year for implementation.[23] It is likely that the wide variety of FBSS pain generators and the variability in pre- and postsurgical patient characteristics (some of which can only be identified in retrospect) contribute to the dissatisfying low rate of robust pain relief across all treatments. In current applications of SCS regimens, treatment options include tonic, burst, high-density, and high-frequency

waveforms. Results from several published studies[17-19, 21] additionally raise the option that DRG stimulation might be a viable option in FBSS patients. This report, in which DRG stimulation was effective in a well-defined FBSS patient group with previous surgical lumbar discectomy, supports that notion. DRG stimulation has been hypothesized to be effective for FBSS pain in the low back by modulating the activity of intrinsic spinal afferents as well as sympathetic nerves.[21] DRG stimulation may also achieve control of the radicular symptoms of FBSS by normalizing the overactive DRG output that is characteristic of neuropathic pain.[24, 25] Technically, DRG stimulation in FBSS can be challenging due to epidural scarring following back surgery. However, in this cohort, the implanters had considerable experience with maneuvering the highly flexible leads and were able to implant the leads in appropriate foramina for the involved regions.

The data reported here suggest that DRG stimulation can induce long-lasting pain relief and improvement in quality of life, function, and mood in subjects diagnosed with FBSS. This case series was limited by its small sample size, instances of missing data, and observational design. Additional prospective studies are warranted to further investigate this application of DRG stimulation for FBSS pain as well as other back pain indications such as discogenic pain in the non-operated patient. Future studies in DRG stimulation may also focus on strategies to individualize neuromodulation by optimizing patient selection, lead placement, and programming, and by quantifying the value of this intervention against medical management and in cases in which SCS treatment delivers insufficient leg or back pain relief.

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CHAPTER 7

A Prospective Study of Dorsal Root Ganglion Stimulation for Non-Operated Discogenic Low Back Pain

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Abstract

Introduction

Disruptions of lumbar intervertebral discs may lead to severe discogenic low back pain (LBP). Severe pain has a deleterious effect on physical function and quality of life. Spinal cord stimulation (SCS) is a robust treatment for many neuropathic pain conditions. New innovations may be well-suited to treat neuropathic chronic LBP, including discogenic pain. The aim of this prospective study was to determine the effect of dorsal root ganglion (DRG) stimulation for a well-selected group of patients with discogenic LBP with no history of previous back surgeries.

Methods

Twenty subjects with confirmed discogenic LBP and no prior history of back surgery underwent trials of DRG stimulation and, if successful with at least 50% pain reduction, were permanently implanted. Subjects rated their pain, disability, quality of life, and mood at baseline, and 14 subjects were followed through 12 months of treatment.

Results

Treatment with DRG stimulation reduced LBP ratings (68.3% reduction), from mean 7.20 ± 1.3 at baseline to 2.29 ± 2.1 after 12 months ($p = < 0.001$). Oswestry ratings of disability significantly decreased ($p = < 0.001$) from 42.09 ± 12.9 at baseline to 21.54 ± 16.4 after six months of treatment and to 20.1 ± 16.6 after 12 months. The average quality of life EQ-5D index score at baseline was 0.61 ± 0.12 and 0.84 ± 0.13 after 12 months.

Discussion:

DRG stimulation treatment for discogenic LBP improved the level of pain, function, and quality of life. Further research is necessary into efficacy of DRG stimulation in patients with chronic discogenic LBP and to determine the place of SCS in the treatment algorithm.

Keywords

Back pain, chronic pain, discogenic pain, dorsal root ganglion stimulation, neuromodulation, neuropathic pain, spinal cord stimulation

Introduction

Low back pain (LBP) is globally a significant healthcare problem with a point prevalence of 9.4%.[1] The 2010 Global Burden of Disease study ranked it the number-one contributor to disability, of 291 conditions studied. Most people with periods of LBP recover within weeks; however, recurrence is common, and a sub-group will develop chronic LBP.[2] Globally, considerable research is aimed at improving the outcomes in pain and disability for this group of patients. Although definitions vary, pain that persists past three months is generally considered chronic.[3-5] Severe chronic pain may have sequelae such as the avoidance of physical activity and sleep loss. An unfortunate cascade can then develop, leading to deconditioning, disability, work absence,[6] decreases in participation, mood changes, and overall lower quality of life.[5, 7-10]

The majority of LBP cases involve mechanical pain. More than 25%[11], and as many as 40%[12], of LBP cases involve the disc[13], although discogenic-only LBP seems to be a more rare phenomenon.[14] The diagnosis and treatment of discogenic pain can be challenging.[15] The leading cause of discogenic pain is internal disc degeneration. Vascularized granulation tissue that contains nociceptive nerves grows from the outer annulus fibrosis into the nucleus pulposus. Sensory signals and/or inflammation processes may be the source of the pain.[16] The most-often involved levels are L4/L5 and L5/S1[12] due to the natural lordosis of the low back.[2, 12]

Treatments for severe chronic discogenic LBP range from anti-inflammatory medications and analgesics, to minimally invasive (intradiscal) pain treatments and invasive surgery.[17] Unfortunately, treatment success is capricious, and many patients may not achieve satisfying results. For example, a 12-month randomized controlled trial (RCT) of individualized physical therapy for non-reducible discogenic LBP showed that approximately 40% of subjects had less than 50% pain relief. [18] Similar results were reported in a 12-month RCT of interlaminar epidural injections for chronic lumbar discogenic pain.[19] An RCT in 64 subjects with discogenic LBP showed that intradiscal electrothermal therapy (IDET) was preferable to sham treatment, but that only about 40% of subjects had 50% or better pain relief.[15, 20] Together, these pieces of evidence suggest that the ideal treatment for discogenic pain has yet to be found

Spinal neuromodulation interventions have been employed for chronic neuropathic low back and leg pain and, because of their reversible and minimally-invasive nature, may be an attractive option for a selected group of patients who eschew back surgery. Spinal cord stimulation (SCS) for neuropathic pain in patients with predominant leg pain and failed back surgery syndrome (FBSS) has been the most frequently employed of the neuromodulation options. Recent cohort trials of SCS using multicolumn paddle leads

have reported good outcomes in FBSS patients. One study (*N* = 76) reported that 42% of subjects had at least 50% relief of LBP after six months of treatment,[21] and another (*N* = 29) reported that median back pain scores decreased from nine to five during 36 months of treatment.[22] However, back pain (in patients with and without back surgery) tends to be less amenable to SCS treatment than leg pain, especially with percutaneous leads, as exemplified in the PROCESS randomized controlled trial in which two-year findings (*N* = 42) showed that the average reduction in back pain was approximately 16%, vs. approximately 43% improvement in leg pain.[23]

SCS modifications have been developed in an attempt to optimize therapy, achieving superior long-term results for leg pain and also for the low back, including new waveforms such as burst and high frequency[24-27] or the addition of peripheral electrodes intended to modulate a greater proportion of the physical pain pathway.[28] A recent study showed promising results with high frequency stimulation in a group of patients with non-operated chronic LBP. Of 21 patients who met the inclusion/exclusion criteria, 20 (95%) subjects were implanted with a permanent pulse generator. Of the 17 subjects that reached the 36-month timepoint, the average pain (on a 100-mm visual analog scale) decreased from 79 mm at baseline to 10 mm. Moreover, the average Oswestry disability index (ODI) score decreased from 53 to 19 and the use of opioids decreased from 18 subjects at baseline to 2 at the 36-month follow-up.[27]

These innovations, without a doubt, have been valuable for some patients for both leg and back pain with long lasting good results. However, because all SCS therapies depend on the recruitment of fibers in the dorsal columns of the spinal cord-which may be challenging to electrophysiologically isolate with current SCS technologies-a highly-effective SCS option that achieves a high responder rate for a subgroup of patients with isolated discogenic LBP may not yet exist. Stimulation of the dorsal root ganglion (DRG) uses similar implants and stimulation strategies as SCS, but its leads are placed near the affected DRG(s) in the intervertebral foramen. It has shown to be a safe and effective treatment for different neuropathic pain syndromes such as complex regional pain syndrome,[29] LBP, FBSS,[30, 31] and FBSS with a discogenic component.[32] Lumbar discs are innervated by sinuvertebral nerves, which flow through the rami communicantes nerves (segmental) and have connections with the sympathetic trunks (non-segmental).[33, 34] The L2 spinal nerve root, and its collateral, the caudal-most white ramus communicans nerve, is the primary afferent for converging pain signals from lower lumbar discs that project rostrally through the sympathetic trunk.[35, 36] This study was launched to investigate the utility of DRG stimulation at the L2 spinal level for patients with chronic discogenic low back pain who had not undergone back surgery.

Patients and methods

This was a prospective, single-arm post-market pilot study that was conducted at two Dutch study centers (Rijnstate Hospital and Maastricht University). Subjects were recruited from investigators' practices according to the inclusion and exclusion criteria in Table 1. Study enrollment was limited to subjects with discogenic LBP as confirmed by medical history and positive provocative discography in accordance with standard guidelines set out by the International Spine Intervention Society.[37] Other sources of mechanical LBP (including severe/operable disc abnormalities, facet joint involvement, endplate degeneration, spinal stenosis, or spondylolisthesis) were ruled out by imaging, diagnostic blocks, and/or physical examination. The study protocol was approved by the local ethics committees and all subjects gave their written informed consent before any study activities.

Each subject underwent a trial of DRG stimulation of approximately 14 days with an external stimulator. Bilateral L2 leads were placed under fluoroscopic guidance, and optimal pain/paresthesia overlap was confirmed intraoperatively. The trial was considered successful if pain relief of 50% or more was reported. If this was achieved, trial devices were converted to fully-implanted systems. Post-implantation wound care and device programming proceeded according to standard practice.

Subjects completed ratings of pain (standard 11-point numeric pain rating scale [NPRS; [38]]) at preimplant baseline, at the end of the trial phase, and at two weeks, three months, six months, and twelve months after permanent implantation. Quality of life (EQ- 5D;[39]) and disability (ODI;[40]) were assessed at baseline and all follow-up time points for permanently-implanted subjects. Assessments of mood (Profile of Mood States [POMS;[41]]) were completed at baseline and after six and twelve months of treatment for permanently-implanted subjects. Additionally, subjects reported their satisfaction with the pain relief achieved and the overall therapy on 0–11 rating scales at all follow-ups after permanent implantation. Complications were recorded throughout the study.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age 18-65. • Chronic LBP refractory to conservative treatment for at least 6 months. • LBP intensity of minimum of 6 on a standard 11-point numeric pain rating scale at baseline. • LBP is discogenic, as confirmed by history (e.g. pain produced on lumbar motion, significant functional limitation in sitting duration and tolerance) and provocative discography. • Deemed suitable candidate for DRG stimulation by multidisciplinary panel and a psychologist. • Negative response to lumbar facet joint block.	• Previous lumbar spine surgery at the levels of intended treatment, including laminectomy, fusion, or discectomy. • Previous spinal neurostimulation therapy. • Indwelling active implant. • Recent injection therapy or radiofrequency treatment for LBP at the levels of intended treatment. • Severe disc degeneration or extruded/ sequestered herniated nucleus pulposus at the levels of intended treatment. • Moderate to severe endplate degenerative (Modic) changes at the levels of intended treatment. • Moderate to severe spinal stenosis. • Grade 1-5 spondylolisthesis. • Marked motor deficit on neurological exam. • Instability of pain condition. • Severe obesity. • Pregnancy (current of planned). • Presence of any contraindication for DRG stimulation, including neurological, medical, psychiatric, or social conditions.

Data were normally distributed. For all assessments, a repeated-measures analysis of variance (RMANOVA) followed by Tukey's post-hoc testing was completed in SAS version 9.4 accepting statistical significance at $p = < 0.05$. Unless otherwise stated, data are presented as means, standard deviations (SD), and percentages for subjects who received permanent implants.

Results

Twenty participants were screened and enrolled for DRG trial stimulation (see Table 2 for baseline characteristics). The trial was not completed in two patients; this was due to extensive epidural adhesions and inability to place the lead in one patient, and the emergence of an exclusionary condition in the other patient. Three patients had limited pain (<50%) relief during the trial. Fifteen patients (75%) received permanent implants; in all patients bilateral leads were placed at L2. During intraoperative testing, subjects reported excellent paresthesia coverage of their painful low back regions, without substantial paresthesias in non-painful regions. This patient report, as well as intraoperative motor recruitment of the multifidus muscle at increased stimulation amplitudes, confirmed

optimal lead placement. During the trial period, patients received DRG stimulation at sub-threshold amplitudes that did not create any paresthesias.

Table 2: Baseline characteristics

Baseline characteristics	Results
Age, years	47.5 ± 13.4
Gender (N/%)	
Males	7 (35%)
Females	13 (65%)
Body mass index (BMI)	26.2 ± 4.7
Level of painful disc (N/%)	
L3-L4	1 (4.6 %)
L4-L5	9 (40.9%)
L5-S1	12 (54.6%)
Duration of discogenic LBP, years	8.5 ± 1.4

All permanently-implanted patients were back-surgery naïve, except for one patient who had had a discectomy outside of the level treated with DRG stimulation more than 20 years earlier. All subjects completed the six-month follow-up visit. Fourteen subjects completed the 12-month follow-up, after one withdrawal due to lack of efficacy (Fig. 1).

Treatment with DRG stimulation reduced NPRS scores for low back pain from 7.20 ± 1.3 to 2.37 ± 2.2 at the end of the trial (67.1% reduction from baseline), to 1.53 ±1.5 after two weeks (78.7% reduction), to 2.53 ± 2.6 after three months (64.8% reduction), to 2.60 ± 2.6 after six months (63.4% reduction), and to 2.29 ± 2.1 after 12 months (68.3% reduction). Compared to baseline, significant pain reduction was achieved at all follow-ups $F_{5,72} = 18.06$, $p < 0.001$; see Fig. 2. The average pain relief at 12 months was 70.3%, with 71.4% (10 of 14) of subjects reporting better than 50% pain relief and 35.7% (5 of 14) subjects reporting complete (100%) pain relief.

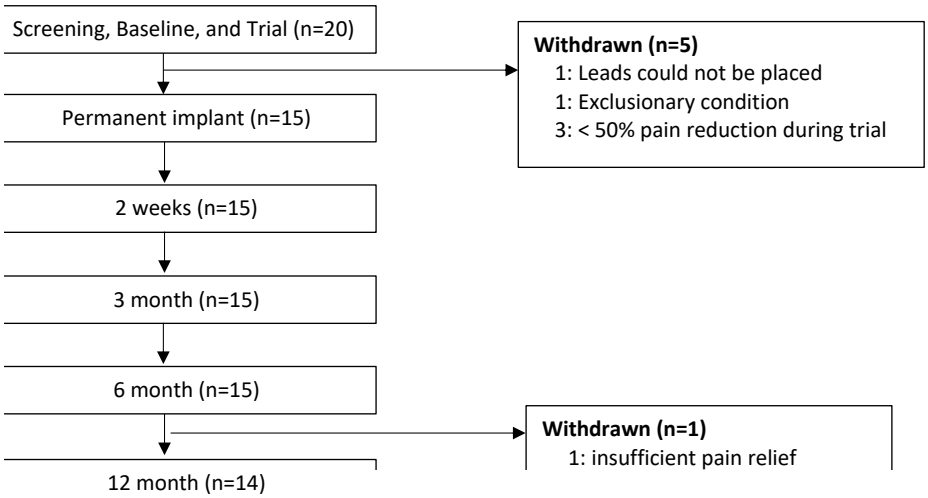

Figure 1. Flowchart showing subject disposition during the study.

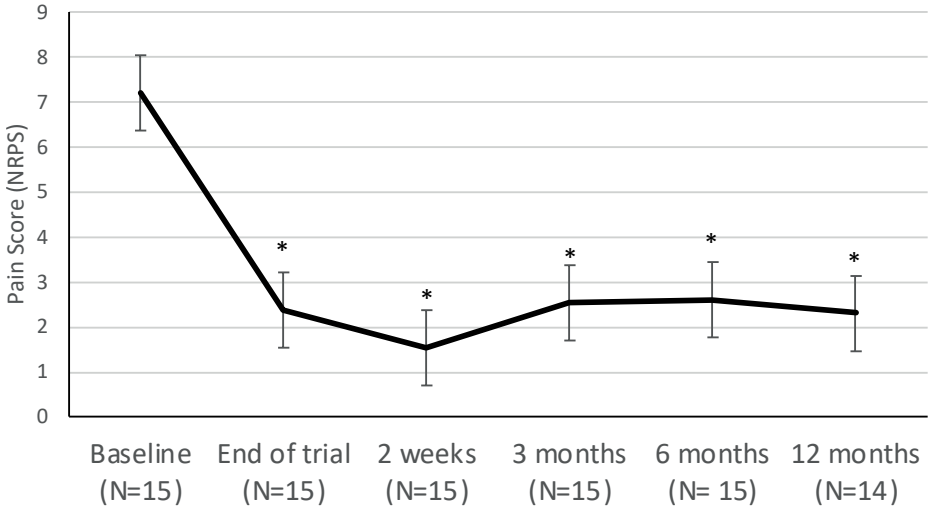

Figure 2. Mean LBP scores over time: NPRS ratings of pain in the low back were significantly reduced from baseline levels during the 12 months of DRG stimulation. Markers represent means SD; * indicates a statistically significant ($p < 0.05$) difference from baseline.

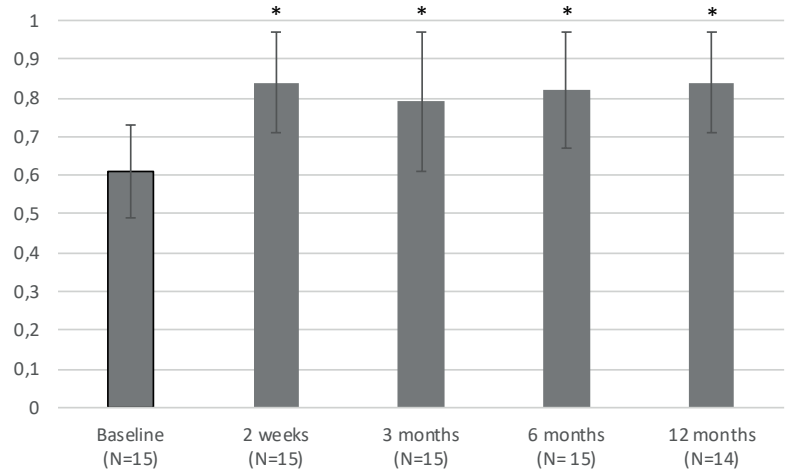

Figure 3. Mean quality of life scores over time: DRG stimulation was associated with improvements in quality of life, as significant improvements in EQ-5D index scores were observed. Markers represent means ± SD; * indicates a statistically significant ($p < 0.05$) difference from baseline.

Quality of life (EQ-5D index) ratings improved with DRG stimulation treatment. At baseline, the average score was 0.61 ± 0.12. This increased to 0.84 ± 0.13 after two weeks, 0.79 ± 0.18 after three months, 0.82± 0.15 after six months, and 0.84 ± 0.13 after 12 months. Compared to baseline, significant pain reduction was achieved at all follow-ups $F_{4,55} = 8.81$, $p < 0.001$; see Fig. 3. Disability (ODI) decreased from 42.09 ± 12.9 at baseline to 21.54 ± 16.4 after six months of treatment and to 20.1 ± 16.6 after twelve months. Reductions from baseline were statistically significant $F_{2,27} = 11.72$, $p < 0.001$; see Fig. 4.

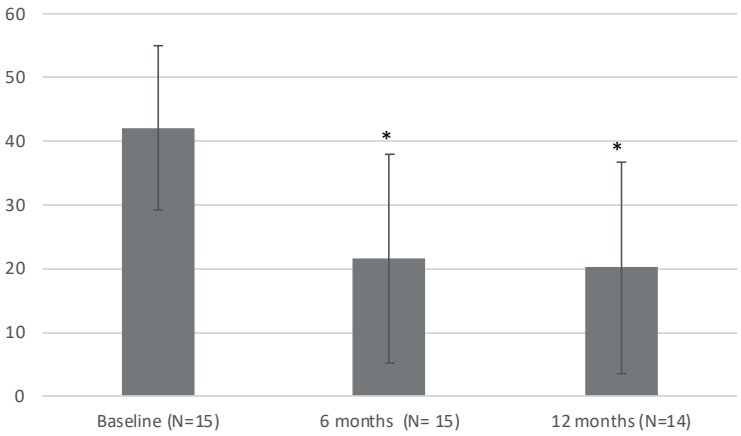

Figure 4. Mean disability scores in time: ODI scores indicated that subject's disability improved during the 12-month study. Markers represent means ± SD; * indicates a statistically significant ($p < 0.05$) difference from baseline.

Disability for individual subjects ranged from modest to large at baseline. After 12 months of treatment, six of the twelve subjects improved from moderate or severe disability to minimal disability (Fig. 5). Mood (POMS), likewise, improved with treatment, from 16.40 ± 18.8 at baseline to 0.47 10.8 at six months and 1.0 ± 11.7 at 12 months; at both follow-ups scores were significantly reduced relative to baseline $F_{2,27} = 6.61$, $p < 0.0046$ (Fig. 6). Subject's satisfaction with pain relief and the overall therapy was high, exceeding seven of a possible ten at each follow-up through 12 months (Fig. 7).

During the temporary trial, three adverse events (AEs) were reported in three subjects: lead migration, changes in sensation related to stimulation, and disconnection of the external trial stimulator. All issues were resolved during routine placement of the permanent systems. After permanent implantation, ten AEs were reported in nine subjects. Four subjects had lead migration of which three resolved after surgical revision; a fourth subject was, by patient's choice, explanted and withdrawn from the study. Three subjects reported a temporary return of their original pain level. This was found to be due to increased lead impedance and this was resolved through lead revisions (two subjects) or turning off the affected lead (one subject). Three subjects experienced pain at the subcutaneous neurostimulator pocket. In all cases, the event resolved after surgical revision. There were no serious AEs. With a single exception, all subjects who experienced an AE went on to complete the study. The average pain relief at 12 months among subjects who experienced an AE was 58.4%.

Discussion

Bilateral DRG stimulation at L2 seems to be an effective treatment for selected patients with chronic lumbar discogenic pain. Of the 18 subjects who completed the trial, 15 (83%) had more than 50% pain relief. Of the permanently-implanted subjects, 14 (93%) completed the study. Eleven subjects (66.7%) had ≥50% pain relief. Consistent positive treatment trends were observed in measures of mood and quality of life, and patients were very satisfied with treatment. Meaningful improvements in function were reported by all subjects: at baseline, all disability ratings were in the "moderate," "severe," or "crippled" categories; after 12 months of treatment, half of the subject's ratings reflected "minimal" disability.

Overall, the rate of complications was higher in this cohort than is typically reported in studies of DRG stimulation. There were four lead migrations among the permanent implants. This may have been due to the considerable improvements in function that this patient group experienced; their increased physical activity could have complicated the settling-in of the implanted systems. This potential increase in physical activity and

the impact of this on lead migration should be further explored in future research. In addition, there were three cases of increased lead impedance and three cases of pocket pain among the permanent implants. Because these issues could not be resolved with reprogramming, it was determined that these were hardware faults, and all were resolved by replacement. All adverse events were readily resolved with appropriate treatment and all subjects had good pain relief outcomes after replacement and were satisfied with the therapy.

SCS can be successful in patients with LBP.[26, 42-44] To our knowledge, though, only a single report focuses specifically on discogenic LBP in a patient group that had not previously undergone back surgery. In 2012, a cohort of nine such subjects were followed for 12 months of treatment with conventional SCS; baseline pain of 7.8 ± 0.5 decreased to 2.9 ± 0.5.[45] Those findings are very similar to those in this report, albeit gathered in another small sample. There are more recent reports of high-frequency SCS in non-operated patients (with good outcomes;[27, 46, 47]). However, because the majority of subjects in those reports exhibited disc degeneration, Modic changes, spinal stenosis, and other relevant baseline characteristics that were exclusionary in the current report, it is not possible to directly compare the findings. Lumbar discs are innervated by sinuvertebral nerves, which flow through the rami communicantes nerves (segmental) and have connections with the sympathetic trunks (non-segmental).[33, 34] Specifically, the L2 spinal nerve root, and its collateral, the caudal- most white ramus communicans nerve, is the primary afferent for converging pain signals from lower lumbar discs that project rostrally through the sympathetic trunk.[35, 36] A study showed that lidocaine injections at the L2 nerve root relieved low back pain in patients with discogenic LBP.[35] DRG stimulation at L2 may achieve bimodal targeting of both segmental and non-segmental neuropathic disc sensory afferents that is not otherwise accessible with traditional SCS.

A limitation of this study is its small sample size. However, despite persistent pain refractory to treatment (pain duration of 8.5 [±1.4] years), improvements were shown in pain intensity, function, and quality of life. This is an indication that this treatment could be effective for this patient population.

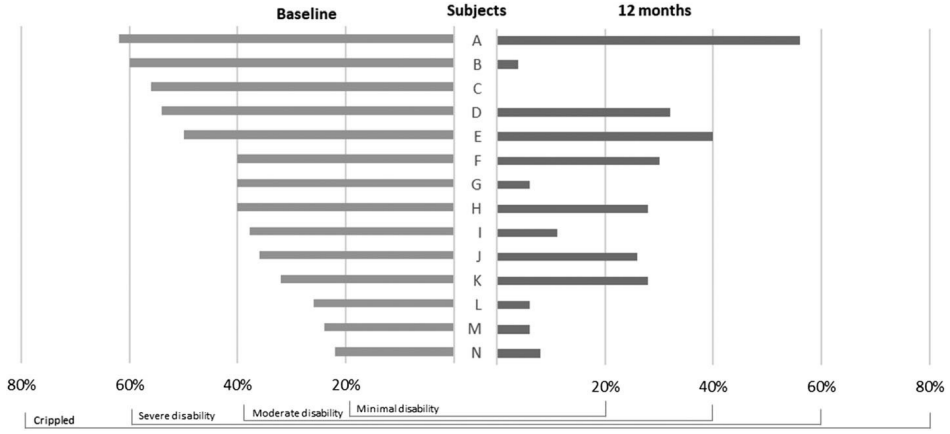

Figure 5. Disability; the 14 subjects are presented individually, with ODI ratings at baseline on the left and after 12 months of treatment on the right. At baseline, all subject's disability ratings indicated moderate or worse disability; after 12 months, seven subjects (50%) reported having minimal disability.

Neuromodulation has traditionally been regarded as an intervention of last resort and is generally employed only after failed conventional treatments and invasive interventions, such as surgery, although SCS has been recognized as preferable to repeated surgeries.[48] At present, in most countries, neuromodulation for LBP and leg pain is only reimbursed in patients with previous back surgery that failed to improve the pain (FBSS).

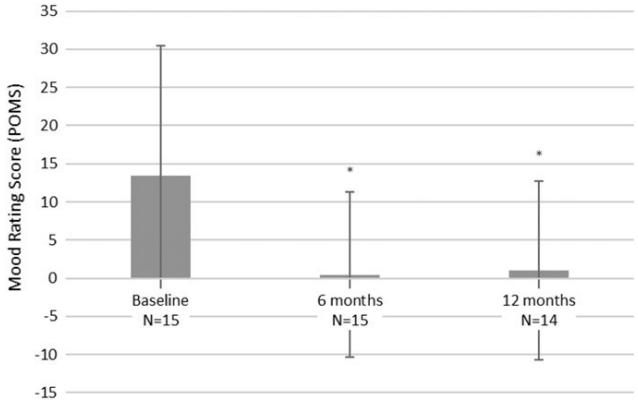

Figure 6. Mean mood scores: reductions in POMS scores throughout treatment showed that treatment was associated with improvements in mood. Markers represent means± SD; * indicates a statistically significant ($p < 0.05$) difference from baseline.

However, dissenting opinions argue that early implementation of neuromodulation, before surgery, may interrupt the pathological neuroplasticity that is hypothesized to be the origin of chronic pain refractory to treatment.[49-51] Another benefit of early neuromodulation may be in prevention or reversal of disability, which can become self-reinforcing when persisting more than extended periods of time.[52, 53] In this report, findings of improvements in pain, function, and associated endpoints were made in subjects who were not responsive to conservative management including physiotherapy, medication, and minimally invasive pain treatments but had not previously undergone back surgery. This supports the notion that it might be valuable to initiate DRG stimulation earlier in the neuropathic pain trajectory. The next step should be a large-scale trial combining clinical and cost-effectiveness outcomes in order to shed light on the intervention's appropriate place in the pain treatment algorithm.[54]

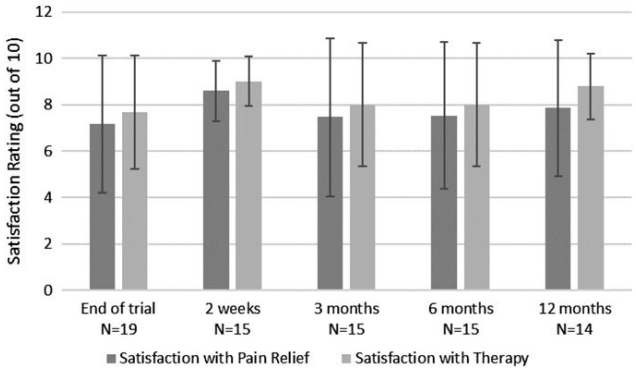

Figure 7. Mean patient satisfaction scores: subjects were consistently satisfied with their pain relief and with DRG stimulation therapy throughout the study.

Stimulation of the L2 DRGs has been demonstrated to effectively reduce back pain with a discogenic component in a group of patients with previous back surgery (FBSS).[32] Future research should investigate the role neuromodulation, and DRG stimulation at L2, can play in the treatment of patients with severe discogenic LBP. The aim of these studies should be to increase the evidence that neuromodulation (SCS with conventional or emerging waveforms, and/or DRG stimulation) is cost-effective in patients with discogenic LBP.

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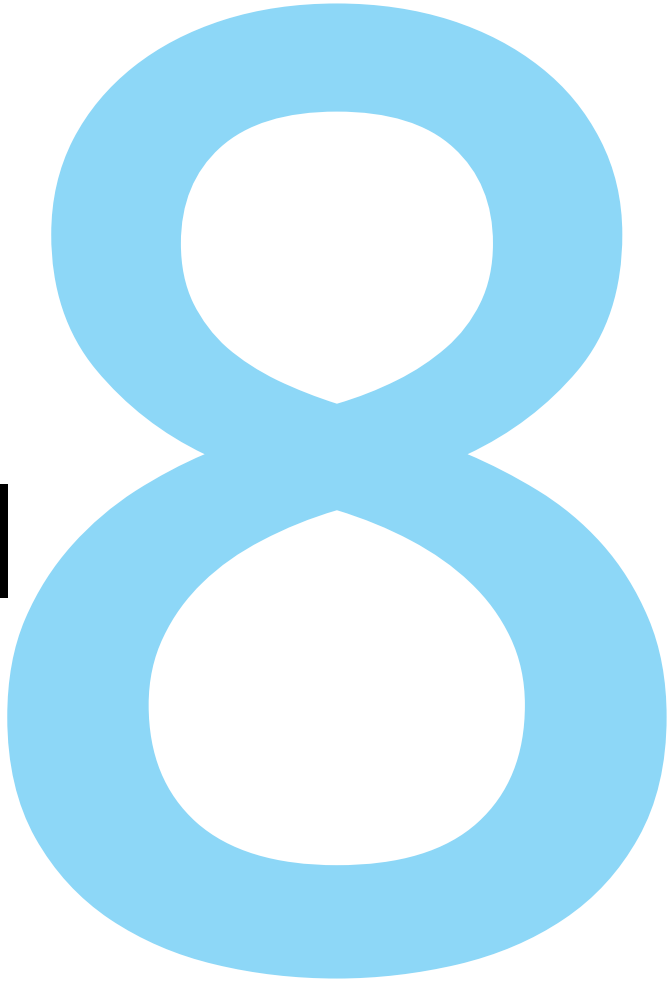
CHAPTER 8



Summary, Conclusions and Future Directions Discogenic pain

This thesis aims to define the diagnostic algorithm for chronic discogenic low back pain (CD-LBP) and to assess the evidence for minimally invasive treatments for CD-LBP, including the reproduction of a randomized controlled trial on the effect of intradiscal methylene blue injection on CD-LBP.

Background

Low back pain is a major and growing problem worldwide. The Global Burden of Diseases, Injuries and Risk factor study (2017[1]) showed that low back pain is the number one cause of years lived with disability. This burden poses considerable challenges to health systems and economies.[2, 3]

Low back pain has a multifactorial origin. In approximately 40% of the cases, LBP appears to be of discogenic origin.[4, 5] The sacroiliac (SI) joint or the facet joints are indicated as the cause of LBP in 13% and 15-40% of the cases, respectively. In clinical practice often more than one cause can be found simultaneously.[5]

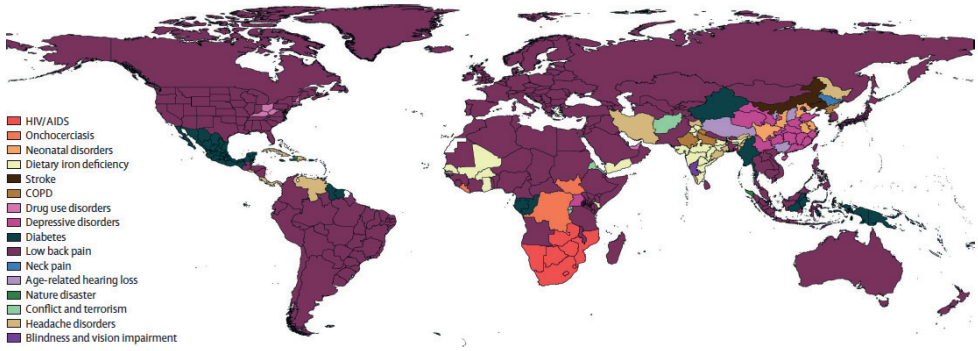


Figure 1: Importance of low back pain as leading cause of age-standardized years lived with disability rated by location, for both sexes combined, 2017. From Global Burden of Disease [1] free of copyright.

Discogenic low back pain, although attributed to a degenerative process, may improve spontaneously over time. For patients presenting with discogenic low back pain conservative management, consisting of medication and a multidisciplinary rehabilitation program that focusses on reducing pain and provides instructions on posture and body movement, is recommended first.

The World Health Organization (WHO) uses a stepwise approach to the pharmacological treatment of pain.[6] The last decades reports on the increasing number of opioid deaths

and addiction, especially in the population of non-cancer pain sufferers, justify a critical assessment of the advantages and disadvantages of long-term opioid use. Recent guidelines on the treatment of low back pain discourage to use opioids for managing chronic low back pain.[7] The development of anti-neuropathic medication added another dimension to the treatment algorithm dividing pain into mechanical pain, neuropathic pain or combined pain syndromes.

The selection of a minimally invasive treatment option can only be made when the pain source is identified. In patients with chronic mechanical low back pain, the facet and sacroiliac joints as pain generators should first be excluded, before the intervertebral disc can be suspected as a pain generator.[8] Disc degeneration and pathologies can best be visualized with Magnetic Resonance Imaging (MRI) in T1 and T2 setting.[9] Desiccation, loss of height, high-intensity zones (HIZ) and Modic signs can be visualized. However, radiologic findings correlate poorly with the clinical presentation. It is well known that asymptomatic discs may appear abnormal on MRI, while normal appearing discs have been shown to be painful on provocation.[10]

The inconsistency of history, physical examination, and radiographic findings leaves the critical question: "How can the diagnosis of discogenic low back pain be made?"

Provocative discography may provide the link in diagnosing suspected discs as the origin of low back pain. The answer is a technique that combines imaging, intradiscal pressure, and pain reproduction, together with morphologic abnormalities observed on MRI. This test can be indicative of the discogenic origin of low back pain.[11] Discography is an invasive procedure and long term follow up of discography patients has demonstrated acceleration of disc degeneration.[12] It was demonstrated in degenerative porcine discs that pressure transfer to the adjacent disc happens during discography.[13]

Although it has yet to be demonstrated that any targeted intervention can reliably treat discs, identified as the anatomic source of pain by provocative discography, it is argued that there is a place for discography as a diagnostic utility.[14, 15]

A good diagnostic test offers the patient a source for their pain, the best patient selection for the treatment of CD-LBP and possibly the best treatment results.

The answers found for the research questions formulated for this thesis, aim at improving diagnosis and selection of the most appropriate minimally invasive treatment strategy for patients with CD-LBP.

Research question1:

What is the current evidence for minimally invasive treatments in discogenic low back pain: A systematic review of the literature?

Chapter 2a summarizes the literature relative to the diagnosis and treatment of discogenic pain up till 2010.[8]
In **Chapter 2b** we present the update of the evidence for the interventional pain management options based on the literature up to March 2018. This review showed evidence of moderate quality for intradiscal biacuplasty, resulting in a moderate strength of recommendation for its use in a highly selected patient group with CD-LBP. The randomized controlled study on the effect of intradiscal methylene blue injection was judged to be of moderate quality: its criticisms and the lack of reproduction of the results, justified a weak recommendation. Intradiscal electrothermal therapy was supported by evidence of low quality.

Research question 2:

Is the pressure transfer to an adjacent disc in disc stimulation real and significant?
Recently, an in vivo porcine study and a study in nine human subjects showed pressure transfer to the adjacent discs during discography. This could mean that the concordant pain the patient describes originates from an adjacent disc.[13, 16]

In **chapter 3** we describe a cohort of patients in which during provocative discography pressure was measured in adjacent discs.[17]

Fifty patients were selected with suspected CD-LBP. An arterial blood pressure monitoring system simultaneously assessed the pressure in the adjacent discs while low-speed flow, pressure-controlled discography was performed on the suspected discs.

In patients with a positive discography, the average intradiscal peak pressure was 15.1psi (SD-11.1). In 48 procedures, no pressure rise in the adjacent discs was found. A small, but not clinically relevant rise (1.1 psi) in the adjacent disc during discography was recorded in 2 patients.

The pressure rise in adjacent discs does not seem to occur during low-speed flow pressure-controlled provocation discography in human discs. False-positive pain reaction caused by potentially painful adjacent discs are therefore unlikely during low-speed flow (low) pressure-controlled discography.

Research question 3:

What is the place of intradiscal methylene blue injection in patients with CD-LBP?

In **chapter 4** we describe the results of a prospective case-cohort study of the intradiscal injection of methylene blue in CD-LBP.[18]

Patients were carefully selected on clinical criteria, magnetic resonance imaging, and a positive provocative discography.
Copying the protocol of Peng et al.,[19] 15 consecutive patients, were injected with 1 ml of methylene blue 10%, 1 ml lidocaine 1% and 0.5 ml of contrast dye.
Patients were recruited in two interventional pain treatment centers of the Netherlands. Six months after the intervention, 40% of the patients claimed at least 30% pain relief. In patients who responded, physical function improved, and medication use diminished. These patients were defined as responders. We observed no complications or adverse events.
These findings justified the set up of a randomized, double-blind, placebo-controlled trial.

In **chapter 5** we describe the results of the multicenter randomized controlled trial on the efficacy of intradiscal methylene blue (MB) injection for CD-LBP: the Intradiscal Methylene Blue Injection (**IMBI**) study.[20]

In this RCT, the design of the previously published study by Peng et al.[19] was replicated. A multicenter RCT was performed to assess whether the extraordinary effect of intradiscal MB on pain intensity could be confirmed. Success was defined as at least a 30% reduction, in pain intensity and the Patients' Global Impression of Change (PGIC) 6 months after the intervention. To include 84 patients, we screened 1364 patients. Patients were excluded from participation because of successful test block of the facet joints (n=191), suffering from a pain syndrome different from CD-LBP (n=409), not fulfilling other inclusion and exclusion criteria (n=177), refusing to participate in the study (n=248), negative discography (n=155) and other reasons (n=100).

Although we exactly replicated the study protocol by Peng et al.[19] we were unable to reproduce their effect size. We included 84 patients with CD-LBP of which 14 (35%) in the MB +lidocaine group showed treatment success compared with 11 (26,8%) in the control group who received isotonic saline plus lidocaine (P=0.43). Twenty-seven percent of all participants treated with MB stated that their overall health improved much or very much vs 26% in the control group (P=0.96).

We were unable to confirm that intradiscal MB injections reduced pain significantly in patients with CD-LBP 6 months after treatment compared with placebo. As a remarkable finding, we observed that over one-quarter of patients receiving only lidocaine injections reported treatment success, which is in contrast with the previously published study.

We recommend further research to study the exact mechanisms of CD-LBP and to define specific characteristics of subgroups of patients with CD-LBP to determine whether intradiscal injections (with MB or lidocaine 1%) may be a treatment option.
At present we do not recommend the routine use of intradiscal MB for CD-LBP.

Research question 4:

Is there a place for spinal cord or DRG stimulation in patients with CD-LBP?

Failed Back Surgery Syndrome (FBSS) is defined as a surgical end stage after one or more interventions on the (lumbar) spine, without persisting effect.
Spine surgeons do not describe this situation anymore as FBSS but "persisting or recurrent pain" after spine surgery.
A systematic review of the literature[21] and an RCT[22] demonstrated that spinal cord stimulation (SCS) is effective for the treatment of FBSS. An RCT compared SCS with reoperation.[23] Patients selected as candidates for reoperation after spine surgery were randomly assigned to reoperation or SCS. If the results of the randomized treatment were unsatisfactory, patients could cross over to the alternative treatment. SCS was more effective than reoperation and fewer patients initially treated with SCS crossed over to surgery than vice versa.

Recently a special electrode allowing to stimulate the dorsal root ganglion (DRG) became available. Stimulation of the DRG is thought to produce targeted stimulation and optimal paresthesia coverage of the painful area compared with SCS.[24] The innervation of the discs is provided by the sinu-vertebral nerves and the rami communicantes, which are sympathetic nerves. The sinu-vertebral nerve is implicated in diffuse low back pain. It cannot directly reach the somatic element of each level of the lumbar spine.[25] The cutaneous innervation from L3 to L5 must therefore, pass through the nearest somatic nervous system structure, which is the spinal ganglion L2. (see figure 2) Therefore, the bilateral DRG L2 is considered a target for interventional pain treatment.

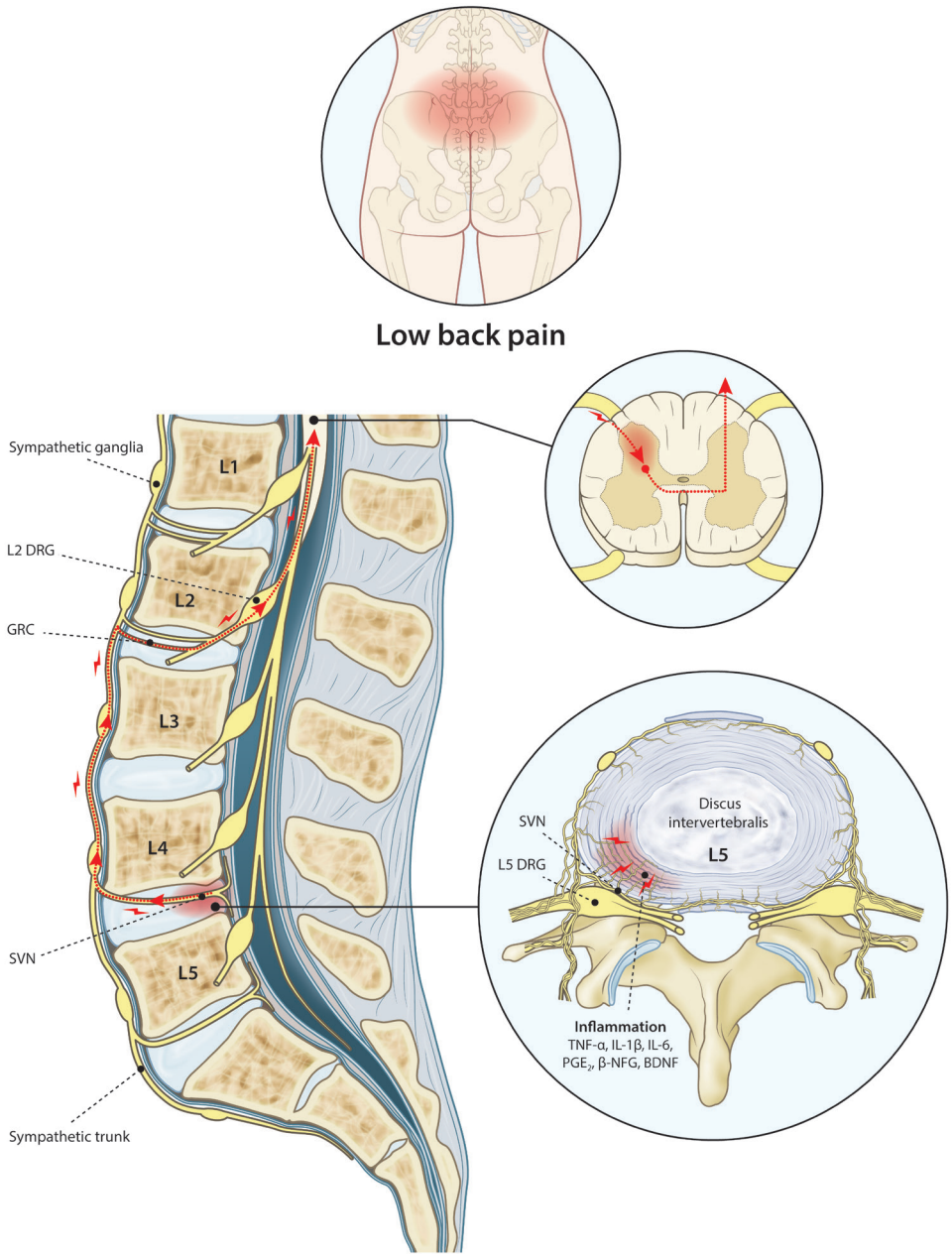


Figure 2: Innervation of the discus intervertebralis.
Rogier Trompert Medical Art. http://www.medical-art.eu.

In **chapter 6**, we describe the results of DRG stimulation in a group of patients with FBSS. We found that DRG L2 stimulation improves low back pain, function, and quality of life of FBSS patients.[26]

This study is a multi-center single arm observational cohort study of patients with persisting back and leg pain after lumbar spine surgery. Patients failed conservative and minimally invasive treatments.

Thirteen patients underwent a trial of DRG stimulation. Good paresthesia coverage of the painful area in the low back region was typically achieved with L2 stimulation, the majority of the DRG leads for leg pain were placed at L4-L5 level to cover chronic neuropathic leg pain. Eleven patients had good results and underwent implantation of a permanent neurostimulator. The pain was reduced from 8.64 (±0.92) at baseline to 2.40 (±2.38 n=9) after 12-months of treatment, a 72.05% reduction. Similar improvements were observed looking at secondary clinical outcome measures.

These results suggest that DRG stimulation induces pain relief in patients diagnosed with FBSS.
An interesting finding was the substantial effect of DRG L2 stimulation on chronic neuropathic low back pain.

In **chapter 7,** we describe a prospective pilot study (non-responders from the IMBI RCT after 24 months) who received DRG L2 stimulation[27]

This study was launched to investigate the utility of DRG stimulation at the L2 spinal level for patients with CD-LBP who had not undergone previous back surgery.

Twenty patients with confirmed discogenic pain, and no prior history of back surgery, underwent trials of DRG stimulation (bilateral DRG L2) and were permanently implanted when pain relief of at least 50% was achieved.
Treatment with DRG L2 stimulation for CD-LBP reduced LBP pain rating (68.3% reduction), from mean 7.20±1.3 at baseline to 2.29±2.1 after 12-months (p=<0.001). Oswestry disability ratings significantly decreased from 42.09±12.9 at baseline to 21.54±16.4 after six months of treatment and to 20.1±16.6 after 12-months of treatment. The average quality of life EQ-5D index score at baseline was 0.61±0.12 and 0.84±0.13 after 12-months.

The outcomes of DRG stimulation in the treatment of CD-LBP are very promising but these are the first results in a small prospective study. These results should be reproduced in a large trial and compared to conventional spinal cord stimulation also looking at the cost-effectiveness and invasiveness of the procedure.
In every patient, a comparative assessment should be made of the invasiveness of a procedure against the health profit to be gained.

Conclusions

Low back pain is worldwide an increasing socioeconomic problem due to the aging and growing population.
Low back pain can have different mechanisms. Mechanical low back pain may originate from the facet and SI joints and the intervertebral disc (40%).[1, 28]
The burden of discogenic low back pain is high. Patients suffer severe pain, are physically limited and experience a serious loss in quality of life.[29]

Regarding the diagnosis of discogenic low back pain

The history, physical examination, and imaging do not allow for a 100% accurate diagnosis of discogenic low back pain. Although under debate, pressure controlled provocative discography is at the moment the best option to define whether a disc is the origin of pain.[8] There are however, drawbacks in the use of provocative discography, notably the possibility to induce accelerated disc degeneration.[12] Recently a study was published which showed no accelerated disc degeneration in a group of patients with symptomatic LBP who underwent discography, but who did not undergo subsequent spinal fusion surgery. 7 years after the discography patients developed disc degeneration and new disc herniations at a similar rate as corresponding discs in matched control patients.[30]

In recent years, several radiological modalities have been studied about chronic discogenic low back pain.

A retrospective analysis of radiographic indexes of a group of patients with and a group without discogenic low back pain found 5 factors that were significantly different between the groups: iCobb angle, lumbar instability, the height of the disc, Modic changes (Type 1 and 2) and High-Intensity Zone (HIZ). Lumbar instability, Modic changes, and HIZ show a high probability value in diagnosing chronic discogenic low back pain.[31]
The correlation between HIZ shown on MRI-imaging and the outcome of a provocative discography was found to be weak with 47.6% of the discs that had a positive discography showing an HIZ. Of the discs that presented a negative pain response upon discography 37.6 % showed an HIZ. These findings confirm that an HIZ on MRI cannot replace discography.[32]

The area of Modic changes type I was demonstrated to increase when the MRI is taken in an upright position. There was a correlation between the of Modic changes extension increase and increase in pain in standing position. Therefore weight-bearing MRI scans can form a valuable complement to standard sequences since they provide additional diagnostic information about discogenic low back pain.[33]

The value of magnetic resonance spectroscopy (MRS) was assessed in a recent observational diagnostic development and accuracy study.[34] MRS data of patients who had received provocative discography for suspected discogenic pain were used to quantify spectral features of the disc structure and acidity. MRS-scores were compared to outcomes of a provocative discography and Pfirrmann grade on MRI. The clinical utility was judged by evaluating surgical success, defined as a 15-point improvement in the Oswestry Disability Index and a 2-point improvement in VAS for back pain. When provocative discography was used as reference, the accuracy of MRS was 85%, the sensitivity was 82%, and the specificity was 88%. In non-herniated discs, accuracy, sensitivity, and specificity were respectively 93%, 91%, and 93%. Surgical success in MRS positive discs, indicative for carbohydrate/collagen decrease, was 97% compared to 57% in MRS negative discs. MRS is less invasive than provocative discography and could be a valuable approach to clarify pain mechanisms and establish the diagnosis of chronic low back pain. Further studies will determine the definitive place of MRS in the diagnosis of CD-LBP.

Regarding the current evidence for minimally invasive therapy in Chronic Discogenic Low Back Pain

The holy grail in minimally invasive therapy for CD-LBP is still yet to be found. Intradiscal injection of Methylene Blue (MB) is a promising intervention. Though, in the most recent systematic review, as described in chapter 2b, the GRADE rating for the intradiscal injection of methylene blue was judged to be of moderate quality. This grading was based on the RCT of Peng et al. [19] The guideline committee downgraded the strength of the recommendation to weak, mainly because of the criticisms on the results. In this thesis, we presented the results of the duplication of this RCT. There were no significant differences in outcome between the methylene/ lidocaine group compared with the placebo/lidocaine group. Therefore, the conclusion was that the recommendation of using intradiscal methylene blue injection for the treatment of CD-LBP cannot be supported.[20] Considering this new information the recommendation would be adapted because of conflicting evidence. The recommendation should be that further research is needed to decide what the place of intradiscal methylene blue injection is and which specific subgroup of patients with CD-LBP could benefit from this therapy.
A recently published *in vitro* study on the effect of different concentrations of methylene blue on rat annulus fibrosis cells showed that methylene blue reduced the cell viability in a concentration- and time-dependent manner. Not only the proliferation and paracrine function of annulus fibrosus cells is observed, but it can also induce cell apoptosis.[35]

At the moment the only minimally invasive treatment that is recommended for the treatment of CD-LBP is biacuplasty. Biacuplasty is a cooled radiofrequency technique aiming to destroy painful nociceptors in the posterior part of the disc.[36-38]

When all therapies, such as conservative therapy, medication, minimally invasive treatments fail and surgery is not an option, neurostimulation could be considered. At this time in most countries, neurostimulation for low back pain is only reimbursed in patients with persisting pain after previous back surgery (FBSS). However, on an international level, the discussion is ongoing to implement neurostimulation before surgery to interrupt pathological neuroplasty, which could reverse disability.
Only a few studies have been published regarding neurostimulation and non-operated patients. The optimal goal is to identify the specific subgroup of low back pain patients that may benefit from neurostimulation. Patients with discogenic low back pain could form such a specific subgroup of low back pain patients.

The sustained effect over 12-months of high-frequency 10kHz stimulation of the spinal cord in chronic low back pain was documented in the literature in patients with suspected CD-LBP.[39] Our prospective study with DRG L2 stimulation in a highly selected group of patients with CD-LBP showed promising results after 12 months.[26]

Further studies are needed to define if there is a place for neurostimulation in CD-LBP in non-operated backs and to find what place it should have in the treatment algorithm of CD-LBP.

Currently, a large scale RCT is running in Europe comparing the effect of neurostimulation for axial (non-operated) low back pain against conventional medical management (CMM) with a follow up of 24 months. Subgroup analysis might show the better result in CD-LBP patients than in other subgroups of chronic low back pain results are expected in 2022.[40]

Our study group will start a prospective study in a selected group of patients with CD-LBP to evaluate the effects of burst stimulation. When the trial phase is negative patients are offered a second trial phase with DRG L2 stimulation. Follow up is 12 month and results are expected in 2020.[41]

Suggestions for future research

Mechanisms of chronic discogenic low back pain

Although CD-LBP is a highly prevalent pathology, the responsible mechanisms are not fully understood. Persistent inflammation and changes in innervation in the posterior part of the disc are thought to be key factors in painful intervertebral discs.[42]

Recent work has revealed a critical role for immune cells, specifically mast cells in the pathogenesis of intervertebral disc degeneration. Mast cells were found to be upregulated in painful human intervertebral disc degeneration tissue and induce an inflammatory, catabolic and pro-angiogenic phenotype in bovine nucleus pulposus tissue and cartilage endplate cells at the gene level. Healthy bovine annulus fibrosus cells however, demonstrated a protective role against key inflammatory (IL-1β and TNFα) and pro-angiogenic (VEGFA) genes expressed by mast cells, and mitigated neo-angiogenesis formation in vitro. Mast cells can infiltrate and elicit a degenerate phenotype in intervertebral disc degeneration cells, enhancing key disease processes that characterize the degenerate intervertebral disc.[43]

A better understanding of the mechanisms underlying painful discogenic pathology will promote the development of new treatment possibilities.

Interventional intradiscal therapies

One new minimally invasive treatment option currently under research is "Gelstix™". This is a hydrogel polymer that is implanted in the disc. It has the form of an elongated matchstick and can be inserted, under local anesthesia through an 18 Gauge needle in the nucleus of the affected disc(s). The Gelstix™ Nucleus augmentation hydrates through the absorption of the body's fluids and expands nearly ten times in volume (with minimal increase in length) in less than 15 minutes. Similar to the native nucleus, the implant acts as a reservoir of permanent hydration, producing increased pressure, and PH balance, thus, restoring the disc.

Several small clinical prospective studies showed long-lasting effects on disability, quality of life and medication use.[44-51] Those results justified the start of a randomized, double-blind, placebo-controlled multicenter efficacy study.[52] Results are expected in 2020.

Another recent development is based on the hypothesis that the rapid transformation of the nucleus pulposus (NP) into connective tissue would attenuate discogenic low back pain through reduced production of algogenic molecules and destabilization of the disc. Lactic acid (LA) is found at high levels in the NP and has been invoked in the sclerotization of the disc that occurs during aging. It was therefore hypothesized that high concentrations of lactic acid quickly fibrotizes the disc.

In an animal study in 2 pigs, the L3-L4 disc was injected with lactic acid (120mg/ml) and iohexol. One week later, 50% of the NP was replaced by connective tissue. A follow-up study showed the same effect in 8 pigs and no effect in a placebo group. Preliminary data suggest that some fibrosis appeared already after 2 days and was maximal after 4 weeks.

The preliminary data show that the nucleus pulposus after lactic acid injection will be replaced by connective tissue. This "biologic fusion" process of a spinal segment could be very useful in CD-LBP.[53]

Stayble Therapeutics™ announced the start of a randomized controlled study comparing 3 different doses of the experimental drug STA363 (Lactic Acid) with placebo intradiscal injection to study the efficacy and safety of this treatment.[54]

Neurostimulation

We reported the effect of L2-DRG stimulation in selected patients with CD-LBP. A study comparing burst spinal cord stimulation with DRG stimulation is planned in the period 2019-2020. The results of these studies should help to establish the place of neurostimulation in the treatment algorithm of CD-LBP. The next step is that a large cost-effectiveness study should be performed.
A large multicenter RCT is performed in which in patients with chronic non-operated low back pain high-frequency neurostimulation is compared to CMM.[40]
This outcome study could have a great impact on the place of neuromodulation in the algorithm of treating patients with chronic non-operated low back pain.

Regenerative therapy

With the advances in understanding the cell biology and internal characteristics of the intervertebral disc at the molecular and cellular levels that have been made, alternative strategies for addressing disc pathology can be discovered.[55]

With aging and degeneration, disc cells experience several biologic changes. The changing of cell types in the Nucleus Pulposus (NP) already begins in childhood with the disappearance of (notochordal) cells in the NP. This disappearance is correlated with the transformation from a NP that contains more fluid to a NP with a more cartilaginous structure.
Factors influencing the structure of the intervertebral disc are nutrient supply, mechanical stress, and decline during the time in cell viability, due to aging alone. Since the thickness of the endplates diminishes with age, nutrition is impaired to cells that affect viability. There is also a consensus that cell proliferation increases with age in the disc. This proliferation is characterized as having a reduced ability to synthesize appropriate matrix constituents and reduced growth factor secretion.

To prevent disc degeneration, the abnormal condition of the aging disc cells are the target for correction. Hence, by better understanding the biological processes underlying these

degenerative changes, cellular therapies can better target these specific dysfunctions. The use of cell therapy for intervertebral disc regeneration was discussed in a symposium "Where Science meets Clinics".[56] The promises of cell therapy include a sustained effect on matrix synthesis, inflammation control, and prevention of angio- and neurogenesis. There are still open questions such as the optimal cell type and delivery method. The optimal animal model is also a point of uncertainty.[57]

A literature review found animal studies involving autologous, allogeneic, and xenogeneic cells showing a good survival of these cells in the intervertebral disc. All studies reported some improvement in disc structure and 2 studies showed attenuation of local inflammation. Choosing the correct type of stem cells is imperative for obtaining favorable results in regenerative medicine. Bone marrow and adipose-derived stem cells are most frequently used for this application. The use of scaffolds to prevent cell leakage and provide biomechanical support needs to be optimized, but also the selection of an accurate animal model is still a point of debate.[55, 58]

With the advances in understanding the cell biology and characteristics of the intervertebral disc at the molecular and cellular levels, alternative strategies for addressing disc pathology can be discovered.

Clinical trials in human degenerative discs that were injected with stem cells show promising results in a limited number of trials. Autologous bone marrow stem cells injected into the NP of 10 patients with CD-LBP resulted after 1 year in improvement in pain and disability. The disc height was not changed but a significant water content was observed. In addition to clinical improvement, no adverse events and additionally no changes on MRI were observed.[59] As an alternative, re-implantation of disc cells has been attempted with the intent to increase the number of viable cells.

In a study on 26 patients suffering from degenerative disc disease who were candidates for spine surgery, 2 ml autologous bone marrow concentrate was injected in the nucleus pulposus. After 3 years of follow-up, 6 patients progressed to surgery. The remaining 20 patients reported improvement in ODI and VAS scores. One year after the intervention the MRI showed improved modified Pfirrmann grade. These results support further investigation of this treatment option.[60]

Large scale randomized clinical trials comparing stem cell therapy with placebo remain urgent areas of further investigation.

General conclusion

There are several possibilities for new therapeutic options for CD-LBP. All these options aim at reducing the degeneration of the lumbar intervertebral disc aiming to achieve pain reduction, reduction of disability and improvement of quality of life in patients with CD-LBP.

Studies on minimally invasive diagnostic and therapeutic techniques aimed at either removing the cause of pain or at restoring the internal architecture of the intervertebral disc are needed. The aim should be to define specific subgroups of patients for newer and (maybe) established treatments and thus increasing the success rate in reducing the burden of CD-LBP. Our research group is involved in all these projects.

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CHAPTER 9

Valorization

Discogenic Low Back Pain: "burden for patient and society"

Valorization is a broad concept encompassing knowledge transfer from the research sector to other sectors for personal, social and economic value.[1]
Low back pain is a vast problem worldwide causing a huge burden for the patient and for society, that is still growing. It is the main cause of years lived with disability in the western world.[2]
Chronic discogenic low back pain (CD-LBP) is defined as pain originating from the intervertebral disc, lasting for more than 3 months. The complaints of patients with CD-LBP result in medical consumption, absenteeism from work and disability. The recently published results from the Global Burden Group showed that chronic low back pain is a worldwide problem that is still growing.[3] The growth is attributed to aging and the growing world population. The incidence of CD-LBP is estimated at 40% of chronic low back pain.[4]

The quality of life of patients with low back pain is reduced. In a study from our group evaluating the burden and costs of CD-LBP in patients selected for participation in a randomized controlled trial on a new treatment option, almost half of the patients with CD-LBP, (46%,) reported severe pain (>7 of NRS 0-10) , and 54% suffered moderate pain.[5] This is in comparison with the findings of a European prevalence study in chronic pain patients[6], that showed 34% have severe pain and 66% have moderate pain.

In 2007 a Chinese research group published a spectacular decrease in pain and improvement of quality of life, after an intradiscal methylene blue injection in a highly selected group of patients with CD-LBP.[7] The publication reported in the methylene blue group, a mean reduction in VAS of 52.5 %, a 35. 8% mean reduction in the Oswestry disability scores and a 91.6 % satisfaction rate compared with 0.70%, 1.68%, and 14.3%, respectively, in the placebo treatment group. These astonishing good results gave rise to skepticism, and if the results of that Chinese study would be true, this intervention would revolutionize the treatment of low back pain, rendering spinal surgery for back pain essentially obsolete.[8] As with any treatment, the results of this study need to be replicated.

What did we find in our studies?

Diagnosing discogenic pain remains a difficult and controversial discussion. Since physical examination and radiology will only give an indication of discogenic pain, pressure-controlled discography remains a very useful test in the workup of diagnosing discogenic low back pain, in spite of the possible disadvantage of accelerating disc generation.[9] In

the current thesis, we refuted the hypothesis that outcomes of discography are flawed by the transfer of pressure to adjacent discs.

The promising results of intradiscal methylene blue injection could not be reproduced in our multicenter RCT, which copied exactly the protocol of the Peng et al.[10] No significant differences in outcome were found between the methylene blue and the placebo control group. Thus, the use of intradiscal methylene blue injections could not be supported.[11]
At the moment only intradiscal biacuplasty is recommended for the minimally invasive treatment of CD-LBP. Biacuplasty is a cooled radiofrequency technique aiming to destroy painful nociceptors in the posterior part of the disc.[12-14]

When all therapies such as conservative therapy, medication, minimally invasive treatments fail and surgery is not an option, neurostimulation could be considered.
The sustained effect over 12-months of high-frequency 10kHz stimulation of the spinal cord in chronic low back pain was documented in the literature in patients with suspected CD-LBP.[15] Our prospective study with DRG L2 stimulation in a highly selected group of patients with CD-LBP showed a promising result after 12 months.[16]
Further studies are needed to define if there is a place for neurostimulation in CD-LBP in non-operated patients and to find what place it should have in the treatment algorithm of CD-LBP.

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Pijnartsen in Nederland. Ik wil jullie danken. Jullie zijn in staat geweest uit heel Nederland patiënten in te sturen onder de waarschijnlijkheids diagnose discogene pijn, naar Velp. In mijn ogen de manier hoe we in de toekomst ook andere indicaties centraal en efficiënt kunnen onderzoeken. Veel dank hiervoor.

Beste maten, Anesthesiologen. Ik zal jullie (20+) niet allen bij naam noemen. Wij hebben de beste vakgroep van het land. We werken in een ziekenhuis met veel diversiteit en alle faciliteiten aanwezig.
We zijn is staat om ieder individu in zijn/haar kracht te zetten en zijn bereid individuele trajecten te faciliteren. Mede hierdoor kan ik sinds enige tijd ook in het AMC werken en heb ik dit promotietraject kunnen vervolmaken.
Ik hoop dat we de komende jaren in de breedte kunnen blijven groeien en naast een brede klinische vakgroep met opleidings affiniteit ook bekend zullen staan als vooraanstaand centrum voor wetenschappelijk onderzoek op het gebied van Anesthesiologie,

Pijnbestrijding en Palliatieve zorg en IC.
Markus Hollmann, Wolfgang Schlack, medewerkers en staf van het pijncentrum in het AMC, Anesthesiologen en AIO's. Fijn dat ik sinds enige tijd ook wat kan bijdragen in het AMC op de pijnpolikliniek. Hopelijk kunnen voor onze pijnklinieken elkaar de komende jaren versterken vooral op wetenschappelijk gebieden kunnen we het gewenste grote pijncentrum realiseren.

Robert Sie, Cas van Oort en Marloes van Grotel; met jullie heb ik de afgelopen jaren zeer veel tijd doorgebracht en ik geniet nog steeds van onze samenwerking. Mooi om te zien dat een actieve bestuursperiode voort kan bestaan de periode erna.
Robert wij werken nu mede samen in het AMC. De wens om ook op vakinhoudelijk niveau intensief samen te werken komt hiermee uit. Hopelijk kunnen we dit de komende jaren nog verder intensiveren.

De beoordelingscommissie Prof.dr.L.van Rhijn als voorzitter , Prof. dr Peul, Prof.dr. A.Boonen, Prof.dr. J.E.M.Smeets en Prof.dr.M.W.van Tulder dank ik voor het nauwgezet doorlezen en beoordelen van dit proefschrift.

Mijn lieve familie, Esther, Willem en Wies. Esther lang heb ik niet openbaar gemaakt dat ik bezig was met een promotietraject. Ik was al druk genoeg en veel te vaak afwezig. Ik heb dit traject hopelijk kunnen volmaken zonder dat we er teveel dingen voor hebben moeten laten varen die we samen kunnen doen. Ik ben blij en gelukkig met jou en de keuzes die we maken. Hopelijk kunnen we dat nog jaren volhouden samen.
Willem en Wies actieve studenten en naast het studentenleven aan hun begin van een academische dan wel maatschappelijke carriere. Ik hoop dat ik er altijd voor jullie zal zijn en voor jullie ben geweest; ik ben trots op jullie ontwikkeling naar volwassenheid toe en kan me geen leukere kinderen wensen.
Willem heel gaaf dat je samen met Carel Jaspers mijn paranimf wilt zijn op deze bijzondere dag.

About the author

Jan Willem Kallewaard was born in Leiden on the first of July 1964.
He went to the "Stedelijk Gymnasium in 's Hertogenbosch from 1976-1982 and studied Medicine at the University of Utrecht (1982-1989). After finishing his study, Jan Willem worked as an Anesthesiology resident as part of his military service. He did his anesthesiology training at the Academic Hospital in Utrecht (UMCU) (1993-1998). During his residency, he was member of the residents' board and member of the board of the NVA. In 1998 he obtained the registration as Anesthesiologist and Pain Physician.
Since his registration he worked as anesthesiologist in the Rijnstate Hospital in Arnhem. He obtained a scientific affiliation with the University Medical Center Maastricht.
He obtained the certificate of Fellow in Interventional Pain Practice in 2011 as winner of the Hassenbush price. Since 2017 he also practices pain medicine at the University Medical Center Amsterdam. Since 2018 he is head of the Pain department in the AMC.

Since 2005 he is member of the board of the Professional Interest Committee (Beroeps Belangen Commissie) of the NVA. He was Vice president of the NVA between 2008 and 2010 and was president of the NVA from 2011 to 2014. He was president of the pain section of the NVA in the period 2014-2018 and still acts as vice president. He was member of the sounding board group of the MinT study: Dutch cost effectiveness study of the effects of RF treatment for aspecific low back pain. He participates in the sounding board group neuromodulation with Zorginstituut Nederland (ZIN) and in the project implementing PROMS, practice variation, quality outcome measures in pain and neuromodulation in the Netherlands. He stimulated the update of the practice guidelines on Evidence-based interventional pain medicine.

Jan Willem is frequently asked as instructor for epiduroscopy training and cadaver workshops for Neuromodulation and the World Institute of Pain. He also is demanded as speaker on discography, epiduroscopy, and neuromodulation.

Jan Willem is married to Esther te Winkel and has 2 children (Willem 1996 and Wies 1999)

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