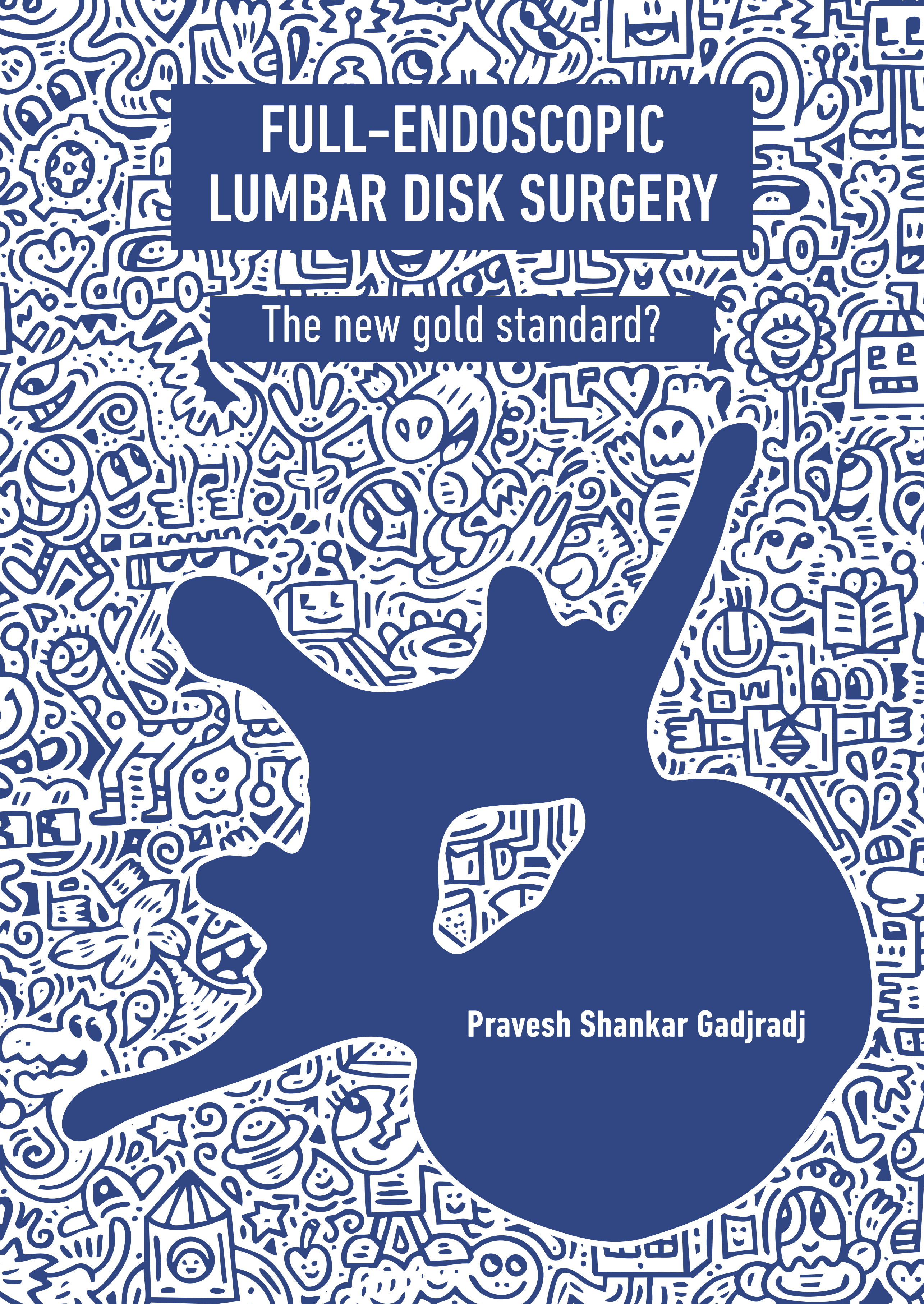

FULL-ENDOSCOPIC LUMBAR DISK SURGERY

The new gold standard?

Pravesh Shankar Gadjradj

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ISBN: 978-94-6522-764-1

Cover design by Ridderprint, Mr. Doodle
Design and lay-out of thesis by Ridderprint, Mr. Doodle
Printed by Ridderprint | www.ridderprint.nl

The study presented in this thesis was performed at the Erasmus MC: University Medical Center Rotterdam, the Netherlands.

The study was funded by a grant from the Health Care Efficiency Research program of the Netherlands Organization for Health Research and Development (ZonMw).

Financial support for this thesis was generously provided by Kliniek Lange VoorhouT, Max-More Spine by Hoogland Spine Products, ChipSoft, Erasmus University Rotterdam, Dutch Spine Society, Nederlandse Vereniging van Rugpatiënten, InSpine en QMediq.

Full-Endoscopic Lumbar Disk Surgery
The new gold standard?

Endoscopische operatie voor een lage rug hernia
De nieuwe gouden standaard?

Thesis

to obtain the degree of Doctor from
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr.ir. A.J. Schuit

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on

Tuesday 7 April 2026 at 15:30 hrs
by

Pravesh Shankar Gadjradj
born in Rotterdam, the Netherlands.

Erasmus University Rotterdam

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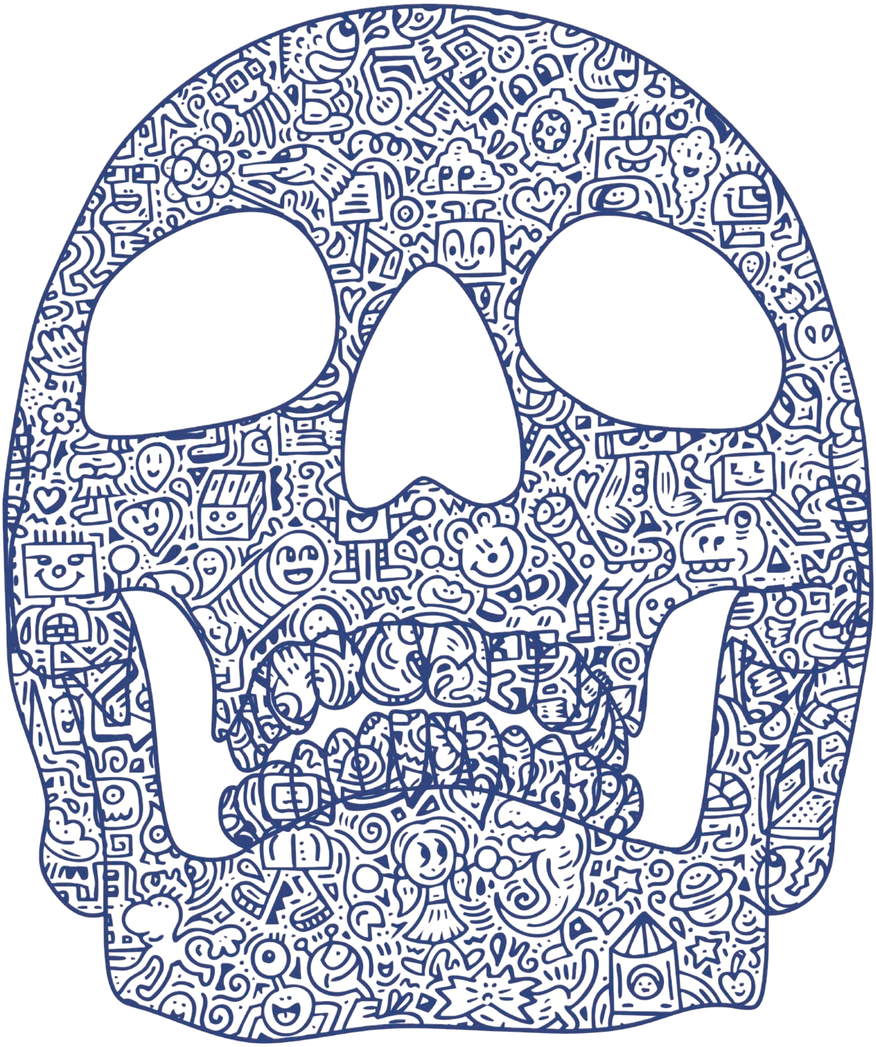
CONTENTS

LIST OF ABBREVIATIONS

American Society of Anesthesiologists	ASA
Full-Endoscopic Transforaminal Discectomy	PTED
Confidence Interval	CI
Discrete Choice Experiment	DCE
European Association of Neurosurgical Societies	EANS
Interquartile Range	IQR
Lumbar Disk Herniation	LDH
Micro-Endoscopic Discectomy	MED
Magnetic Resonance Imaging	MRI
Micro-Tubular Discectomy	MTD
Numeric Rating Scale	NRS
Oswestry Disability Index	ODI
Patient Reported Outcome Measure	PROM
Percutaneous Endoscopic Lumbar Discectomy	PELD
Percutaneous Transforaminal Endoscopic Discectomy	PTED
Quebec Back Pain Disability Scale	QBPDS
Randomized Controlled Trial	RCT
36-Item Short Form Survey	SF-36
Standard Deviation	SD
Standardized Mean Differences	SMD
Visual Analogue Scale	VAS



1

Chapter

INTRODUCTION AND OUTLINE THESIS

INTRODUCTION

Sciatica

Sciatica, also known as the lumbosacral radicular syndrome, is one of the most frequently observed pathologies of the spine, with a lifetime prevalence of up to 43% in selected populations[1]. The most important symptom of sciatica is radiating leg pain, which follows a dermatome[2]. Additionally, patients may experience numbness with or without paresthesia in the leg, muscle weakness, other sensory deficits, or back pain[3]. Sciatica can be the result of nerve root compression in the lumbar spine which is most frequently caused by a lumbar disk herniation (LDH)[2]. The diagnosis is confirmed using magnetic resonance imaging (MRI).

Conservative treatment

Previous research has shown that most cases of sciatica resolve with conservative treatment (approximately one-third of the patients recover within two weeks and approximately 75% recover three months after onset)[4]. Conservative treatment includes managing pain with medication, encouraging patients to stay active, exercise therapy, manual therapy, or more invasive analgesic therapy, such as spinal injections[3]. During the initial treatment with conservative therapy, patients are requested to monitor progression of symptoms. If there is an increase in motor deficits, surgery may be indicated.

Surgery

Currently, the gold standard procedure to remove a LDH is microdiscectomy through a transflaval approach[5,6]. The role of surgery has been widely studied in the 21st century[7-9]. In a randomized controlled trial (RCT) comparing surgery with prolonged conservative therapy in patients with sciatica, both surgery and conservative therapy led to similar relief of leg pain 12 months after surgery[8]. Patients who underwent surgery, however, recovered faster. Another RCT which compared surgery to conservative treatment could not make any firm conclusions on the equivalence or superiority of surgery due to the large number of patients that crossed-over[9]. For chronic sciatica, it has recently been shown that microdiscectomy was superior to conservative treatment in leg pain reduction at 6 months of follow-up, further underlining the importance of surgery[7]. Nevertheless, surgery for a symptomatic LDH remains one of the most frequently performed spinal procedures with 11.000 lumbar discectomies performed annually in the Netherlands according to the Dutch Association for Neurosurgery.

Minimally Invasive Surgery

Due to inventions and innovations made in the past decades, surgical endoscopes have made their way into medical practice[10]. The rationale of using endoscopes is that by reducing the surgical incision site, the procedure would be less invasive and therefore lead to reduced length of hospital stay and improved patient-reported outcomes, such as pain and function. In other medical disciplines, the use of endoscopes has proven their merits and are widely applied. For example, in general surgery, laparoscopic cholecystectomy has become the standard of care compared to traditional invasive open procedure[11]. In spine surgery, such a paradigm shift has not yet been made. In the past, other surgical techniques such as micro-endoscopic discectomy (MED) and micro-tubular discectomy (MTD) have been introduced with similar aims of improving patient outcomes[10,12]. These techniques, however, failed to show merits over conventional microdiscectomy[13]. Another group of techniques are the percutaneous endoscopic lumbar discectomy techniques (PELD) which, unlike MED or MTD, are full-endoscopic and are performed either from an interlaminar or far-lateral approach (Figure 1).

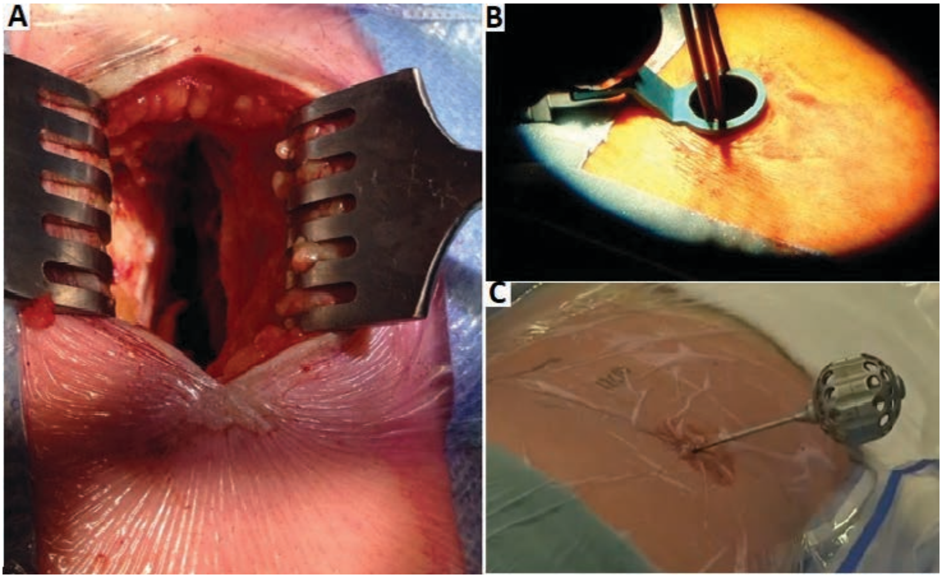


Figure 1: overview of discectomy techniques with (A) microdiscectomy, (B) micro-tubular discectomy and (C) transforaminal PELD.

Full-Endoscopic Transforaminal Discectomy

One of these PELD-techniques uses the transforaminal route[14.] Transforaminal PELD is performed under local anesthesia and conscious sedation[15]. After verification of the target lumbar level by fluoroscopy, a line is drawn from the center of the spine. Then a needle is placed with consequently insertion of a guidewire. After insertion of the guidewire, a series of conical rods are introduced, and subsequently a drill is introduced through the cannula. By drilling, the neuroforamen is enlarged. Hereafter, the instruments are removed with the guidewire remaining in place. Then, the endoscope with the working channel is introduced via the cannula (Figure 2). Following removal of the loose disk fragments, the cannula and endoscope are removed.

Figure 2: Intraoperative photograph showing the handling of the endoscope and the view through the endoscope in the upper-right corner.

In the literature, multiple names are used for the transforaminal approach to the lumbar disk i.e., arthroscopic discectomy, full-endoscopic transforaminal discectomy or posterolateral endoscopic excision[16]. For purposes of consistency in this thesis, Percutaneous Transforaminal Endoscopic Discectomy (PTED) is used, as is customary in the Netherlands.

A specific advantage of PTED is the possibility to decompress (extra)foraminal disk herniations, which may be more challenging to decompress with microdiscectomy. Furthermore, PTED is expected to lead to less postoperative back pain, shorter hospital admission, and a faster recovery because paraspinal muscles are not detached from their insertion, bony anatomy is not changed, and general anesthesia is not used[14]. Some concerns exist, however, in the scientific literature about the effectiveness for leg pain and recovery of function after PTED compared with open microdiscectomy, and previously published studies may have been influenced by commercial enterprises[17-19]. Furthermore, as PTED has a learning curve and exposes surgeons and patients to a higher radiation dose, these concerns need to be overcome with high quality evidence before PTED can be widely implemented[19-22].

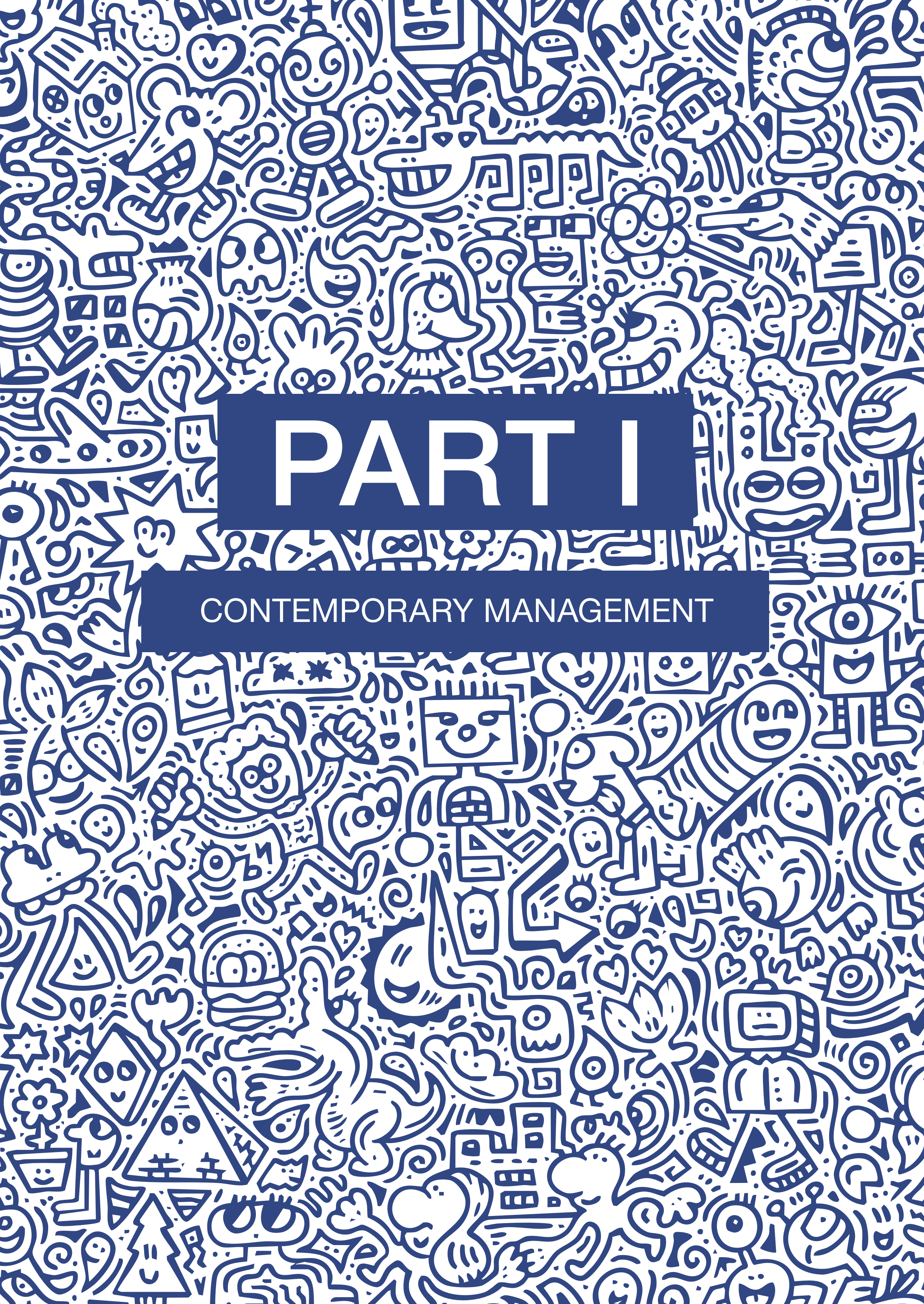
Previous studies that have compared PTED with open microdiscectomy found either no differences in outcomes or small differences of uncertain clinical relevance[17,19]. However, these studies were of small sample size, were not randomized, or involved only one surgeon[23,24]. Therefore, a randomized controlled trial with adequate sample size and low risk of bias is warranted.

OUTLINE THESIS

The main objective of this thesis was to assess whether PTED was non-inferior to conventional microdiscectomy in the treatment of sciatica. This thesis can be divided in three parts. Part I focuses on the contemporary management of sciatica before the PTED-study was published. **Chapter 2** aimed to give an overview of how sciatica is treated internationally by surgeons. The following question was addressed: what procedures are performed worldwide and how many surgeons perform PTED? In **chapter 3,** the clinical outcomes of PTED for a primary LDH are presented during 1-year follow-up. Another prerequisite for the conduction of a RCT is a systematic literature review to identify other studies which already reliably answer the primary research question. **Chapter 4** presents the results of a systematic review and meta-analysis on the effectiveness of PTED compared to microdiscectomy.

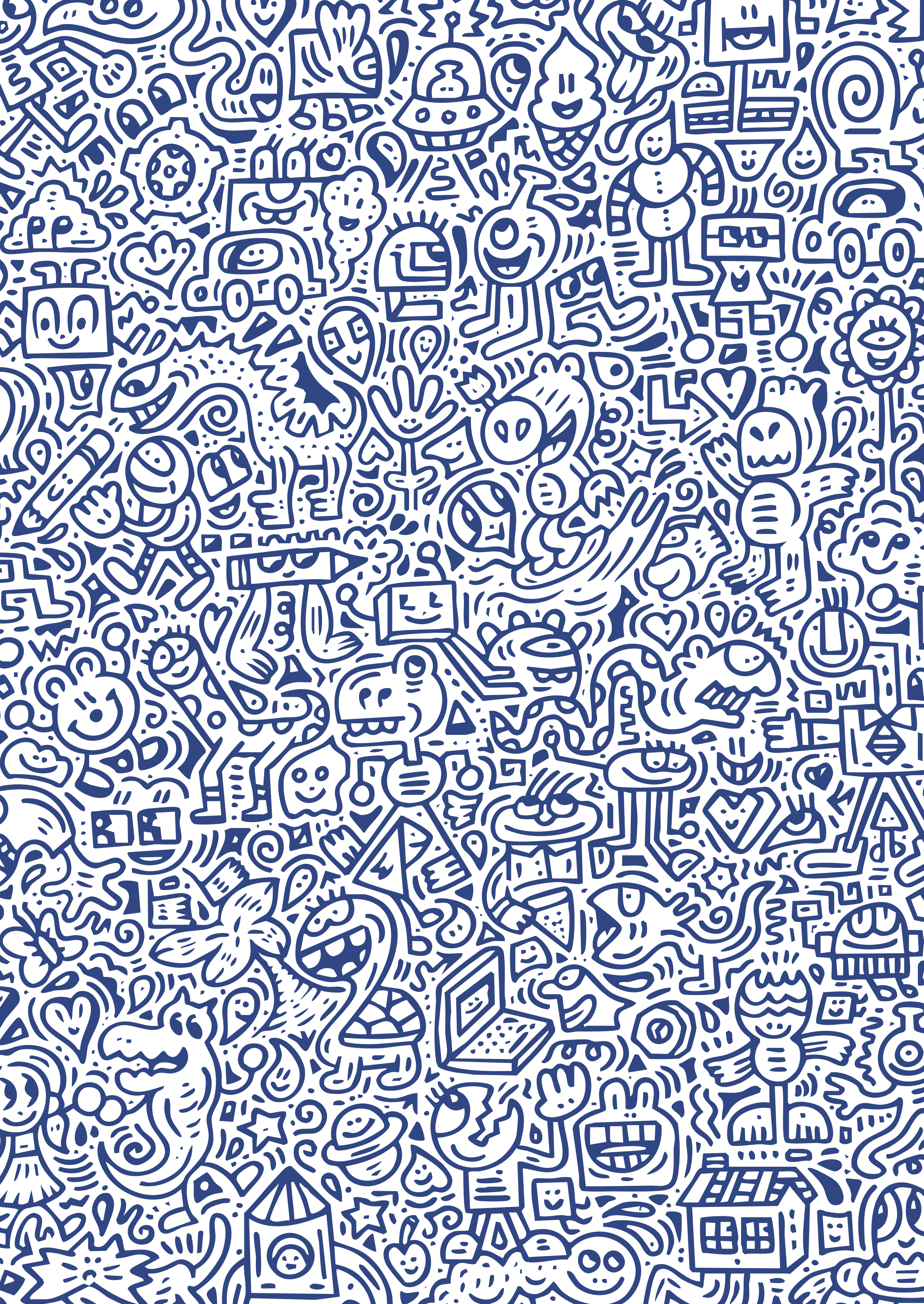
Part II of this thesis focusses on preferences: what expectations or preferences do surgeons or patients have regarding lumbar discectomy? Based on the literature, it was to be expected that no differences in effectiveness would be found when comparing PTED with microdiscectomy. These studies aimed to identify what other characteristics of lumbar disk surgery were deemed to be important in case non-inferiority would be shown. Would surgeons prefer a procedure with a lower complication risk? Would patients rather opt for a procedure under local anesthesia? To answer these questions, two discrete choice experiments (DCEs) were designed. **Chapter 5** presents the result of a DCE conducted among surgeons internationally treating sciatica. In **chapter 6** the preferences of patients are explored using a DCE.

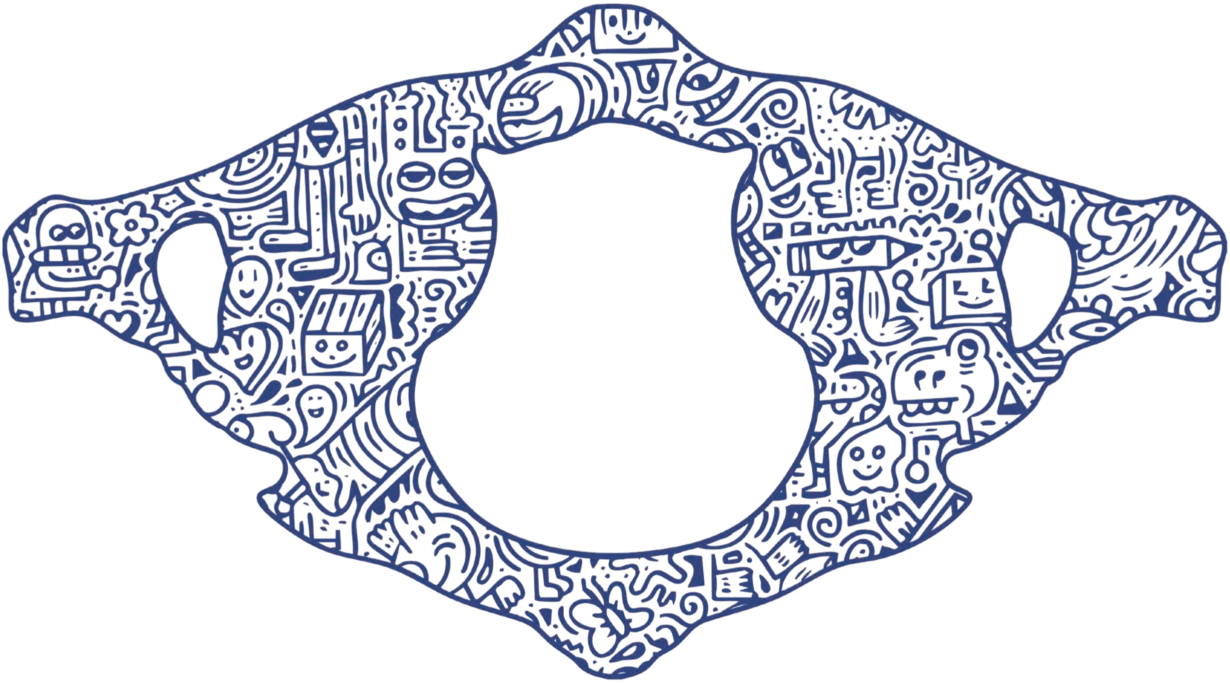
Part III of this thesis focusses on the first results of the PTED-study; a robust, multicenter, randomized controlled, non-inferiority trial assessing the effectiveness and cost-effectiveness of PTED compared to microdiscectomy. **Chapter 7** describes the results of the effectiveness analyses at 1-year follow-up. **Chapter 8** presents the results of the economic evaluation. In case of non-inferiority and thus similar effects, costs can play an important role in decision-making. **Chapter 9** provides a general discussion of the studies presented in this thesis, while **chapter 10** concludes this thesis with a summary of the studies.



PART I

CONTEMPORARY MANAGEMENT





2

Chapter

MANAGEMENT OF LUMBAR DISK HERNIATION: AN INTERNATIONAL SURVEY

Pravesh S. Gadjradj, Mark P. Arts, Maurits W. van Tulder, Wim J. Rietdijk, Wilco C. Peul, Biswadjiet S. Harhangi

Spine (Phila Pa 1976). 2017 Dec 1;42(23):1826-1834

ABSTRACT

Introduction

Sciatica is a common diagnosis in the general population. Sciatica is most frequently caused by LDH. Multiple surgical techniques and treatment modalities are available to treat LDH, albeit some with small differences between effect sizes or without compelling evidence. The objective of the current study was to evaluate the current practice patterns of surgeons regarding both the surgical and nonsurgical management of LDH worldwide and to compare this with the current literature.

Methods

A survey including questions on the application of physical examination, expectations regarding different surgical treatment and nonsurgical techniques, factors influencing the outcome of surgery were distributed among members of AOSpine International and the EANS.

Results

Eight hundred and seventeen surgeons from 89 countries completed the questionnaire. Pain medication and steroid injections were expected to be the most effective nonsurgical treatments. The severity of pain and/ or disability and failure of conservative therapy were the most important indications for surgery. A period of one to two months of radiculopathy was regarded as a minimum for indicating surgery. Unilateral transflaval discectomy was the procedure of choice among the majority and was expected to be the most effective technique with the lowest complication risk. Surgeons performing more lumbar discectomies, with more clinical experience and those located in Asia, were more likely to offer minimally invasive surgical techniques.

Conclusion

This study shows that current international practice patterns for lumbar disk surgery are diverse. There seems to be a discrepancy between preferred surgical techniques, the attitudes of surgeons worldwide, and the published evidence. Further research should focus on developing international guidelines to reduce practice variety and offer patients the optimal treatment for sciatica.

INTRODUCTION

Sciatica is defined as radiating pain from the buttock downwards to the leg[2,25]. Other symptoms may include low back pain, paresthesia, muscle weakness, or reduction of reflexes. Sciatica is most frequently caused by LDH, followed by spondylolisthesis, synovial cyst, and piriformis syndrome. Because of differences in study populations, acquisition of data, and definitions of sciatica, the reported prevalence of sciatica varies in the literature from 1.6% to 43%[1].

The natural course of symptomatic LDH is favorable due to resolution of leg pain in the majority of the cases without the necessity of surgery[26]. About a third of the patients visiting a general practitioner will recover within two weeks, which will increase to 75% after three months[4]. Nonsurgical therapy may include various strategies, including steroid injections, physical therapy, bed rest, manipulation, or medication while strong evidence is frequently lacking due to small effect sizes between treatments or high risks of bias in published studies, amongst others. Surgery is usually considered when leg pain persists, or progressive neurologic deficits develop. According to Dutch guidelines, surgery is indicated when at least six to eight weeks of conservative treatment has failed[27].

Oppenheim and Krause were the first to report on the surgical treatment of a ruptured intervertebral disk in 1909[28]. Due to innovation and development, surgical approaches have evolved and nowadays different surgical techniques, such as MTD, or the endoscope assisted MED, and PELD, are being practiced worldwide[10,18]. The rationale behind most of these novel surgical techniques is to reduce the invasiveness, hospitalization, and rehabilitation. Despite these alternative surgical approaches, conventional open microdiscectomy still is regarded as the gold standard for surgical treatment of LDH[5,6].

In 2008, the results of a survey on the treatment of LDH in the Netherlands were published[29]. That survey assessed the surgical management as of 2004 and differences in clinical practice and attitudes towards different surgical techniques were observed. These could be explained by the lack of high-quality evidence and consensus. Meanwhile, multiple randomized controlled trials have been published providing level I evidence on the efficacy of certain surgical techniques and treatment modalities albeit some without compelling evidence and small effect sizes[8,9,13,30]. Therefore, it can be expected that the gap between eminence-based medicine and evidence-based medicine in the current treatment of LDH will be shortened. By the means of this study, the authors attempt to evaluate the current practice patterns and to compare this with the current available literature.

METHODS

Survey and Sample

A previously conducted survey was modified by adding questions regarding physical examination, factors influencing the outcome of surgery, and the use of PROMs[29]. Questions regarding the operative techniques were extended by including full-endoscopic techniques, as these techniques are gaining popularity among both patients and surgeons[31]. The final survey consisted of 20 questions regarding (1) demographic characteristics, (2) applications and expectations of nonsurgical treatments, (3) surgical techniques and expectations of those techniques, (4) postoperative management, and (5) the use of PROMs. Questions regarding physical examination, standard surgical procedures used, and advise on timing of resuming daily activities were answered by using a 3-point Likert scale. Expectations regarding both surgical and nonsurgical treatments, and factors influencing indication for surgery were rated on a 5-point Likert scale[32,33]. To test the face validity and comprehension, a pilot survey among a subset of neurosurgeons and orthopedic surgeons was performed before distributing the final survey.

Between October 2015 and December 2015, an invitation to participate in the online survey (hosted on SurveyMonkey, Palo Alto, CA) was sent to all members of the EANS and of AOSpine International. EANS is a professional organization encompassing 1500 members, mostly European neurosurgeons. AOSpine is a worldwide community of 6179 members, mostly spine surgeons. To improve the response rate, a reminder was sent to members of both organizations. Residents and respondents who did not perform surgery for LDH were excluded for analysis.

Statistical Analysis

Descriptive statistics were used to report characteristics of the surgeons and their expectations of different treatment modalities. All percentages are based on valid responses. For analyzing purposes of the answers on 5-point Likert scales such as “most and very,” “less and least,” “highest and high,” “low and lowest” were dichotomized. Differences in continuous variables were analyzed using a t-test. Three multivariate logistic regressions were employed to analyze the association between surgeon's demographics and characteristics and whether they offer minimally invasive surgery (i.e., MTD, PELD, or both). For the regression analyses no missing data were accepted. Analyses were performed using STATA version 12 (StataCorp LLC Texas, USA). Statistical significance was set at 0.05.

Table 1: Demographics of respondents

	Number of respondents (%)
Male	773 (96.5)
Continent	
Africa	33 (4.0)
Neurosurgeon	12 (1.4)
Orthopedic surgeon	21 (2.6)
Asia and Oceania	195 (23.9)
Neurosurgeon	62 (7.6)
Orthopedic surgeon	133 (16.3)
Europe	362 (44.3)
Neurosurgeon	240 (29.4)
Orthopedic surgeon	122 (14.9)
North America	67 (8.2)
Neurosurgeon	25 (3.1)
Orthopedic surgeon	42 (5.1)
South America	160 (19.6)
Neurosurgeon	74 (9.1)
Orthopedic surgeon	86 (10.5)
Lumbar disk surgeries performed annually	
0-25	214 (26.2)
26-50	328 (40.1)
51-100	99 (12.1)
101-200	137 (16.8)
More than 200	39 (4.8)

RESULTS

Characteristics of Respondents

A total of 817 surgeons completed the survey, resulting in a response rate of 10.6%. Most of the surgeons (96.5%) were male. Surgeons were employed in 89 countries with the majority being active in Europe (Figure 1). 50.6% of the respondents were trained in neurosurgery and 49.4% in orthopedic surgery. The surgeons had a mean of 14.4 (±9.2) years of clinical practice (Table 1). The cumulative amount of lumbar disk surgeries performed were 62.477 per year, with an average of 76 disk surgeries performed annually per surgeon. Neurosurgeons performed a higher number of procedures annually, compared with orthopedic surgeons (91 *vs.* 62, $P < 0.001$).

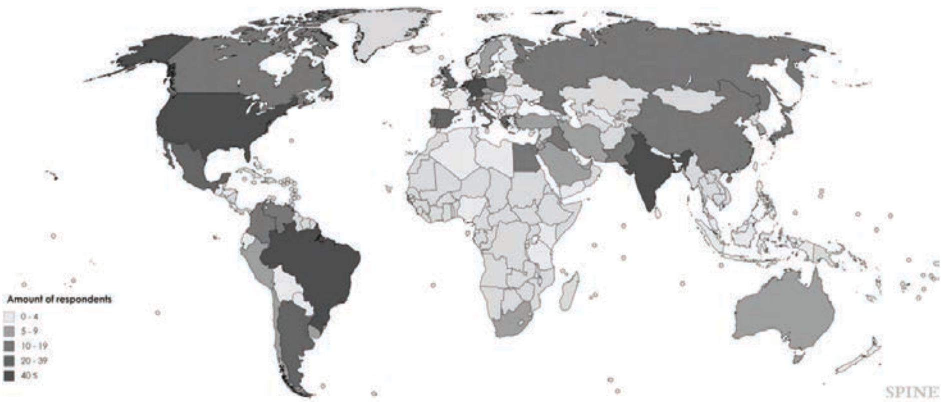


Figure 1: Geographical distribution of the respondents.

Physical Examination

All surgeons, except one, performed one or more diagnostic tests during physical examination when LDH is suspected. The straight leg raising test and testing for muscle weakness were most frequently performed by 92.9% and 94.0% of the responders, respectively. The crossed leg raising test was the least performed technique with 36.1% stating that they either “sometimes” or “never” assessed it.

Expectations for Conservative Treatment

Figure 2 provides an overview of the expected effectiveness of different conservative treatment modalities. Pain medication was regarded to be the most effective treatment. The effectiveness of steroid injections, exercise therapy, and counseling (by general practitioner, neurologist, or neurosurgeon) were expected to be “highest” or “high” by many responders, ranging from 44.7% to 55.9%.

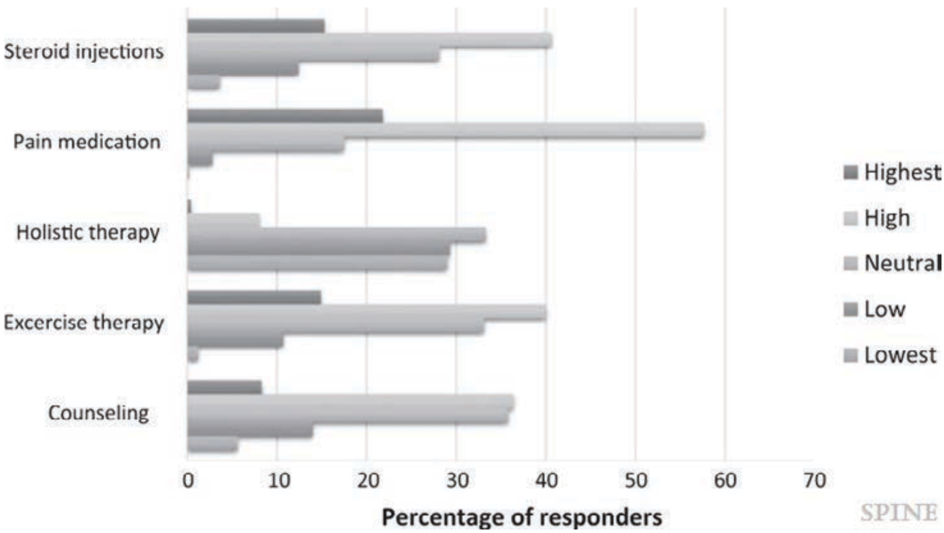


Figure 2: Perceived effectiveness of nonsurgical treatment modalities.

Indication for Surgery

When indicating surgery, 46.1% of the surgeons regarded a period of four to eight weeks of conservative treatment as the minimum. One-third regarded leg pain lasting for eight to twelve weeks (23.0%), and more than twelve weeks (11.3%) as a minimum period before deciding to perform surgery, while 19.5% of the surgeons who performed surgery within four weeks. Of these surgeons, more than one-fifth (N = 36), even reported to indicate surgery within two weeks.

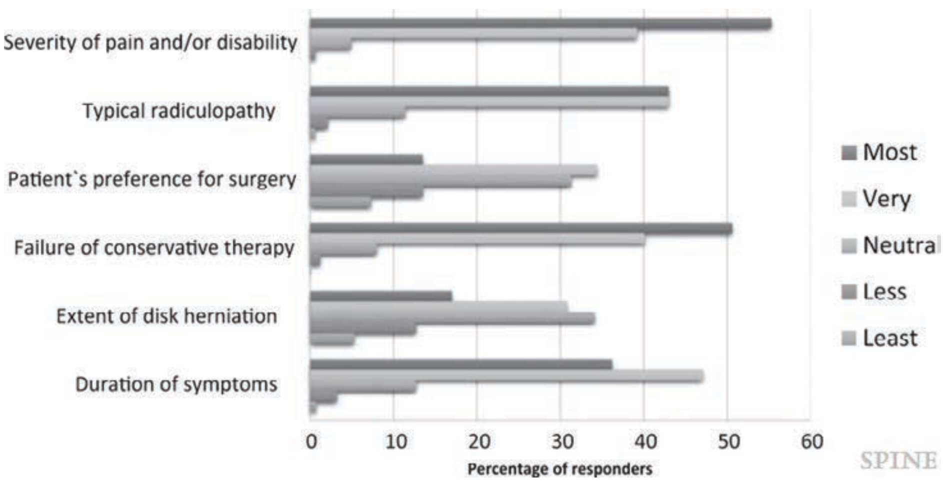


Figure 3: Expected importance of clinical aspects of LDH to indicate surgery.

Severity of pain and/or disability (55.3%) was the most import indication for surgery (Figure 3). Other important indications were failure of conservative treatment (50.6%), classic radiculopathy with neurological deficit (43.0%), and the duration of complaints (36.2%). The extent of the LDH and patient‘s preferences were less important indications.

Routinely Performed Surgical Techniques

More than 80% of the surgeons reported to “usually” perform unilateral transflaval discectomy. Other frequently performed procedures were the MTD and bilateral muscle retraction with unilateral discectomy by 14.2% and 10.9%, respectively. Percutaneous laser disk decompression (PLDD) and PELD were performed the least, with 93.3% and 80.7% of the surgeons claiming to “never” perform these techniques (Figure 4). Multivariate logistic regression analysis revealed that surgeons performing a higher volume of discectomies annually, surgeons based in Asia and surgeons with more years in clinical practice were significantly more likely to offer minimally invasive surgery ($P < 0.05$, see Table 2). Furthermore, orthopedic surgeons were more likely to offer PELD ($P < 0.001$) as compared with neurosurgeons. Regarding the extent of disk removal during discectomy, 6.1% and 1.7% of the surgeons reported to remove the disk subtotal bilateral and completely bilateral, respectively. Unilateral limited disk removal and unilateral extensive disk removal was performed by 28.3% and 30.5% of the surgeons, respectively. The remaining 33.4% of the surgeons stated that they only removed the sequester in case of sequestration.

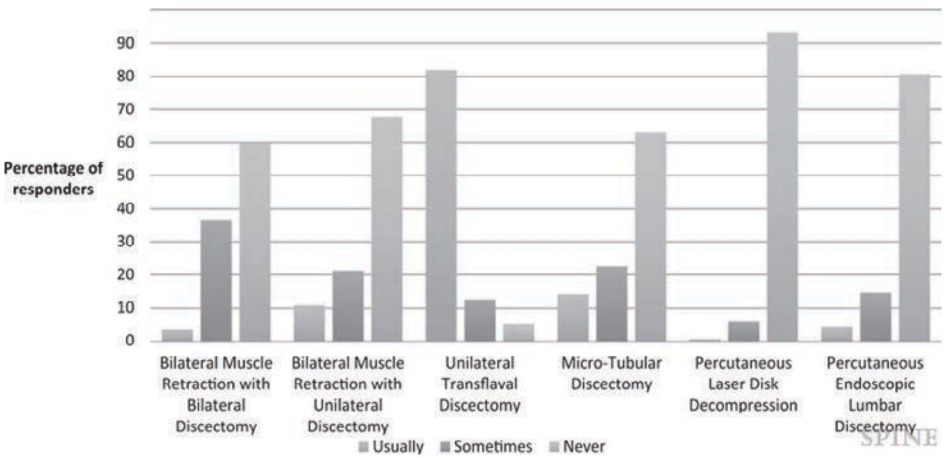


Figure 4: The performed operative techniques among the respondents.

Table 2: Effects of surgeon characteristics on performing minimally invasive spine surgery using multilevel logistic regression analysis.

	MTD		PELD		Minimally invasive surgery	
Variable	**OR**	**95% CI of OR**	**OR**	**95% CI of OR**	**OR**	**95% CI of OR**
Performed cases per year (ref. 0—50)						
50—100	1.21	(0.81—1.80)	2.12	(1.28—3.52)	1.29	(0.87—1.90)
>100	1.99	(1.34—2.93)	4.55	(2.78—7.45)	2.80	(1.89—4.14)
Surgical specialty (ref. neurosurgery)						
Orthopedics	1.06	(0.76—1.47)	2.19	(1.41—3.38)	1.33	(0.96—1.83)
Years of clinical experience (ref. 0—10)						
10—20	1.66	(1.15—2.39)	1.40	(0.88—2.23)	1.85	(1.29—2.64)
>20	1.44	(0.97—2.13)	1.16	(0.70—1.93)	1.48	(1.01—2.17)
Continent of practice (ref. Asia)						
Africa	0.23	(0.09—0.60)	0.24	(0.07—0.83)	0.20	(0.08—0.50)
Europe	0.35	(0.23—0.51)	0.32	(0.19—0.54)	0.32	(0.22—0.48)
North America	0.52	(0.29—0.96)	0.39	(0.16—0.93)	0.47	(0.26—0.86)
South America	0.46	(0.29—0.72)	1.08	(0.64—1.82)	0.55	(0.35—0.85)
Constant	0.57	(0.36—0.88)	0.10	(0.06—0.18)	0.57	(0.37—0.89)

2

Expectations of Different Surgical Techniques

Regarding the expectations of the different surgical techniques, unilateral transflaval discectomy was expected to have the highest effectiveness by 92.3% of the surgeons (Table 3) followed by MTD. More than half of the respondents estimated that PLDD would have the lowest effectiveness, followed by bilateral muscle retraction with unilateral discectomy. Regarding postoperative low back pain of the different techniques, PELD was expected to result in the lowest low back pain, followed by PLDD and MTD. Concerning the risk of complications, more than two-third of the responders expected the unilateral transflaval approach to have the lowest risk. Surgical techniques expected to have the highest risk for complications were bilateral muscle retraction with either bilateral (38.6%) or unilateral (30.8%) discectomy. More than half expected that the risk of recurrent LDH would be the highest after PLDD. Other techniques with a high expected recurrent LDH were PELD (more than one-third of the surgeons) and MTD (more than a quarter of the surgeons). The lowest risk of recurrent LDH was expected after bilateral muscle retraction, with or without bilateral discectomy, and unilateral transflaval discectomy, with percentages ranging from 46.4% to 52.3%.

Table 3: Expectations of different surgical treatments for LDH

	Effectiveness			Postoperative low back pain			Complication risk			Risk of recurrent disk herniation		
	Most	**Neutral**	**Least**	**Most**	**Neutral**	**Least**	**Most**	**Neutral**	**Least**	**Most**	**Neutral**	**Least**
Bilat. muscle retraction, bilat. discectomy	34.6	31.0	34.4	74.4	18.7	7.0	38.6	33.1	28.3	15.8	31.9	52.3
Bilat. muscle retraction, unilat. discectomy	38.2	26.7	35.2	69.6	21.3	9.1	30.8	37.3	31.9	12.3	41.2	46.4
Unilat. transflaval discectomy	92.3	5.8	1.9	14.1	34.6	51.3	3.9	28.2	67.8	6.9	41.3	51.8
MTD	58.3	29.7	12.0	9.5	28.1	62.4	14.2	36.6	49.1	26.8	44.5	28.8
PELD	35.0	40.2	24.8	6.2	29.9	63.9	22.3	38.2	39.4	37.0	43.1	19.9
PLDD	8.6	34.2	57.2	5.8	30.8	63.4	19.1	41.4	39.5	51.9	34.9	13.3

Postoperative Management

More than half of the surgeons reported to advise their patients to mobilize the same day of the surgery. One-third of these responders advised mobilization directly after returning to the ward, while the other two-third after a few hours (Table 4).

Directly after discharge, resumption of work and daily activities was never recommended by most of the surgeons, while almost 30% of the surgeons either sometimes or usually recommended resumption of work and daily activities directly after discharge. The majority recommended return-to-work and daily activities 4 or 6 weeks after surgery.

Table 4: Timing of postoperative mobilization and return to daily activities

Postoperative mobilization		Percentage of responders	
Day 0, directly after returning to the ward		18.0	
Day 0, after a few hours		36.2	
Day 1		40.6	
Day 2		3.8	
Day 3 or later		1.5	
Resuming work and/or Daily activities	**Usually**	**Sometimes**	**Never**
Directly after discharge	6.7	22.8	70.5
After 2 weeks	27.6	51.2	21.2
After 4 weeks	48.5	42.4	9.1
After 6 weeks	48.5	30.0	21.4

Registration of PROMs

Almost one-third of the surgeons reported not to register any PROMs. VAS for pain was the most frequently used PROM worldwide with 59.1% of the responders stating that their clinic monitors VAS. The ODI was used by 51.7% of the surgeons worldwide. Documentation of the Functional Rating Index, COMI-back, Roland-Morris Disability Questionnaire, and QBPDS ranged from 2.7% to 9.2%.

DISCUSSION

The results of this survey provide an overview of the preferred surgical techniques and the attitudes of surgeons worldwide regarding both the surgical and nonsurgical management of sciatica. Surgery is a frequently performed procedure among both neurosurgeons and orthopedic surgeons, with a wide variation in the number of discectomies performed per surgeon per year. More than 80% of the responders reported to “usually” perform unilateral transflaval discectomy. After the transflaval technique, MTD and bilateral muscle retraction with unilateral discectomy were the most performed techniques. More than 80% reported to “never” use PELD and more than 90% to “never” use PLDD.

In 2004, Arts *et al* conducted a survey among Dutch spine surgeons to obtain an overview of the surgical management of symptomatic LDH.[29] Among the 86 surgeons surveyed, unilateral transflaval discectomy was the most frequently performed technique and was also expected to have the highest effectiveness and the lowest risk for complications, which is also observed in the current survey. Expectations of surgeons worldwide in 2015 about minimally invasive techniques as MTD and PLDD were similar to the expectations of Dutch surgeons in 2004. These techniques were expected to give the lowest postoperative low back pain, but at the same time these techniques were expected to give the highest risk for recurrent disk herniation and a higher complication risk, compared with the transflaval approach. Timing of discectomy remained highly variable among the respondents.

An adequate indication for surgery and the timing of discectomy have remained subject of debate throughout the years. The severity of pain and disability in daily functioning were the most important indications for surgery. The results of the Sciatica-trial showed that although patients who were randomized to early surgery recovered faster, functional outcomes at 1- and 2-years of follow-up were similar[8]. Remarkable was that of the 142 patients who were assigned to prolonged conservative treatment after an average of 9.5 weeks of sciatica, 55 (31%) of the patients eventually underwent surgery after a mean of 18.7 weeks while the remaining 87 (61%) patients didn’t need surgery at all after 1 year of follow-up. These data emphasize the self-resolving character of sciatica in a substantial proportion of patients and warrants not offering surgery too early after the onset of radicular pain. Yet almost a fifth of the responders reported to regard a period of four weeks of radicular pain as a minimum for offering surgery.

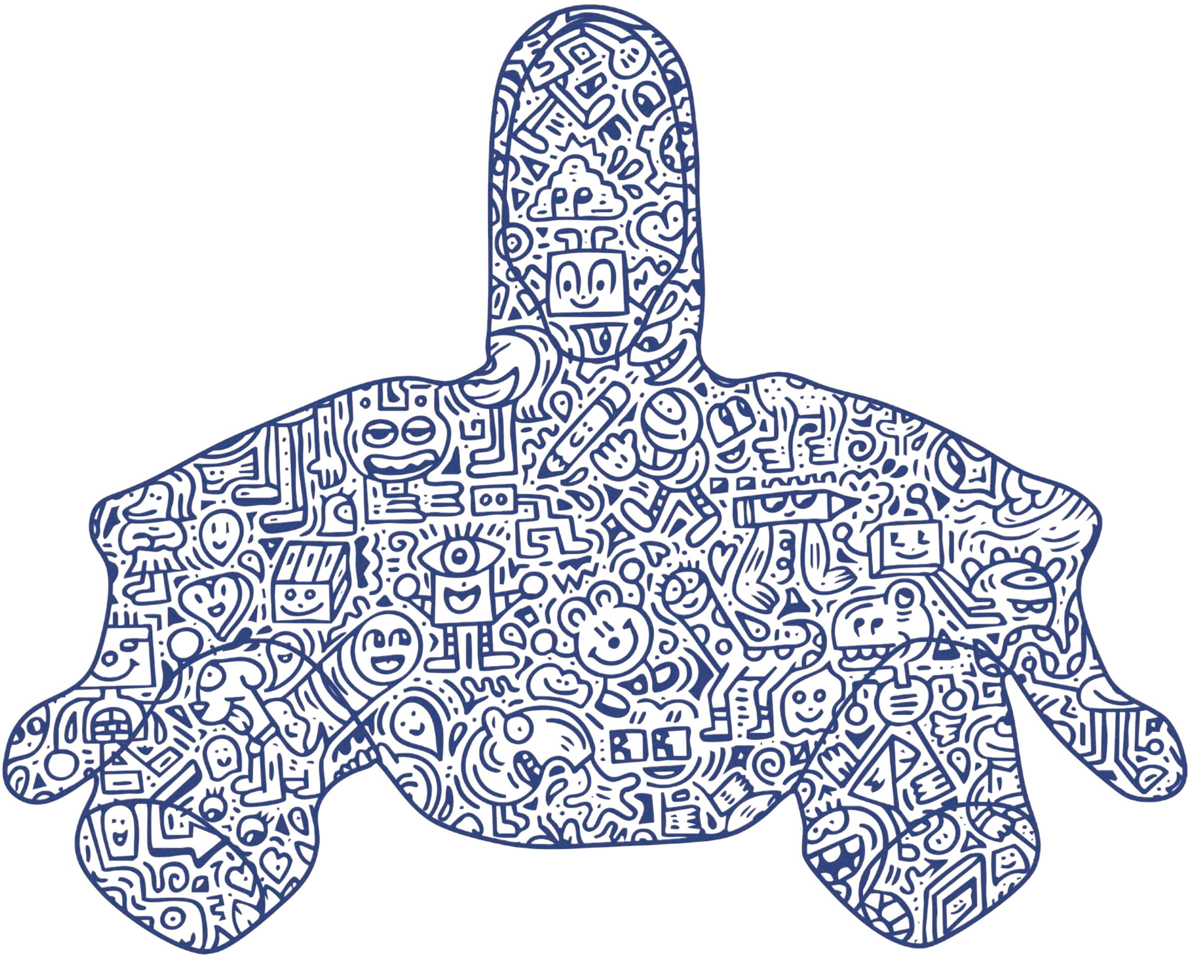
During the past decade, more research has been conducted on the cost-effectiveness of MTD and PLDD. These two surgical techniques, along PELD, are usually dubbed as minimally invasive techniques, a name which already raises expectations as less tissue damage. Consequently, MTD, PELD, and PLDD were expected to give the lowest postoperative back pain and the speediest recovery. Interestingly enough, two robust randomized controlled trials comparing MTD and respectively PLDD with open microdiscectomy could not confirm these expectations. There was no significant difference in back pain of the patients who underwent PLDD compared with the control group, but the PLDD group had a significantly higher rate of reoperations[34]. Furthermore, patients who had undergone MTD appeared to have favorable results for patient self-reported leg pain, back pain, and recovery, compared to patients who underwent microdiscectomy[13]. Despite the disappointing results of minimally invasive techniques, MTD and PLDD are still being performed "usually" or "sometimes" by 36.8% and 6.7% of the responders, respectively.

PELD was expected to give the lowest postoperative back pain. However, around 40% of the responders had a neutral expectation regarding the effectiveness, complication risk, and risk of recurrent disk herniation. There seems to be lack of a clear consensus on the advantages and disadvantages of this technique. A recently conducted meta-analysis concluded that patients who underwent endoscopic discectomy had a shorter hospitalization and less blood loss during surgery, while patients reported a significantly higher satisfaction rate compared with patients who underwent conventional open microdiscectomy. No significant differences were found in the complication rate, duration of surgery, and the rate of recurrent disk herniation. The authors concluded, however, that more high-quality randomized controlled trials with a sufficient sample size are necessary[35].

Some potential limitations of this study must be acknowledged. As this study is a survey using non-validated questions, there will always be the risk of reporting and recall bias. Another limitation may be the interpretation of the Likert-scales, as they can be scored as relative of each other or as a stand-alone item. The impact of these disadvantages is limited, as it was our aim to evaluate the attitudes of surgeons worldwide. Both a strength and a limitation are the number of responses received for this survey. A total of 817 surgeons from 89 countries completed the survey, which supports the generalizability of the results. However, it is inevitable that sampling bias has occurred as participating surgeons were all members of two professional organizations. Furthermore, orthopedic surgeons were from all continents and spine dedicated. In contrast to this, the neurosurgeons were mostly from Europe and to a lesser extent spine dedicated. Because the survey was distributed to two organizations, the EANS and AOSpine International, the calculated response rate should be even higher than the calculated one, because some surgeons are members of both organizations. Additionally, not all members were eligible to fill in the survey because we only included responses of surgeons who perform surgery for LDH.

CONCLUSION

This study presents the diversity among the current international practice patterns and the discrepancy between eminence-based medicine and evidence-based medicine in the treatment of sciatica. Further research should focus on developing international guidelines to reduce practice variety and offer patients the optimal treatment for sciatica.



3

Chapter

CLINICAL OUTCOMES AFTER FULL-ENDOSCOPIC TRANSFORAMINAL DISCECTOMY FOR SCIATICA

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Neurosurg Focus. 2016 Feb;40(2):E3

ABSTRACT

Introduction

Throughout the last decades, full-endoscopic techniques to treat LDH have gained popularity in clinical practice. To date, however, no high-quality evidence on the efficacy of PTED has been published, and studies describing its safety and short- and long-term efficacy are scarce. In this study the authors aimed to evaluate the clinical outcomes and safety in patients undergoing PTED for sciatica.

Methods

Patients who underwent PTED for sciatica between January 2009 and December 2012 were prospectively followed. The primary outcomes were the VAS for leg pain and the QBPDS. Secondary outcomes were the perceived experience with the local anesthesia used and satisfaction with the results of surgery at 1 year using Likert scales.

Results

A total of 166 patients underwent surgery for 167 LDHs. The 1-year follow-up rate was 95.2%. The mean reported scores on the VAS and QBPDS were 82.5 ± 17.3 and 60.0 ± 18.4 at baseline, respectively. Six weeks after surgery, the scores on the VAS and QBPDS were significantly reduced to 28.8 ± 24.5 and 26.7 ± 20.6, respectively ($p < 0.001$). After 52 weeks of follow-up, the scores were further reduced compared with baseline scores ($p < 0.001$) to 19.6 ± 23.5 on the VAS and 20.2 ± 18.1 on the QBPDS. A total of 4 complications were observed, namely 1 dural tear, 1 deficit of ankle dorsiflexion, and 2 cases of transient paresis in the foot due to the use of local anesthetics.

Conclusion

PTED appears to be a safe and effective intervention for LDH and has similar clinical outcomes compared to reported outcomes of conventional open microdiscectomy. High-quality randomized controlled trials are required to study the effectiveness and cost-effectiveness of PTED.

INTRODUCTION

With an annual incidence of 5 cases per 1000 persons, sciatica caused by LDH is a frequently observed problem[1]. The most important symptom is radicular leg pain following a dermatomal pattern from below the knee till the feet and toes. Other clinical findings may include unilateral spasm of the paraspinal muscles, gait deformity, limited forward flexion, and sensory deficits such as muscle weakness and reflex changes[2].

Sciatica can be managed variably: conservatively, with interventional pain treatment, or surgically[36]. In patients with persistent or progressive symptoms after six to twelve weeks of conservative treatment, surgery is indicated. A previous study showed that patients who were randomized to undergo early surgery had disability scores after 1 year that were similar to those of patients who underwent prolonged conservative management (with eventual surgery if needed)[8]. However, patients in the early surgery group reported earlier relief of leg pain and reported a faster rate of recovery, demonstrating the benefits of surgery.

Currently, open microdiscectomy is considered the gold standard for treating LDH[5]. Improvements in the use and design of optics and surgical instruments have led to the utilization of full-endoscopic surgical procedures, such as PELD. The effectiveness of these endoscopic techniques is expected to be at least comparable to that of the conventional, open procedures, but with reduced hospitalization and a shorter time to recover. PTED is a minimally invasive treatment in which the incision size is further reduced, to approximately 8 mm. Furthermore, no paraspinal muscle is cut or detached from the insertion. Consequently, PTED is thought to have a further reduced invasiveness due to reduced muscle injury and less epidural scarring. Throughout the years, PTED has been shown to be a promising minimally invasive technique[37]. The minimal tissue damage during PTED could make a difference in effectiveness or complications, and this could potentially lead to a lower intensity of both leg and back pain, faster rehabilitation and integration, and thus lower costs for society. However, studies describing the safety and short- and long-term efficacy of PTED are scarce. In this article we describe our experience with PTED for LDH in a large case series.

METHODS

All patients presenting with sciatica were primarily evaluated by neurologists. If symptoms persisted despite conservative treatment, MRI of the lumbar spine was requested. Patients who were diagnosed with LDH and had persisting signs and symptoms were referred to Park Medical Center and examined by the neurosurgeon.

When surgery was indicated, PTED was scheduled within two weeks after consultation. This study was approved by the institutional review board.

Patient Population

Patients between the ages of 18 and 80 years who presented for surgical treatment of LDH between 2009 and 2012 were enrolled in this study. The indication for surgery was according to Dutch guidelines, which included an MRI study showing an LDH with or without concomitant spinal or lateral recess stenosis or sequestration in patients with at least 6 weeks of persistent radicular irritation with or without motor or sensory loss[27]. PTED was only contraindicated in patients with severe spondylolisthesis or severe congenital spinal canal stenosis. Patients who had undergone previous surgery on the same spinal level, were pregnant, were diagnosed with the cauda equine syndrome, or had inadequate knowledge of the Dutch language were excluded from the study.

Surgical Procedure

All procedures were performed under local anesthesia and sedation with propofol and remifentanil. PTED was performed as previously published[14].

Outcomes

Primary outcomes of this study were the scores on the QBPDS and the VAS for leg pain[38]. The QBPDS measures the disabilities caused by back pain, ranging from 0 for no functional impairment to 100 indicating maximum functional impairment[39]. The VAS for leg pain measures the pain from 0, indicating no pain, to 100 representing the worst pain ever experienced in the leg. The QBPDS and the VAS scores were assessed at baseline and 6 and 52 weeks prospectively. Patients were seen at the outpatient clinic, six weeks after surgery. In case of recurrent or persistent radiculopathy, a postoperative MRI was requested to identify recurrence of LDH.

Furthermore, patients were asked to indicate their experience with local anesthetics on a 5-point Likert-type scale postoperatively, with a score of 0 indicating a very bad experience and a score of 5 a very good experience. After 1 year of follow-up, the patients' satisfaction with the result of PTED was measured using two questions. Patients were asked whether they would undergo the surgery again if they would experience the same symptoms and whether they would recommend the PTED technique to other patients with similar cases. Any new symptoms, complications of surgery, or recurrence of LDH were also evaluated after 52 weeks of follow-up.

Statistical Analyses

Descriptive statistics were used to analyze demographic data and Likert-type scales. Paired t-tests were performed to compare pre- and postoperative scores on the QBPDS and VAS. Results are presented as means with SDs. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (version 21.0, IBM Corp.).

RESULTS

From January 2009 through December 2012, 166 patients underwent PTED for treatment of 167 LDHs. Conversion to microdiscectomy was not required in any of these cases. At 52 weeks of follow-up, data were available for 158 patients (95.2%). The remaining eight patients were lost to follow-up for the following reasons: relocating without leaving a forwarding address (6 patients), being out of the country for an extended period (1 patient), and death due to a cause unrelated to the surgery (1 patient). The mean age of our study population was 43.5 ± 13.5 years. The most common level of LDH was L5–S1 (49.1%), followed by L4–5 (41.3%), L3–4 (8.4%), and L2–3 (1.2%). At baseline the mean reported score on the QBPDS was 60.0 (range 18–100). The mean VAS score for leg pain was 82.5 (range 5–100) (Table 1).

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Table 1: Baseline characteristics of the 166 patients in this study.

Characteristic	Value
Sex	
Male	85 (51.2%)
Female	81 (48.8%)
Mean age (years)	43.5 ± 13.5
Mean body mass index (kg/m^2)	27.1 ± 5.0
Mean duration of symptoms (weeks)	51.2 ± 15.3
Level of disk herniation*	
L2–3	2 (1.2%)
L3–4	14 (8.4%)
L4–5	69 (41.3%)
L5–S1	82 (49.1%)
Mean QBPDS	60.0 ± 18.4
Mean VAS	82.5 ± 17.3

*One patient underwent PTED at both L4–5 and L5–S1.

Table 2: surgical outcomes

Characteristic	Value
Mean duration of surgery (mins)	51.0 ± 9.0
Complications	4 (2.4%)
Dural tear	1 (0.6%)
Ankle/toe dorsiflexion weakness	1 (0.6%)
Transient paresis	2 (1.2%)
Day of mobilization	
Day of surgery	164 (98.8%)
Day 1 after surgery	2 (1.2%)
Repeated surgery within 1 year	12 (7.2%)
Recurrent LDH at same level	11 (6.6%)
LDH at another level	1 (0.6%)
Experience w/ local anesthesia*	159 (95.8%)
Very bad	2 (1.2%)
Bad	3 (1.9%)
Neutral	33 (20.8%)
Good	51 (32.1%)
Very good	51 (32.1%)

The duration of surgery varied from 34 to 94 minutes (mean 51.0 minutes). Thirty-three patients (20.8%) reported a neutral experience with the local anesthetics, while 102 (64.2%) patients had a good or very good experience (Table 2). Complications occurred in four cases (2.4%): one dural tear occurred, one patient experienced dysfunction in the dorsiflexion of the foot ankle, and two patients had a transient paralysis due to lidocaine anesthetics in the neuroforamen. No postoperative wound infections, thrombosis, or hemorrhages were observed; 164 (98.8%) of the patients could be discharged successfully two hours after surgery, and the remaining two patients (1.2%) could be discharged one day after surgery. Twelve patients (7.2%) needed to undergo additional surgery within 1 year after PTED; 11 (6.6%) of these patients had a recurrence of the disk herniation, and one patient developed a de novo LDH at another level.

Figure 1 shows the course of our primary outcome parameters at baseline and 6 and 52 weeks after surgery. After 6 weeks of follow-up, the mean reported score on the QPBDS decreased significantly ($p < 0.001$), with a mean difference of 33.3 points (95% CI 29.5–36.4), and the mean VAS for leg pain decreased by a mean of 53.7 (95% CI 49.4–58.3) ($p < 0.001$). Fifty-two weeks after surgery, the mean score on the QBDS and VAS leg decreased further to 20.2 and 19.6 ($p < 0.001$ for both, in comparison with baseline scores, although the differences were not statistically significant in comparison with the 6-week follow-up scores).

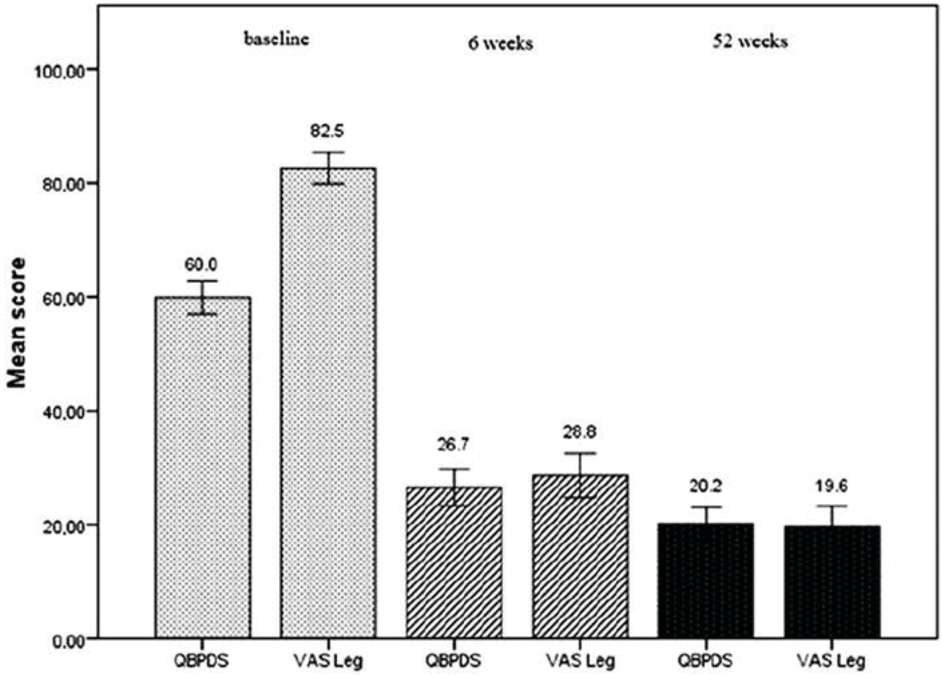


Figure 1: Graphs showing the mean values of the primary outcome measures for 166 patients at baseline and after 6 and 52 weeks of follow-up.

Finally, 154 patients (92.8%) indicate that they would recommend the PTED-technique to people with similar symptoms caused by LDH. When asked whether they would undergo PTED again, if they would experience the symptoms due LDH, 152 patients (91.6%) answered positively.

DISCUSSION

The results of this study showed statistically significant and clinically relevant relief of functional disability and leg pain on the short-term and improvement on these results on the long-term. The mean duration of surgery was less than one hour, and the recurrence rate for repeated LDH surgery was 6.6% within 1 year in this group with a high follow-up percentage (95.6%). Furthermore, almost all (98.8%) of the patients could be discharged on the day of surgery. Only 2.4% of the 166 patients experienced minor complications.

Prospective studies reporting on clinical outcomes of PTED for sciatica describing its safety and short- and long-term efficacy are scarce. However, some other research groups have also evaluated results of PTED and have demonstrated comparable efficacy. In a large single-center retrospective review of 10,228 cases, one research group investigated why PELD failed in treating LDH and found that failure was mostly explained by incomplete removal of herniated disk material[40]. Furthermore, they found a short-term recurrence rate of 4.3%, which is comparable to our data.

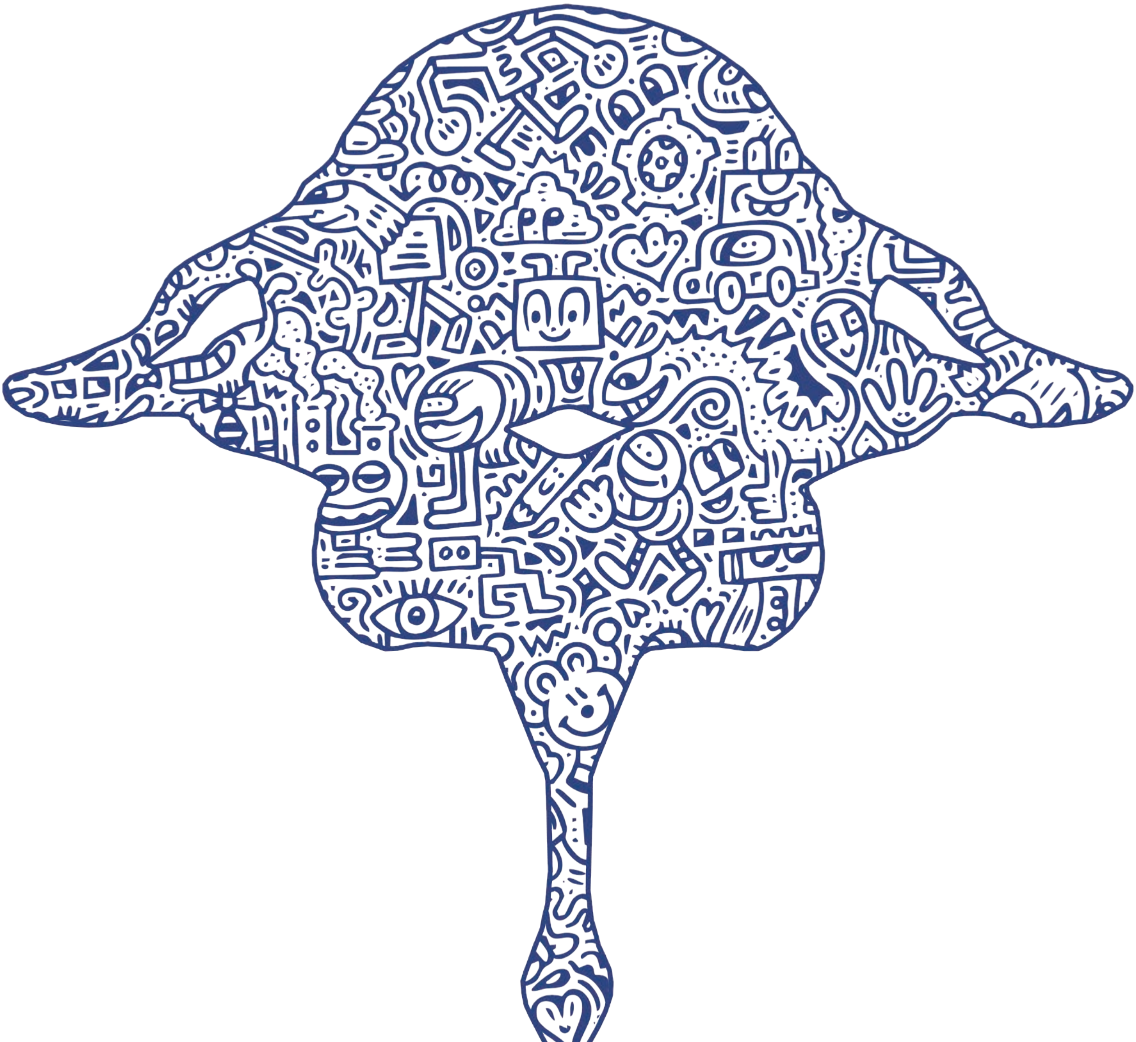
The number of observed complications, four in total, was lower than expected. No infection, thrombosis, or hemorrhage was observed. One patient experienced a foot drop, while two patients experienced transient paralysis. Transient paralysis can be prevented by infiltrating with less lidocaine in the neuroforamen. Using too much local anesthetic in the foramen can also lead to impaired direct feedback from the patient when the surgeon approaches the nerve root during surgery. Nevertheless, the rate of complications was very low and comparable to the rates reported in the literature[41,42].

Nellensteijn *et al* were the first to provide a systematic review of the PTED-technique[43]. Their review included studies up to May 2008 and identified only one RCT with a low risk of bias[44]. However, this trial has a disputable generalizability due to inclusion of only certain types of LDHs. In a more recently published review and meta-analysis, Cong *et al* pooled results comparing endoscopic discectomy versus open microdiscectomy and found a significantly higher satisfaction rate in patients who underwent endoscopic discectomy[35]. Furthermore, endoscopic surgery was associated with less blood loss and a shorter duration of hospitalization. No significant differences in operating time, recurrence, or complication rates were found. Both reviews, however, emphasized the need for more high-quality randomized controlled trials that also assess cost-effectiveness.

An important strength of this study is the prospective collection of data of consecutive patients reducing the possibility of selection and recall bias. Another strength is our limited loss to follow-up. The present study also has several limitations. Due to the design, a proper control group is lacking; however, as previously mentioned, the objective of this study was not to emphasize the merits of PTED over other procedures, but to share the short- and long-term results that show its potential. A limitation of PTED is its learning curve due to the concept of operating through a two-dimensional view[45]. Considering the impact of learning curve of PTED on outcomes, all surgeries of this study were performed by a single neurosurgeon who already had overcome the learning curve.

CONCLUSION

Based on our findings, PTED seems to be a promising technique to effectively treat sciatica. The reported complication rate of PTED is low, as is the percentage of patients requiring additional surgery due to recurrent LDH. Due to its learning curve, however, PTED should be further investigated before widespread implementation. Microdiscectomy remains the current standard for surgical decompression due to LDH. Randomized controlled trials are needed to generate high-quality evidence on the effectiveness and cost-effectiveness of PTED.



4

Chapter

FULL-ENDOSCOPIC TRANSFORAMINAL DISCECTOMY VERSUS MICRODISCECTOMY FOR SCIATICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Spine (Phila Pa 1976). 2021 Apr 15;46(8):538-549

ABSTRACT

Introduction

The current standard procedure for the treatment of sciatica caused by LDH, is microdiscectomy. PTED is an alternative surgical technique which is thought to be less invasive. It is unclear if PTED has comparable outcomes compared with microdiscectomy. Therefore, we aimed to give a systematic overview of effectiveness of PTED compared with microdiscectomy in the treatment of sciatica.

Methods

Multiple online databases were systematically searched up to April 2020 for RCTs and prospective studies comparing PTED with microdiscectomy for LDH. Primary outcomes were leg pain and functional status. Pooled effect estimates were calculated for the primary outcomes only and presented as SMDs with their 95% CIs at short (1-day postoperative), intermediate (3–6 months), and long-term (12 months).

Results

We identified 2276 citations, of which eventually 14 studies were included. There was substantial heterogeneity in effects on leg pain at short term. There is moderate quality evidence suggesting no difference in leg pain at intermediate (SMD 0.05, 95% CI −0.10 – 0.21) and long-term follow-up (SMD 0.11, 95% CI −0.30 – 0.53). Only one study measured functional status at short-term and reported no differences. There is moderate quality evidence suggesting no difference in functional status at intermediate (SMD −0.09, 95% CI −0.24 – 0.07) and long-term (SMD −0.11, 95% CI −0.45 – 0.24).

Conclusion

There is moderate quality evidence suggesting no difference in leg pain or functional status at intermediate and long-term follow-up between PTED and microdiscectomy in the treatment of sciatica. High quality, robust studies reporting on clinical outcomes and cost-effectiveness on the long term are lacking.

INTRODUCTION

Sciatica is a frequently used term to describe radiating leg pain. It is mostly caused by LDH[1,2]. Even though the natural course of sciatica is favorable, and most cases respond to conservative treatment, surgery is deemed necessary in some cases[46]. The current standard procedure to decompress the nerve root by removing disk fragments, is conventional open microdiscectomy[6,47].

In attempts to reduce the surgical invasiveness, techniques which use endoscopes to remove disk fragments were developed. The expectation was that by causing less tissue damage during surgery, patients would have less postoperative back pain, recover sooner from surgery, and have shorter duration of hospitalization[10]. Development of methods facilitating insertion of surgical endoscopes into the safe entry zone in the neuroforamen formed (also known as Kambin triangle), enabled the development of PTED[48]. During PTED no paraspinal muscles are detached from their origin and bony anatomy is affected limited. Previous studies which have examined PTED demonstrated favorable clinical outcomes, with the result that percutaneous full-endoscopic discectomy has made its way into small scale clinical practice[47,49].

A previous review published in 2009 which compared the effects of PTED with microdiscectomy concluded that the quality of the evidence regarding effectiveness of PTED is low and PTED could not be recommended for the treatment of LDH[43]. Since then, large observational studies as well as RCTs have examined the effects of endoscopic discectomy techniques *versus* microdiscectomy, which have been summarized in recent reviews, including meta-analyses[17,35]. Despite similar aims, these meta-analyses differ in methodology. As a result, the uncertainty regarding the effectiveness of PTED compared with microdiscectomy remains.

In 2014, a systematic review was published by our research group, comparing minimally invasive surgery with microdiscectomy[18]. Due to the low number and high risk of bias of the included studies as well as small sample sizes, no pooled effect estimates were calculated for the effects of PTED *versus* microdiscectomy. Preliminary analysis of studies published since then, suggested that there were sufficient studies to warrant an update of our previous review, focusing on the effects of PTED *versus* microdiscectomy in the treatment of LDH[50].

METHODS

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[51].This study was registered in the international prospective register of systematic reviews (Prospero CRD 42020177053).

Inclusion Criteria for Studies

Studies were considered to be eligible according to the following inclusion criteria: (1) prospective studies, including RCTs and quasi-randomized studies *(*e.g.*,* randomization which could include allocation by alternating the date of birth); (2) compared PTED with microdiscectomy in the treatment of sciatica caused by a primary LDH; (3) measured one of the clinical outcomes (i.e. VAS for leg pain, back pain, functional status, improvement, work status), surgical outcomes (i.e., blood loss, length of stay, complications, reoperations); radiological or biochemical outcomes; or costs (i.e., costs of interventions, health care utilization, total costs); (4) were published in English, German, or Dutch. Retrospective studies were excluded because the level of evidence provided by these studies is low compared with prospective observational and randomized studies.

Intervention

PTED is defined as a lateral, full-endoscopic approach in which the disk fragments are removed through the neuroforamen. PTED is usually performed under local anesthesia[14].

Control Group

Microdiscectomy is defined as removing the disk fragments from an open transflaval approach by laminotomy[5]. Microdiscectomy is usually performed under general anesthesia.

Search Strategy

An experienced librarian conducted a systematic search using a combination of terms related to endoscopic techniques, percutaneous techniques, and LDH. As this study updates our previously published review, the previous search terms were optimized and this search only included studies published after January 2013, the search date used by Kamper et al[18]. The updated search is available in supplementary Table 1. On the April 20, 2020, MEDLINE, PubMed, Embase, Emcare, Web of Science, and the Cochrane library were systematically searched for eligible articles. In addition, additional eligible articles were searched for by reference checking the included studies. All available records were screened by two reviewers independently based on title and/or abstract. In case of disagreements, a third independent reviewer was consulted. Following this step, two authors independently screened the full text of the manuscripts based on the inclusion criteria. Disagreements were resolved through consensus with the involvement of a third reviewer.

Data Collection and Analysis

Two authors independently extracted all data in a prespecified spreadsheet. Discrepancies in extraction were resolved by consensus. This spreadsheet included (1) study characteristics; (2) clinical outcomes; (3) surgical outcomes; (4) biochemical outcomes, namely c-reactive protein (CRP) and creatine kinase (CK) which are indicators of inflammation and muscle injury, respectively; (5) radiological outcomes (6) costs; and (7) timing of the outcomes.

Assessment of Risk of Bias

Risk of bias analysis was performed for only RCTs using the criteria recommended by the Cochrane Collaboration[52]. These criteria cover selection bias, performance bias, attrition bias, detection bias, and selective outcome reporting bias. Two authors independently scored these criteria as: low risk of bias, high risk of bias, or unclear. Disagreements were resolved by consensus and if necessary, by evaluation of a third author.

Bias Across Studies

Conflict of interest was determined for all included studies based upon the information provided by the authors in their publication. Publication bias was assessed using a funnel plot and based upon symmetry.

Data Analyses

Measures of Treatment Effect

Only data from RCTs were considered for the meta-analysis, as the observational studies may be of limited value due to the risk of selection bias. Primary continuous outcomes (leg pain and functional status) were expressed as a SMD, including 95% CIs. A negative effect size indicates that PTED is more beneficial than microdiscectomy, meaning subjects have less pain or better functional status. The primary outcomes were defined as short-term (1 day), intermediate (3–6 months), and long-term (12–16 months) and data were analyzed according to the closest time interval. When multiple outcomes were available from a single study, the value was used which was thought to be best correlated to that time interval. A random-effects model was used for all analyses based upon the DerSimonian and Laird approach[53]. RevMan 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Denmark) was used to perform the meta-analysis. Data from prospective studies and data of the secondary outcomes were described.

TABLE 1. Overview of the Included Studies

Study	Study Period	Study Location	Study Type	Sample Size (PTED/OM)	Average age	Inclusion Criteria	Outcomes
Mayer *et al*, 1993	1987	Germany	RCT	40 (20/20)	41	Radiculopathy caused by small non-contained LDH, confirmed on imaging, failed cons. Rx	Surgical outcomes, patient satisfaction, RTW, clinical scoring system modified from Suezawa and Schreiber.
Hermantin *et al*, 1999	-	USA	RCT	60 (30/30)	40	Radiculopathy, positive tension signs, imaging confirming single small intracanalicular LDH at L2-S1, failed cons. Rx, absence of central or lateral stenosis, absence of litigation claim due to LDH.	Surgical outcomes, pain, improvement, RTW, patient satisfaction, narcotic usage.
Krappel *et al*, 2001	1996–1997	Germany	RCT	40 (20/20)	40	Persistent radiculopathy of 4 to 6 weeks, failed cons. Rx, MRI confirmed LDH at L4–5 or L5–S1, no motor or only limited sensory neurological deficit.	Surgical outcomes, patient satisfaction, RTW, complications, radiological outcomes, costs.
Akcakaya *et al*, 2016	-	Turkey	RCT	30 (15/15)	44	Indication for LDH surgery	Surgical outcomes, sciatica VAS, functional outcomes, serology.
Gibson *et al*, 2017	-	UK	RCT	140 (70/70)	41	Age 25–70, single level LDH, failure of cons.Rx.	Surgical outcomes, leg pain, back pain, QoL, patient satisfaction.
Tao *et al*, 2018	2011–2016*	China	RCT	462 (231/231)	45	LDH >1 year, VAS pain >6, confirmed by imaging, failed cons.Rx for 4 to 8 weeks.	Surgical outcomes, pain, functional outcomes, patient satisfaction, serology.
Tacconi *et al*, 2019	2014–2018	Italy	RCT	38 (18/20)	45	Age >18 years, clinical diagnosis of extraforaminal LDH, confirmed on MRI, symptoms lasting >6 weeks, failed cons. Rx, at least 14 months clinical follow-up.	Surgical outcomes, leg pain, functional outcomes.
Tacconi *et al*, 2020	2017–2019	Italy	RCT	50 (25/25)†	44	Confirmed single-level LDH, protrusion preferentially localized at disk level, invalidating radicular pain lasting >6 weeks and adequate imaging studies.	Surgical outcomes, back pain, leg pain, radiological outcomes.
Dai *et al*, 2020	2017–2018	China	RCT	94 (47/47)	43	LDH	Surgical outcomes, pain, QoL, serology.

Study	Study Period	Study Location	Study Type	Sample Size (PTED/OM)	Average age	Inclusion Criteria	Outcomes
Pan *et al*, 2016	2009–2012	China	Pros.	106 (48/58)	41	LDH confirmed by imaging.	Surgical outcomes, leg pain, back pain, functional outcomes, patient satisfaction, serology, radiological outcomes.
Wang *et al*, 2017	2015–2016	China	Pros.	110 (60/50)	54	Single segment LDH, confirmed by imaging and conforming diagnostic criteria, failed cons.Rx after three months, no contraindication for surgery.	Surgical outcomes, pain, functional outcomes, serology.
Choi *et al*, 2018	-	Korea	Pros.	40 (20/20)	43	Sciatica and back pain >6 weeks, failed cons.Rx, clinical LDH confirmed by imaging.	Surgical outcomes, leg pain, back pain, functional outcomes, serology, radiological outcomes.
Chang *et al*, 2018	2015–2016	China	Pros.	110 (60/50)	45	Meeting diagnostic criteria of LDH, single segment LDH confirmed by imaging, failed cons. Rx, no surgical contraindications.	Surgical outcomes, pain, functional outcomes, serology.
Xu *et al*, 2020	2017–2018	China	Pros.	145 (58/87)	37	LDH meeting diagnostic criteria, failed cons.Rx, without spondylolisthesis and spinal stenosis	Surgical outcomes, patient satisfaction functional outcomes, serology, pain.

The abstract of Tao *et al* describes June 2012 to May 2016, while the methods section June 2011 to May 2014 as enrollment period.
[†]Tacconi *et al* 2019 performed OM through Wilkes approach.
cons.Rx indicates conservative therapy; LDH, lumbar disk herniation; QoL, quality of life; RTW, return to work; VAS, visual analogue scale. Surgical outcomes: duration of surgery, length of hospital stay, reoperations, complications and/or blood loss.
Serological outcomes: CRP, CK, TNF-a, IL-4, IL-6, CD3+ T-cells, CD4+ T-cells, CD8+ T-cells, malondialdehyde, myeloperoxidase, superoxide dismutase, total antioxidant capacity.
Patient satisfaction: modified McNab-score, Odom‘s criteria.
Functional outcomes: Oswestry disability index.

Statistical Heterogeneity

Statistical heterogeneity was examined by inspecting the Forest plot and formally tested by the Q-test (chi-square) and I^2. There was insufficient data to explore cases of considerable heterogeneity.

Data Synthesis and Quality of the Evidence

We evaluated the overall quality of the evidence for the primary outcomes, back pain, and the following complications: durotomies, (transient) neurological deficits, and wound infections. The GRADE-method was applied, which ranges from high to very low quality and is based upon the following five domains: limitations of design, inconsistency of results, indirectness, imprecision, and other factors (e.g., publication bias)[54].

RESULTS

Search Results

The initial search retrieved 2276 studies. Of these, 2255 were excluded based on title and/or abstract checking, while an additional 10 studies were excluded based on assessing the full-text articles (see supplementary Table 2). With the addition of the three studies identified by Kamper et a[18]l, 14 studies were included for this systematic review and meta-analysis comprising a total of 1465 patients (Figure 1)[23,24,44,55-65]. Of the 14 studies, nine were (quasi)randomized studies and the remaining were observational studies (Table 1).

Risk of Bias Analysis

The results of the risk of bias analysis are shown in Figure 2. Three studies reported a random sequence generation, of which two had an adequate allocation concealment[23,57]. All studies had a high risk of performance bias due to the fundamental differences of PTED and microdiscectomy. As all studies measured patient-reported outcome measures, all had a high risk of detection bias.

Bias Across Studies

Eight out of nine RCTs reported on the conflict of interest[23,44,55-60].Of these studies, only one had authors that would receive benefits from a commercial party[44]. The remaining studies declared no conflict of interest. Publication bias was not formally assessed given too few data.

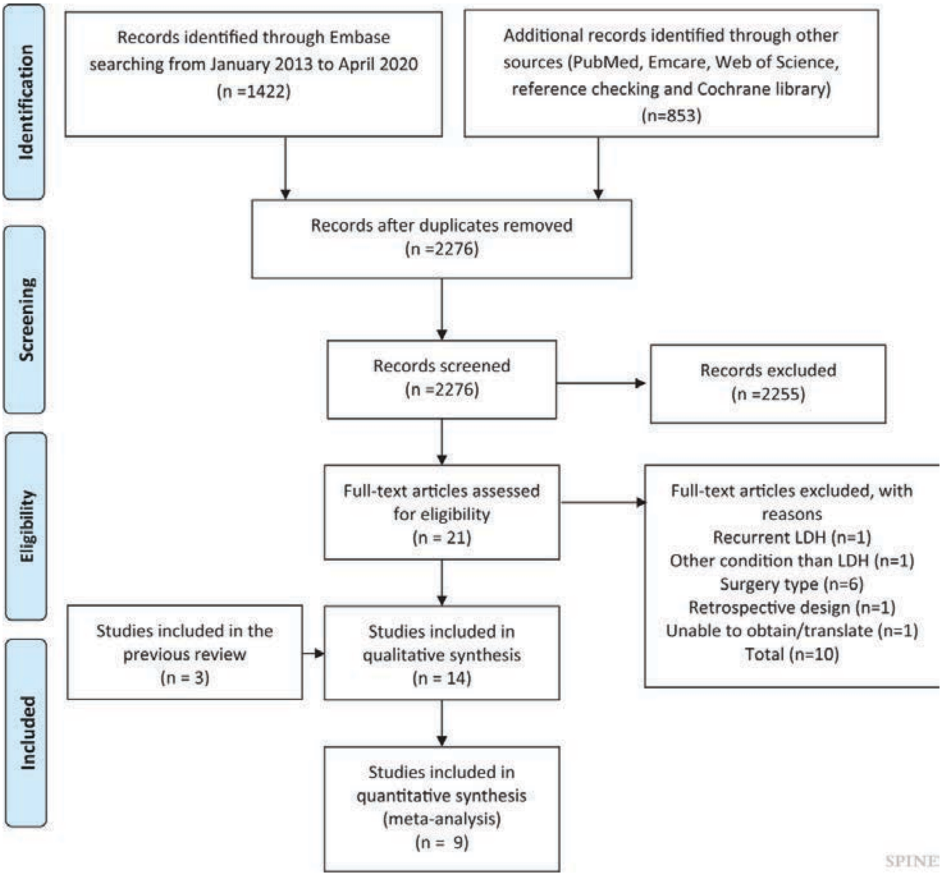

Figure 1: Flow-chart of the study selection process.

Primary Outcomes

Leg Pain

Twelve studies reported VAS scores, of which seven were RCTs (Table 2). Four of these RCTs did not specifically describe that the VAS-score referred to leg pain[44,55,58,59]. Only two provided data which could be used for meta-analysis[58,59]. Short-term leg pain did not differ between groups (SMD –1.28, 95% CI –3.65 – 1.08; two studies, N = 556) but there was high heterogeneity (*I*2 = 99%) (Figure 3).

TABLE 2. Outcomes of RCTs and of Observational Studies

Study (PTED/OM)	Leg Pain	Functional Outcome	Back Pain	Patient Satisfaction	Serology	Radiology	Blood Loss	Length of Hospital Stay	Reoperation for LDH	Return to Work	Costs
Mayer *et al*, 1993N=40 (20/20)				70% *vs.* %55					3 *vs.* 1	95% *vs.* %72	
Hermantin *et al*, 1999N=60 (30/30)	12 *vs.* 19			73% *vs.* %67					0*vs. 2	27 *vs.* 49 days	
Krappel *et al*, 2001N=40 (20/20)				84% vs. 75%		+			1 *vs.* 0	100% *vs.* %100	-
Akcakaya *et al*, 2016N=30 (15/15)	18 *vs.* 28	12 *vs.* 14			+			1 *vs.* 1.2			
Gibson *et al*, 2017N=140 (70/70)	19±26 *vs.* 35±31	22±20 *vs.* 18±17	25±25 *vs.* 30±28	1.40±0.1 *vs.* 1.80±0.1				0.7±0.7 *vs.* 1.4±1.3	5 *vs.* 2	78% *vs.* %82	
Tao *et al*, 2018N=462 (231/231)	19±10 *vs.* 18±10	22±5 *vs.* 23±5		85% *vs.* %88	+		+	3±1.5 *vs.* 14±1.8			
Tacconi *et al*, 2019N=38 (18/20)	19±7 *vs.* 16±7	13±7 *vs.* 16±7					+		NR *vs.* 1		
Tacconi *et al*, 2020N=50 (25/25)	20 *vs.* 20		20 *vs.* 40			+/+/–†			1 *vs.* 0		
Dai *et al*, 2020N=94 (47/47)	17±2 *vs.* 30±7						+	5.1±1.0 *vs.* 8±1.2			
Pan *et al*, 2016N=106 (48/58)	+/–	+/–	+/–	+/–	+	+‡/ +/–	+	+			+
Wang *et al*, 2017N=110 (60/50)	+	+					+		+/–		
Choi *et al*, 2018N=40 (20/20)	+/–	+/–	+/–		+	+		+			

Study (PTED/OM)	Leg Pain	Functional Outcome	Back Pain	Patient Satisfaction	Serology	Radiology	Blood Loss	Length of Hospital Stay	Reoperation for LDH	Return to Work	Costs
Chang et al. 2018N=110 (60/50)	+	+					+				
Xu *et al*, 2020N=145 (58/87)	+	+		+/–			+	+			

*
One additional procedure in PTED group due to lumbar spinal stenosis.
†
Favors PTED on two different MRI reconstructions, but found no difference on two other MRI reconstructions.
‡
Favors PTED in reduction of the Cobb angle but no differences in intervertebral space height were found.
For clinical outcomes of RCTs values measured at the latest moment of follow-up are shown with their standard deviations, when reported. + indicates the outcome is in favor of PTED, – , the outcome is in favor of OM; +/–, there is no difference between PTED and OM. Favors means a statistically significant difference was shown in individual studies. In case if differences were not tested, no symbol is shown. Scores for leg pain, back pain and functional status are reported from 0 to 100 with 0 indicating no pain or disability. NR, not reported

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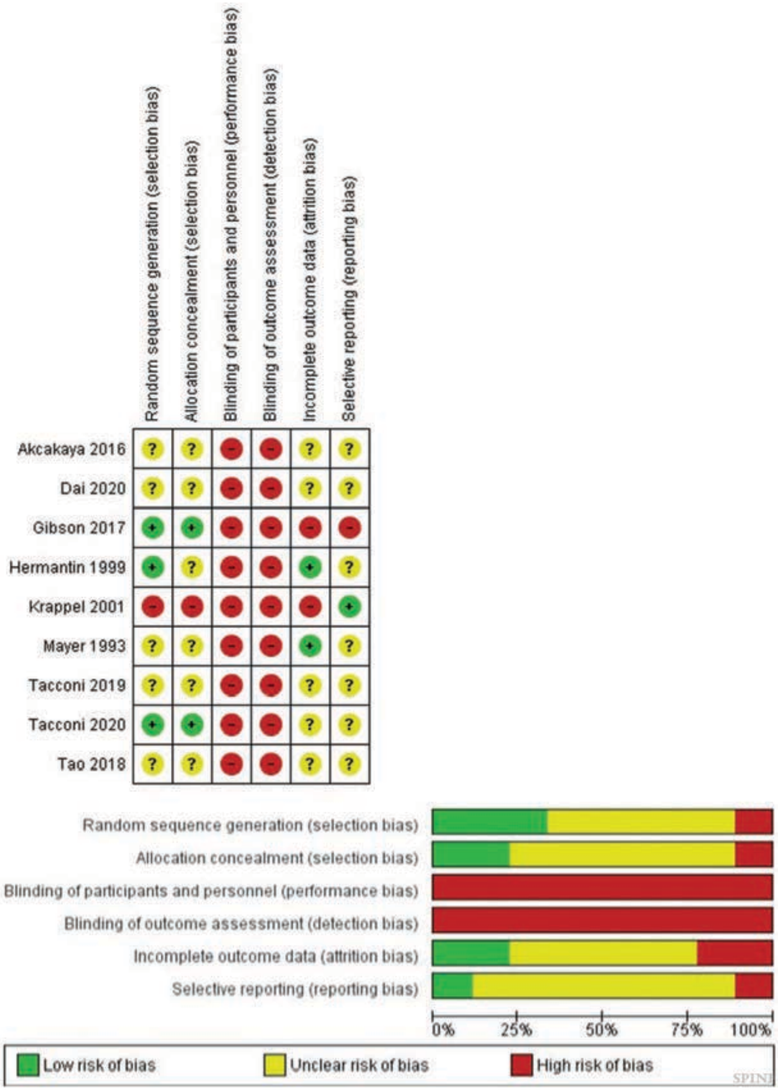


Figure 2: Risk of bias assessment for all included RCTs.

At intermediate and long-term, there was moderate quality evidence of no difference in leg pain between groups (SMD 0.05, 95% CI −0.10–0.21; three studies, N = 621 and SMD 0.11, 95% CI −0.30–0.53, two studies, N = 152, respectively) (see Table 3). Omitting the RCT that did not specifically mention VAS for leg pain did not affect the results[58,59]. Of the studies that were not included in the meta-analysis, Akçakaya et al showed that patients who underwent PTED had less leg pain at short-term and Tacconi et al showed no difference in leg pain at intermediate-term. In the study of Hermantin et al the average pain score was 1.9 in the microdiscectomy-group versus 1.2 in the PTED group on a scale of 0 to 10. At 2 years of follow-up, Gibson et al showed that patients who underwent PTED had less leg pain than patients who underwent microdiscectomy (35 vs. 19, N = 123).

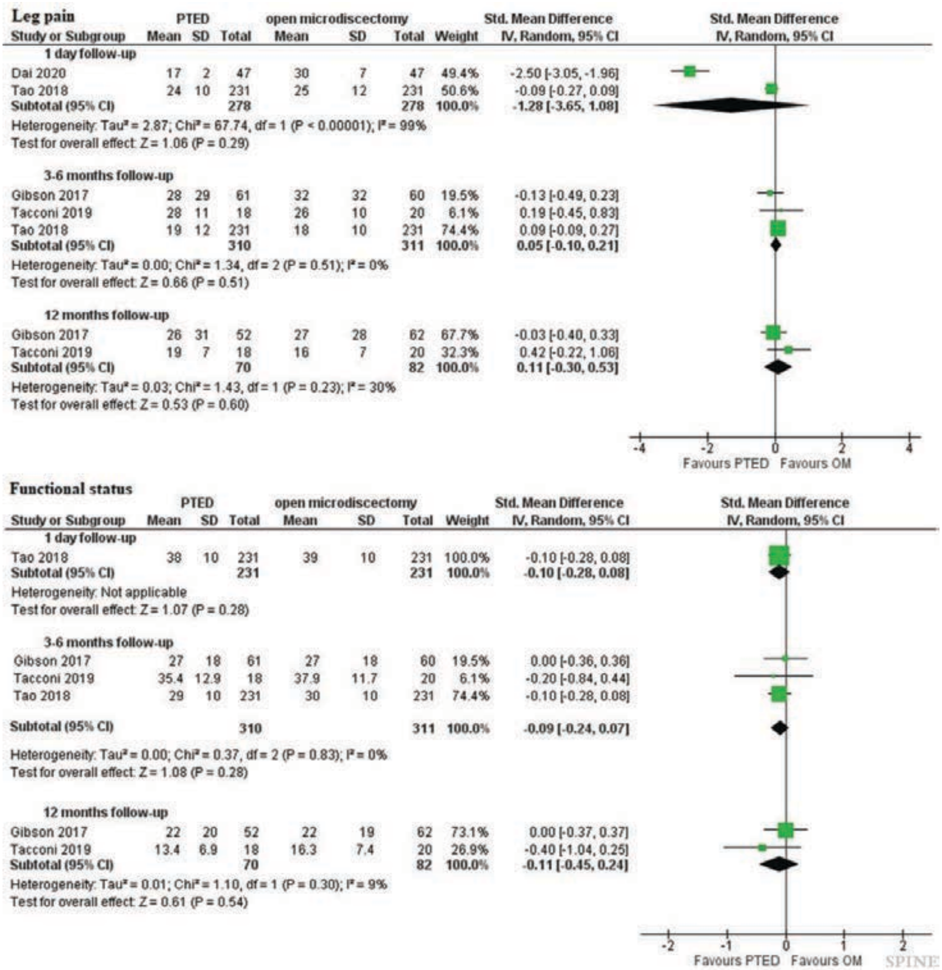


Figure 3: Pooled results of PTED versus microdiscectomy on the primary outcomes

TABLE 3. GRADE Evidence Summary of Findings for the Effect of PTED *Versus* Open Microdiscectomy

Quality Assessment					
	No. of Studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**
Leg pain (intermediate term)	4	RCT	Serious limitations*	No serious inconsistency	No serious indirectness
Leg pain (long term)	3	RCT	No serious limitations	No serious inconsistency	No serious indirectness
Functional outcome (intermediate term)	3	RCT	Serious limitations*	No serious inconsistency	No serious indirectness
Functional outcome (long term)	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness
Back pain (intermediate term)	1	RCT	No serious limitations	Serious inconsistency†	No serious indirectness
Back pain (long term)	1	RCT	No serious limitations	Serious inconsistency†	No serious indirectness
Complications‖	12	RCTProsp.	Serious limitations*	No serious inconsistency	No serious indirectness

*
Quality of evidence is downgraded if >50% of the study population origins of studies with a high or unclear risk of bias for allocation concealment.
†
Quality of evidence is downgraded if the I^2 statistic >75% or if only one study reports on the outcome.
[3] Quality of evidence is downgraded if study results are not generalizable.
§
Quality of evidence is downgraded if there are <400 patients in the study sample for continuous outcomes or if there are less than 300 events in the study sample for dichotomous outcomes.
¶
Quality of evidence is downgraded if there are signs of publication bias or conflicts of interest.
‖
Dural tears, (transient) neurological deficits and wound infections were taken into this analysis.

Functional Outcomes

Functional outcomes were measured with the ODI in nine studies[23,56,57,59,60]. Two studies reported on short term function and did not find a difference between PTED and microdiscectomy[55,59]. At intermediate term there was evidence of moderate quality of no difference between PTED and microdiscectomy (SMD −0.09, 95% CI −0.24–0.07; three studies, N = 621); the same was found at long term (SMD −0.11, 95% CI −0.45–0.24; two studies, N = 152).

		No. of Patients			
Imprecision	Other	PTED	OM	Effect (95% CI)	Quality of Evidence
No serious imprecision	No serious considerations	335	336	SMD 0.05 (–0.10 to 0.21)	Moderate
Serious imprecision§	No serious considerations	100	112	SMD 0.11 (–0.30 to 0.53)	Moderate
No serious imprecision	No serious considerations	309	311	SMD –0.09 (–0.24 to 0.07)	Moderate
Serious imprecision§	No serious considerations	70	82	SMD –0.11 (–0.45 to 0.24)	Moderate
Serious imprecision§	No serious considerations	61	60	SMD –0.04 (–0.39 to 0.32)	Low
Serious imprecision§	No serious considerations	52	62	SMD 0 (–0.37 to 0.37)	Low
Serious imprecision§	Serious considerations¶	647	678	Not calculated	Very low

4

Secondary Outcomes

Back Pain

Two RCTs reported VAS scores for back pain[23,57]. Gibson et al reported no differences between PTED or microdiscectomy in back pain at intermediate (30 vs. 31, N = 121) and long-term follow-up (31 vs. 31, N = 114). Tacconi et al reported lower postoperative back pain at short term in favor of PTED (20 vs. 40; N = 50). Overall, there is low quality evidence suggesting no difference in back pain between techniques at intermediate and long term (see Table 3).

Patient Satisfaction

Seven studies reported on patient satisfaction following surgery; five of which were RCTs[23,24,44,59,60,63,65]. Gibson et al used the Odom's criteria to assess patient satisfaction and found a higher rate of satisfaction in the PTED group 2 years after surgery, but no difference at 3 and 12 months. Hermantin et al used an unclear instrument to measure patient satisfaction while the other RCTs used the modified McNab score. Two of these reported no differences in patient satisfaction using the McNab score[59,60].

Surgical Outcomes: Blood Loss, Stay in Hospital, Complications, Reoperation for Recurrent LDH, Return to Work

Blood loss was reported in seven studies and all showed results in favor of PTED (Table 2)[56,58,59,62-65]. Of the studies that measured postoperative length of hospital stay all but one RCT found shorter hospitalization duration in the PTED group.

Complications among patients who underwent PTED and microdiscectomy were reported in 12 studies (Table 4). Overall, there was very low quality of evidence that complication rates (of dural tears, neurological deficits, and wound infections) between PTED and microdiscectomy were comparable.

Six RCTs reported reoperation rates for recurrent disk herniation. Reoperation rates were low (2%–10%) and none of the studies showed significant differences between groups. Return-to-work was reported in four studies. Hermantin et al reported that patients who underwent PTED returned earlier to work than patients who underwent microdiscectomy (27 vs. 49 days). Mayer et al reported that 95% of the patients in the PTED group returned to work after 12 months compared with 72% in the microdiscectomy group. Krappel et al and Gibson et al found no differences in return-to-work rates.

Biochemical Outcomes

Five studies reported on CRP and were all in favor of PTED at one or more postoperative time points (ranging from 1 hour to 7 days after surgery). Four studies reported on the CK values; all studies showed significantly higher CK rates in the microdiscectomy group at one or more time points.

Radiological Outcomes

Four studies reported radiological outcomes of PTED versus microdiscectomy. One study compared scarring measured on postoperative MRIs and found less scarring in the PTED group, but no correlation to clinical outcomes[44]. Another study assessed lumbar stability by measuring the Cobb angle and the height of the intervertebral space as measured on x-rays and found a significant reduction in the Cobb angle in the PTED group postoperatively[65]. No differences were found in the postoperative Cobb angle in the microdiscectomy group or in the measured intervertebral space height in either group. Choi et al[61] measured the cross-sectional area of high-intensity lesions in the paraspinal muscles on MRIs postoperatively, which were larger in patients that underwent microdiscectomy compared with PTED. Finally, in a randomized study that analyzed paraspinal muscle signal intensity changes on postoperative MRI, higher mean volume of paravertebral muscle alterations was found in the microdiscectomy group on two specific MRI reconstructions[57].

Costs and Cost-Effectiveness

Two studies reported on some of the costs of the interventions. Krappel et al calculated the costs by computing the costs of the operating room, hospitalization, endoscopes, and sterilization of the equipment. Total costs of PTED were higher than for OM (U.S.$ 7707 vs. U.S.$ 1417, respectively). Of the total costs of PTED, 66.2% were attributable to the costs of the endoscope. Pan et al only reported the costs of hospitalization which were lower in the PTED group (U.S.$ 1279 for PTED vs. U.S.$ 1622 for microdiscectomy)[65]. None of the identified studies performed economic evaluations.

DISCUSSION

The update of our systematic review which examined the effect of PTED versus microdiscectomy for the treatment of LDH suggests that there is moderate quality evidence of no difference in leg pain and functional status at the intermediate and long-term follow-up. Data on short-term leg pain showed substantial heterogeneity, and only one study provided data on short-term functional status. These data on leg pain and functional status didn't show any differences between PTED and microdiscectomy. Our review could not affirm a lower rate of back pain which could be expected from full-endoscopic spine surgery. Back pain was only assessed by one RCT and there was low quality evidence of no difference in back pain between patients who underwent PTED versus microdiscectomy. Overall, complications were more frequently reported in patients who underwent microdiscectomy, although the incidence of complications after lumbar discectomy is low.

TABLE 4. Complications Mentioned in All Included Studies

Study	Sample Size (PTED/OM)	Total Complications N (%)	Complications PTED N (%)	Description	Complications OM N (%)	Description
Mayer *et al*, 1993	40 (20/20)	0	0	–	0*	–
Hermantin *et al*, 1999	60 (30/30)	1 (1.7%)	0	–	1 (3.3%)	1 (3.3%) incidental durotomy
Krappel *et al*, 2001	40 (20/20)	0	0	–	0	–
Gibson *et al*, 2017	140 (70/70)	7 (5%)	6 (8.6%)	2 (2.9%) possibly dural tears4 (5.7%) mild dysesthesia	1 (1.4%)	1 (1.4%) persistent foot drop
Tao *et al*, 2018	462 (231/231)	77 (16.6%)	14 (6.1%)	14 (6.1%) transient leg paresthesia	63 (27.3%)	7 (3.0%) incidental durotomy56 (24.2%) chronic low back pain
Tacconi *et al*, 2019	38 (18/20)	3	1 (5.5%)	1 (5.5%) reversible hypothermia	2 (10%)	1 (5%) superficial wound infection1 (5%) transient leg paresthesia
Tacconi *et al*, 2020	50 (25/25)	0	0	–	0	-
Dai *et al*, 2020	94 (47/47)	5 (5.3%)	1 (2.1%)	1 (2.1%) dystasia	4 (8.5%)	1 (2.1%) lumbar deformation1 (2.1%) aggravated pain2 (4.3%) dystasia
Pan *et al*, 2016	106 (48/58)	16 (15.1%)	3 (6.3%)	3 (6.3%) transient leg paresthesia	13 (22.4%)	3 (5.2%) transient leg paresthesia2 (3.4%) dural lacerations4 (6.7%) transient leg weakness4 (6.7%) urinary retention
Wang *et al*, 2017	110 (60/50)	0	–	0	–	–
Choi *et al*, 2018	40 (20/20)	0	0	–	0	–
Xu *et al*, 2020	145 (58/87)	29 (20%)	5 (8.6%)	3 (5.2%) wound infections2 (3.4%) transient nerve paralysis	24 (27.6%)	7 (8.0%) wound infections10 (11.5%) transient nerve paralysis7 (8.0%) spinal instability
Overall	1325 (647/678)	138 (10.4%)	30 (4.6%)		108 (15.9%)	

*

One patient in the OM group underwent a revision procedure due to scar tissue. This revision procedure was complicated due to the development of spondylodiscitis.

Comparison With Other Studies

In recent years, other reviews with different methodology have been published[17,18,35]. The current review differs in that we only compared full endoscopic transforaminal discectomy with microdiscectomy which is considered to be the golden standard to treat sciatica. Furthermore, our review included four RCTs published after completion of the previous reviews[56-59]. Nevertheless the results of the present review are in concordance with prior reviews; clinical outcomes such as leg pain, back pain, functional status, and rate of recurrent disk herniation, are comparable or differed minimally between PTED and microdiscectomy, but PTED is associated with shorter hospitalization duration and blood loss[17,35].

In our previous review, we identified three RCTs comparing PTED with microdiscectomy[18]. Of these RCTs, only one evaluated pain and none assessed specifically back pain or functional status as is customary in lumbar spine surgery nowadays[24,44,60]. Furthermore, cautious interpretation of these trials was also warranted because of the unclear or high risk of selection bias. The current search added six RCTs to the results of which two had a low risk of selection bias[23,57]. Of these two studies only the trial by Gibson et al with moderate sample size (N = 140) provided relevant clinical outcomes on short and long term.

Strengths and Limitations

Despite the inclusion of 11 new studies to this update, there remains a paucity of high-quality studies with a low risk of bias reporting on patient-centered outcomes relevant to lumbar disk surgery[18]. For instance, postoperative leg pain was only reported in three and two studies at intermediate and long term respectively, and postoperative back pain was only measured by one study at intermediate and long term. The paucity of studies also led to the inability to formally assess publication bias. Another limitation is inherent to cultural and time differences between the studies. For example, cultural differences may explain the difference in postoperative length of hospital stay following discectomy between studies conducted in European countries in comparison to studies conducted in other countries. An example of timely differences is the trend that the duration of hospitalization for lumbar disk surgery is decreasing over the years[13,66]. Nevertheless, because these cultural and time differences are applied on both patient categories, we expect the influence of these differences on the outcomes to be limited but they may explain heterogeneity between the studies on these other outcomes. The inability of blinding patients is a limitation which may also warrant cautious interpretation of some outcomes. For instance, some expected short-term benefits such as patient satisfaction, and return-to-work and length-of-hospital stay rates, may be influenced by the patient's own expectation of undergoing endoscopic surgery, also frequently named as minimally invasive surgery.

The findings of the current review warrant further studies of high methodological quality and sufficient sample size to further explore clinical merits of PTED in comparison to microdiscectomy on core clinical outcomes as leg pain, functional status, and back pain. As we would expect no differences in clinical outcomes or small difference of limited clinical relevance based on the results of this meta-analysis, prospective economic evaluations are essential, especially since PTED is expected to be more expensive as procedure but to have lower hospitalization costs. Results of a RCT comparing the effectiveness and cost-effectiveness of PTED to microdiscectomy are expected[67].

An important concern for the use of PTED for sciatica is the surgical learning curve, which is relatively long and difficult[20,45]. Two studies that focused on the learning curve of full-endoscopic surgery show a steep learning curve of full-endoscopic surgery and suggest that the procedure may be more difficult to master as compared with microdiscectomy[45]. Despite this learning curve, however, clinical outcomes such as functional status and pain appear to be comparable to those after microdiscectomy.

CONCLUSION

There is moderate level evidence of no difference in leg pain or functional status at intermediate and long term between PTED and OM in the treatment of LDH. High quality and robust studies reporting on clinical outcomes on the long-term and performing economic evaluations are lacking.

SUPPLEMENTARY TABLE 1

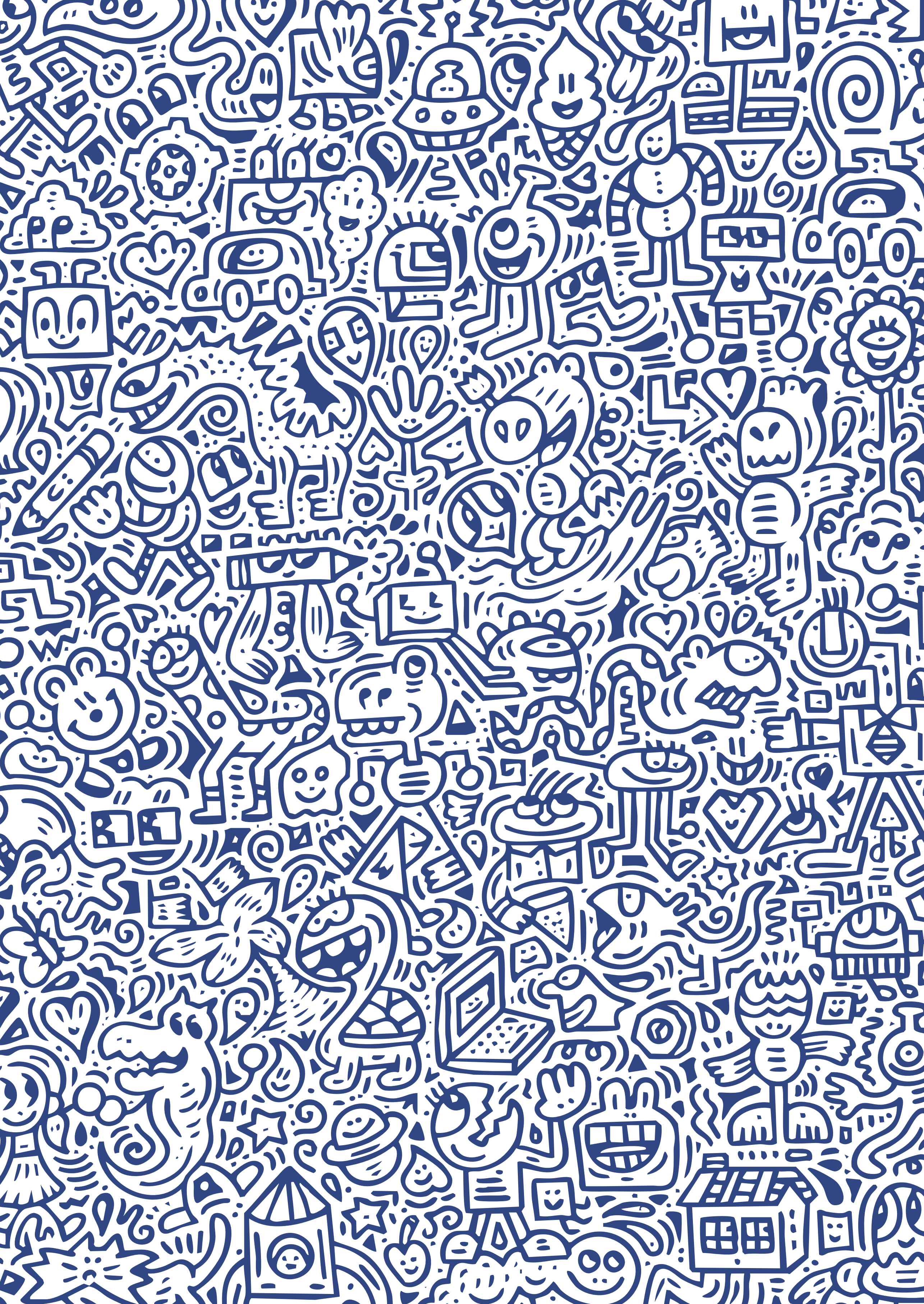
(((exp *"Spinal Diseases"/ OR Spinal diseases.ti,ab OR Intervertebral disk displacement.ti,ab OR Spinal osteophytosis.ti,ab OR Spinal stenosis.ti,ab OR Spondylarthritis.ti,ab OR Spondylitis.ti,ab OR Spondylolisthesis.ti,ab OR "Spinal Osteophytosis".ti,ab OR exp *"Back Pain"/ OR Back pain.ti,ab OR *"Sciatica"/ OR sciatica.ti,ab OR radiculopathy.ti,ab OR "Spinal Cord Compression".ti,ab OR back.ti,ab OR spine.ti,ab OR ((stenosis.ti,ab OR osteophytosis.ti,ab.) AND (spine.ti,ab OR spinal.ti,ab OR vertebr*.ti,ab)) OR discopath*.ti,ab OR diskopath*.ti,ab OR disk displacement.ti,ab OR disc displacement.ti,ab OR spondylarthritis.ti,ab OR spondylitis.ti,ab OR spondylolisthesis.ti,ab OR sciatica.ti,ab OR back pain.ti,ab. OR "lumbar disc herniation".ti,ab OR "lumbar disk herniation".ti,ab OR "lumbar disc herniations".ti,ab OR "lumbar disk herniations".ti,ab OR "lumbar disc prolapse".ti,ab OR "lumbar disk prolapse".ti,ab OR exp *"Intervertebral Disc Displacement"/) AND (exp *"Endoscopy"/ OR "Endoscopy".ti,ab OR "Arthroscopy".ti,ab OR *"Arthroscopy"/ OR "Video-Assisted Surgery".ti,ab OR exp *"Minimally Invasive Surgical Procedures"/ OR **"Minimally Invasive surg*".ti,ab** OR "Microsurgery".ti,ab OR **"Percutaneous Diskectomy".ti,ab** OR endoscop*.ti,ab. OR microendoscop*.ti,ab. OR *"Microsurgery"/ OR microsurgery.ti,ab. OR microsurgical.ti,ab. OR arthroscop*.ti,ab. OR Foraminotom*.ti,ab. OR foraminoplast*.ti,ab. OR minimally invasive surgery.ti,ab. OR video assisted surgery.ti,ab. OR discoscop*.ti,ab. OR Percutaneous transforminal endoscopic discectomy.ti,ab OR Percutaneous transforminal endoscopic discectomy.ti,ab. OR Surgical procedures.ti,ab OR Surgical procedures.ti,ab. OR Discectomy Spinal cord compression.ti,ab OR Discectomy Spinal cord compression.ti,ab. OR Discectomy Spinal cord decompression.ti,ab OR Discectomy Spinal cord decompression.ti,ab. OR Percutaneous Sciatica.ti,ab OR Percutaneous Sciatica.ti,ab. OR microdiscectom*.ti,ab OR microdiskektom*.ti,ab OR microdiskectom*.ti,ab) AND (exp "randomized controlled trial"/ OR controlled clinical trial.pt. OR randomized.**ti,**ab. OR placebo.**ti,**ab. OR randomly.**ti,**ab. OR trial.**ti,**ab. OR groups.**ti,**ab. OR RCT.ti,ab OR Comparative Study.pt)) **OR** (("percutaneous endoscopic discectom*".ti,ab OR "endoscopic microdiscectom*".ti,ab OR "percutaneous endoscopic diskectom*".ti,ab OR "endoscopic microdiskectom*".ti,ab OR "percutaneous endoscopic diskektom*".ti,ab OR "endoscopic microdiskektom*".ti,ab) AND (exp "randomized controlled trial"/ OR controlled clinical trial.pt. OR randomized.ti,ab. OR placebo.ti,ab. OR randomly.ti,ab. OR trial.ti,ab. OR groups.ti,ab. OR RCT.ti,ab OR Comparative Study.pt))**)**

SUPPLEMENTARY TABLE 2

Study	Reason
Ding ZM, Tao YQ (2017) Clinical outcomes of percutaneous transforaminal endoscopic discectomy versus fenestration discectomy in patients with lumbar disk herniation. Journal of International Translational Medicine 5:29-33	Recurrent LDH
Kong L, Shang XF, Zhang WZ, Duan LQ, Yu Y, Ni WJ, Huang Y (2019) Percutaneous endoscopic lumbar discectomy and microsurgical laminotomy : A prospective, randomized controlled trial of patients with lumbar disk herniation and lateral recess stenosis. Orthopade 48:157-164	Other condition than LDH
Ahmed M, Nawaz MF, Ullah H, Sameja MS (2019) To compare the frequency of unintended durotomy in open discectomy versus endoscopic discectomy. Medical Forum Monthly 2019 30:105-108	Surgery type (N=6)
Arestov SO, Vershinin AV, Gushcha AO (2014) [A comparative analysis of the effectiveness and potential of endoscopic and microsurgical resection of disk herniations in the lumbosacral spine]. Zh Vopr Neirokhir Im N N Burdenko 78:9-14	
Belykh E, Giers MB, Preul MC, Theodore N, Byvaltsev V (2016) Prospective Comparison of Microsurgical, Tubular-Based Endoscopic, and Endoscopically Assisted Diskectomies: Clinical Effectiveness and Complications in Railway Workers. World Neurosurg 90:273-280	
Meyer G, ID DAR, Cristante AF, Marcon RM, Coutinho TP, Torelli AG, Petersen PA, Letaif (2020) Percutaneous Endoscopic Lumbar Discectomy Versus Microdiscectomy for the Treatment of Lumbar Disk Herniation: Pain, Disability, and Complication Rate-A Randomized Clinical Trial. Int J Spine Surg 14:72-78	
Pan L, Zhang P, Yin Q (2014) Comparison of tissue damages caused by endoscopic lumbar discectomy and traditional lumbar discectomy: A randomised controlled trial. International Journal of Surgery 12:534-537	
Singh S, Sardhara JC, Khatri D, Joseph J, Parab AN, Bhaisora KS, Das KK, Mehrotra A, Srivastava AK, Behari S (2018) Technical pearls and surgical outcome of early transitional period experience in minimally invasive lumbar discectomy: A prospective study. J Craniovertebr Junction Spine 9:122-129	
Liu X, Yuan S, Tian Y, Wang L, Gong L, Zheng Y, Li J (2018) Comparison of percutaneous endoscopic transforaminal discectomy, microendoscopic discectomy, and microdiscectomy for symptomatic lumbar disk herniation: minimum 2-year follow-up results. J Neurosurg Spine 28:317-325	Retrospective design
Ning HX, Yuan YW, Zhang QY, Sun ZZ, Ning HY, Wang P (2018) Percutaneous transforaminal endoscopic discectomy and miniincision surgery in the treatment of lumbar intervertebral disc protrusion. J Biol Regul Homeost Agents 32:565-569	Unable to obtain/ translate

PART II

PREFERENCES



5

Chapter

SURGEONS PREFERENCE FOR LUMBAR DISK SURGERY: A DISCRETE CHOICE EXPERIMENT

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Eur Spine J. 2021 Apr 19.

ABSTRACT

Introduction

Multiple surgical techniques are practiced to treat sciatica caused by LDH. It is unknown which factors surgeons find important when offering certain surgical techniques. The objective of this study is threefold: 1) determine the relative weight surgeons place on various characteristics of sciatica treatment, 2) determine the trade-offs surgeons make between these characteristics and 3) identify preference heterogeneity for sciatica treatment.

Methods

A DCE was conducted among members of two international neurosurgical organizations. Surgeons were asked on their preferences for surgical techniques using specific scenarios based on five characteristics: effectiveness on leg pain, risk of recurrent disk herniation, duration of postoperative back pain, risk of complications and recovery period.

Results

Six-hundred and forty-one questionnaires were filled in, the majority by neurosurgeons. All characteristics significantly influenced the preferences of the respondents. Overall, the risk of complications was the most important characteristic in the decision to opt-in or opt-out for surgery (35.7%). Risk of recurrent disk herniation (19.6%), effectiveness on leg pain (18.8%), postoperative back pain duration (13.5%) and length of recovery period (12.4%) followed. Four latent classes were identified, which was partly explained by the tenure of the surgeon. Surgeons were willing to trade-off 57.8% of effectiveness on leg pain to offer a treatment that has a 1% complication risk instead of 10%.

Conclusion

In the context of this DCE, it is shown that neurosurgeons consider the risk of complications as most important when a surgical technique is offered to treat sciatica, while the risk of recurrent disk herniation and effectiveness are also important factors. Neurosurgeons were prepared to trade off substantial amounts of effectiveness to achieve lower complication rates.

INTRODUCTION

The natural course of sciatica caused by LDH is favorable, and most cases in the general population resolve with conservative care. Surgery, however, is recommended in patients whose symptoms are persistent despite conservative care[3,68].In 1909, the first report on the surgical treatment of LDH was published [28]. Due to invention and technical innovation, the surgical technique has been modified to conventional open microdiscectomy that is currently regarded as the golden standard procedure [5,6]. Due to further developments such as the introduction of the endoscope to the surgical field, other techniques for performing lumbar discectomy were introduced such as MTD and PTED[10].

Based on pooled results from previous comparative studies, clinical outcomes of MTD are largely equivalent to those of microdiscectomy. Furthermore, full-endoscopic procedures may be associated with significantly improved clinical outcomes, e.g., blood loss, durotomies, length of hospital stay and leg pain, as compared to microdiscectomy [17]. The differences of these outcomes between surgical techniques, however, may be small and not clinically important. Because of these ambiguous results, it is unclear whether any of these techniques have clear benefits over the other.

Currently, it is unknown based on which features, surgeons decide what surgical techniques they offer patients. For instance, patients who undergo PTED have shorter hospitalization duration compared to patients who undergo microdiscectomy, but at the same time they may be more at risk to undergo revision surgery [23]. This trade-off between duration of hospitalization and a potential higher risk for revision surgery makes it difficult for policy makers and surgeons to decide which technique to offer patients. Previous research did not evaluate surgeons' preferences in offering lumbar disk surgery beyond efficacy and safety and did not measure the acceptable trade-offs of risk and benefits of different surgical techniques. The goal of the current study is threefold: 1) to determine the relative weight that surgeons place on various characteristics of lumbar disk herniation treatment, 2) to determine the trade-offs surgeons make between these characteristics and 3) to identify preference heterogeneity among surgeons for lumbar disk herniation treatment.

METHODS

Discrete choice experiment

To elucidate and quantify preferences for offering a surgical procedure among neurosurgeons, a DCE was developed. DCEs are increasingly advocated in health care studies to quantify preferences [69]. A DCE is a survey method which is based on the concept that when choices are made for interventions, characteristics of the interventions are weighted off next to each other. An example of a choice set is given in Figure 1. Respondents are asked to choose for surgical treatment "A," treatment "B" or to opt-out. In a DCE, respondents are offered multiple choice sets in which the levels of the characteristics are variable[70].

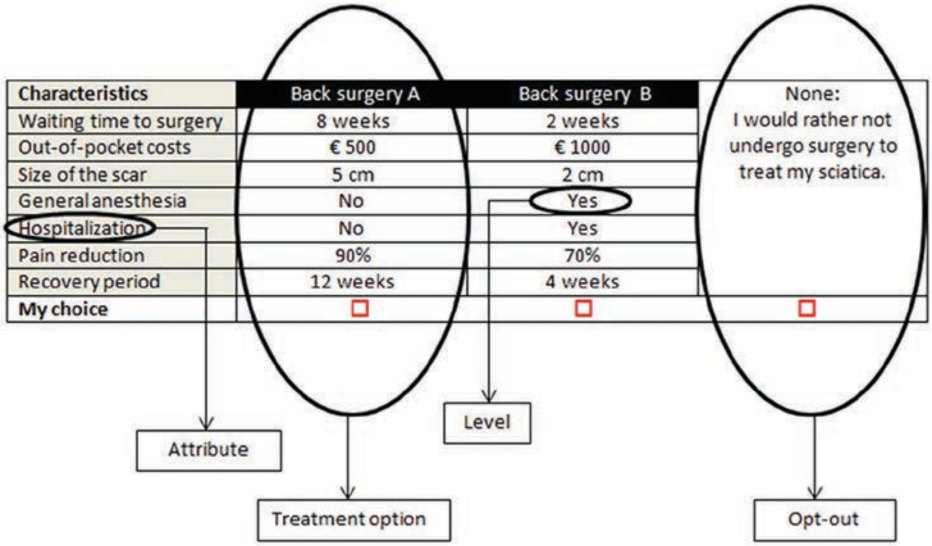


Figure 1: example of a DCE choice set.

Study design

By means of a literature search, a list of characteristics and matching levels was made [18,36]. Based on interviews of patients at the outpatient clinic and on further consensus of the research group existing of a neurosurgeon, a researcher and a physician specialized in the care of patients with musculoskeletal disorders, a final selection of characteristics and levels was made (see Table 1). These characteristics were chosen because they represent core outcomes of lumbar spine surgery. The characteristics of the surgical procedure included are (1) the effectiveness on leg pain, (2) the risk of recurrent disk herniation, (3) the duration of postoperative back pain, (4) the risk of complications and (5) the recovery period. An opt-out option was also added because—as in real-life lumbar discectomy for sciatica is usually an elective procedure. Levels were chosen based on expert opinion and on the literature[13,18,66]. The characteristics and levels produce 243 (3^5) possible treatment profiles. Because testing of 243 treatment profiles comes with a large burden to the respondents; a Bayesian efficient DCE was produced (Ngene software version 1.1.; Choice metrics, Sydney, Australia) to be able to estimate the parameters of interest in an efficient way, while taking respondent burden into account. The efficient design contained 24 choice sets divided over two survey versions. Hence, each respondent filled out 12 choice sets.

To pilot test the survey, it was distributed among neurosurgeons that were affiliated with the national Netherlands Society of Neurosurgery. Based on the 39 surveys received and following best practice, the 24 choice sets divided among two survey versions were further optimized[71]. The final survey consisted out of three parts: (1) demographics of the respondents; (2) opinions on what makes a surgical technique to treat LDH "minimally invasive"; and (3) 12 choice sets, alternating per version. Based on a rule of thumb, at least 63 respondents were needed to adequately perform analyses[72].

Table 1: Characteristics and levels of the surgical options used in the DCE

Characteristics	Levels
Effectiveness on leg pain The reduction of leg pain after surgery	70%
	80%
	90%
Risk of recurrent disk herniation The risk of recurrent disk herniation within one year requiring surgery.	1%
	5%
	10%
Duration of postoperative back pain	1 week
	6 weeks
	12 weeks
Risk of complications The overall complication risk	1%
	5%
	10%
Recovery period Period to return to work/daily activities	1 week
	4 weeks
	12 weeks

Study setting and population

The final survey was distributed to members of the EANS and members of the CNS, using SurveyMonkey. Both the EANS and the CNS are international professional organizations representing neurosurgeons worldwide. While the EANS is more focused on European neurosurgeons, the CNS is more focused on neurosurgeons from the USA. After initial distribution of the survey, reminders were sent after one and two months to increase the response rate. Because no patients were involved in this study, the institutional review board waived the need for medical ethical approval.

Statistical analysis

Demographics and opinions of respondents were analyzed using descriptive analyses using SPSS version 25.0 (IBM Corp. NY, USA). Valid percentages were used to present the data. Using NLogit 4.0 software (Econometric Software, NY, USA), panel latent class logit model was estimated. This form of logistic regression analysis can take preference heterogeneity into account by identifying groups (latent classes) of respondents with similar treatment preference patterns. To determine the number of classes, we selected the model with the best fit based on the Bayesian information criterion. We tested several different specifications for the utility function (e.g., categorical, or numerical attribute levels and two-way interactions between attributes). The optimal utility function was:

$$V_{nsj|c} = \beta_{0|c} + \beta_{1|c}\text{effectiveness}_{nsj|c} + \beta_{2|c}\text{risk of recurrence(5\%)}_{nsj|c} + \beta_{3|c}\text{risk of recurrence(10\%)}_{nsj|c}\ \beta_{4|c}\text{duration of back pain(6wks)}_{nsj|c} + \beta_{5|c}\text{duration of back pain(12wks)}_{nsj|c} + \beta_{6|c}\text{complication risk(5\%)}_{nsj|c} + \beta_{7|c}\text{complication risk(10\%)}_{nsj|c} + \beta_{8|c}\text{recovery period(4wks)}_{nsj|c} + \beta_{9|c}\text{recovery period(12 wks)}_{nsj|c}$$

where

$V_{nsj|c}$ represents the observable utility that respondent *n* belonging to class segment *c* has for alternative *j* in choice set *s;*
$\beta_{0|c}$ represents an alternative specific constant for a certain class; and
$\beta_{1\text{-}9|c}$ are class specific parameter weights (coefficients) associated with each attribute(level) of the DCE

In addition to the utility function, the final model allowed for one covariate (surgeon's tenure) to enter the class assignment model. The class assignment utility function for the final model was:

$$V_{nc} = \beta_{0_c} + \beta_{1_c}\text{tenure}_n$$

Only effectiveness on leg pain acted as linear characteristic. Coefficients, also known as class-specific parameter weights, associated with each characteristic were calculated. A coefficient with a p value≤0.05 indicated statistical significance of a characteristic level and therefore importance of a characteristic in the decision to opt-in or opt-out for surgical treatment. A covariate with a p value≤0.05 indicated that

that covariate can distinguish between different classes. A positive coefficient means that the characteristic has a positive effect on the preference of a treatment, while a negative coefficient has an adverse negative effect on the preference of a treatment. The value of the coefficient also indicates the importance of characteristics.

In addition to this, the ranking of the importance scores of all characteristics were determined[69]. The ranking was made per latent class with "1" ranking the most important characteristic and "5" the least important characteristic. Furthermore, the coefficients were translated to calculate clinically relevant trade-offs. In this way, we can estimate whether surgeons were willing to trade off effectiveness on leg pain to shorten the duration of postoperative back pain, decrease the risk of complications, decrease the risk of recurrent disk herniation, or shorten the recovery period. Hereto the ratio of one of the coefficients of these last four characteristics was taken as nominator and with effectiveness on leg pain as the denominator.

RESULTS

Demographics

The final survey was filled in by 602 respondents. The 39 responses that were used to pilot test the DCE design were added to these responses. Of all the responses, 16 had no answers on the DCE choice sets leading to 625 responses for the DCE analyses. Demographics of the respondents are depicted in Table 2. 581 out of the 638 (91.1%) respondents were neurosurgeons and mean tenure was 17.0 (±11.8 SD) years. All respondents performed an annual mean of 85 (±74.5 SD) procedures for LDH.

Opinions on what makes a surgical technique "minimally invasive"

The importance of characteristics of minimally invasive surgery is depicted in Figure 2. A limited amount of damage to tissue was most important (47.5%) followed by a small scar size (27.4%), early resumption of work and daily activities (26.8%) and a low rate of postoperative back pain (24.4%). A low rate of recurrent disk herniation, effectiveness on radicular pain and a low complication risk were deemed less important.

Table 2: demographics of respondents.

	N (%)		N (%)
Gender	641	**Years in clinical practice**	636
Male	599 (93.4%)	≤5 years	117 (18.4%)
Female	42 (6.6%)	6-10 years	134 (21.1%)
		11-20 years	177 (27.8%)
Function	639	>20 years	208 (32.7%)
Neurosurgeon	581 (90.9%)		
Neurosurgeon in training	57 (8.9%)	**Continent**	641
Orthopedic surgeon	1 (0.16%)	Africa	11 (1.7%)
		Asia and Oceania	58 (9.0%)
Amount of lumbar disk surgeries performed annually	637	Europe	96 (15.0%)
		North America	443 (69.1%)
≤50	304 (47.7%)	South America	33 (5.1%)
51-100	183 (28.7%)		
101-200	117 (18.4%)		
>200	33 (5.2%)		

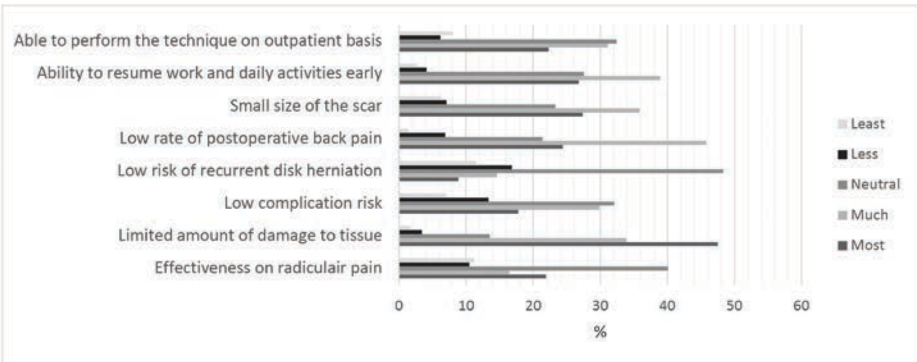


Figure 2: What makes a surgical technique for lumbar discectomy minimally invasive?

Latent classes

Based on the latent class analyses, four groups of preference patterns could be identified (see Figure 3):

- Class I with a 62% probability of respondents belonging to this class. This class was characterized by surgeons who thought that the risk of complications was of the most importance (44.5%) in their treatment decision, followed by the recurrence rate (21.2%), the effectiveness (20.2%), the postoperative back pain duration (7.9%) and the recovery period (6.2%).

- Class II (probability of 16%): the recovery period was of most importance (36.3%) followed by the postoperative back pain duration (25.5%), the effectiveness (19.5%), the risk of complications (9.7%) and the risk of recurrence (9%).
- Class III (probability of 11%): recurrence risk (26.3%) and risk of complications (25.9%) were seen as most important, followed by the recovery period (20.7%), the postoperative back pain duration (18.2%) and the recovery period (8.8%).
- Class IV(probability of 10%): risk of complications was most important (32.6%) followed by the recovery period (22.2%), the risk of recurrent disk herniation (21.3%), the postoperative back pain duration (21.0%) and effectiveness (2.9%).

Where the risk of complications mainly decided the preferences of class I and IV, the recovery period and the risk of recurrent disk herniation mainly decided the preference of class II and III, respectively. Of all demographics tested, only tenure was significantly associated with belonging to class I (p=0.009). Gender, function, amount of annually performed discectomies and continent of employment were all not associated with any of the latent classes.

Almost all coefficients proved to significantly influence preferences. A surgical technique to treat LDH was more preferred if it had a higher effectiveness on leg pain, had less risk of recurrent LDH, had a shorter duration of postoperative back pain, less complication risk, and a shorter recovery period.

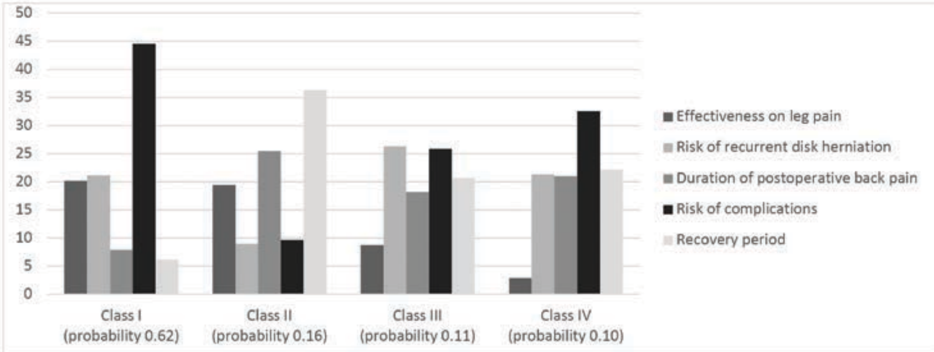


Figure 3: Comparison of relative importance of characteristics of lumbar disk surgery between latent classes.

Importance score

Overall, the complication rate determined the preference of surgeons for a surgical procedure for 35%. Risk of recurrent disk herniation (19.6%), effectiveness on leg pain (18.8%), postoperative back pain duration (13.5%) and recovery period (12.4%)

followed. The importance scores of the characteristics in decision making of the four latent classes were also calculated and are shown in Figure 3.

Trade-offs

Trade-offs that surgeons are willing to make with effectiveness on leg pain are presented in Table 3. For instance, surgeons were willing to trade-off 58% of effectiveness in leg pain to offer a treatment that has a 1% complication risk instead of 10%. Furthermore, surgeons were willing to trade-off 32% of effectiveness to offer a treatment that has a 1-week recovery period compared to 12 weeks and 31% of effectiveness to offer a treatment that has a 1% recurrence risk compared to 10%.

Table 3: willingness-to-trade effectiveness.

Characteristics	is willing to trade-off (...%) effectiveness	.. to offer a treatment that
Risk of recurrent disk herniation	0.7	… has a 1% risk of recurrence compared to 5%
	30.6	… has a 1% risk of recurrence compared to 10%
Duration of postoperative back pain	19.1	… has a 1-week duration of low back pain instead of 6 weeks
	28.7	… has a 1-week duration of low back pain instead of 12 weeks
Risk of complications	21.8	… has a 1% risk of complications compared to 5%
	57.8	… has a 1% risk of complications compared to 10%
Recovery period	9.8	… has a 1-week recovery period compared to 4 weeks
	31.6	… has a 1-week recovery period compared to 12 weeks

DISCUSSION

This study presents the results of a DCE among 625 surgeons, mostly neurosurgeons, employed at all continents. All surgical treatment characteristics that were tested in the DCE significantly influenced the preferences of the respondents. Overall, surgeons considered the risk of complications the most important characteristic. Risk of recurrent disk herniation, effectiveness on leg pain, postoperative back pain duration and length of recovery period were also considered important. Based on substantial heterogeneity in preferences, four latent classes were identified. Rather than complication risk, the risk of recurrent disk herniation and the recovery period were deemed most important in two of these latent classes. Surgeons with a longer tenure were significantly represented in latent class I, in which the risk of complications was most important and the recovery period less. Overall, surgeons were willing to trade-off more than half of effectiveness on leg pain to offer a treatment that has a 1% complication risk instead of 10%.

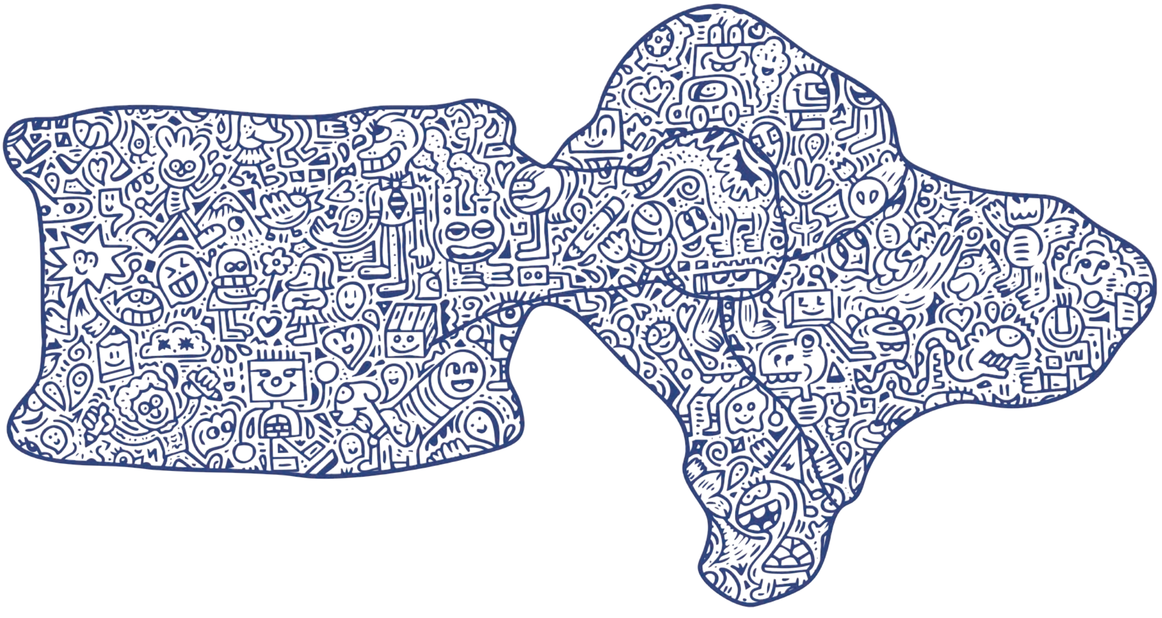
"Primun non nocere" which is translated from Latin as "first, do no harm," is a fundamental principle in Medicine which is underlined by the preferences of the surgeons included in this study. By 35.7%, the risk of complications was the most important characteristic to opt-in or opt-out for surgery for sciatica. Nowadays, lumbar discectomy is a safe and effective procedure with low rates of serious adverse events[19]. Previous research comparing conventional open microdiscectomy with tubular discectomy or with full-endoscopic discectomy shows no statistically or clinically relevant differences in complications between these different techniques. Nevertheless, the hypothetical situation to offer a procedure which has a 4% or 9% higher complication rate than another procedure raises considerable resistance for surgeons emphasized by surgeons being prepared to trade off up to 57.8% of effectiveness to achieve lower complications rates.

Strengths of the study include the large number of responses received and the mixed method approach used. Some limitations, however, must be acknowledged. One may be that only clinical characteristics were considered. Factors such as financial factors or the difficulty of mastering a surgical technique were not applied in this DCE. For instance, partially due to a limited view through an endoscope, PTED might be more difficult to master for surgeons compared to conventional microdiscectomy[14,66]. Therefore, only a limited number of surgeons may offer full-endoscopic techniques to treat LDH[47]. Another limitation may be the hypothetical nature of the DCE as most choice sets in the survey do not represent actual surgical techniques. This, however, might not have influenced the results substantially as most DCE investigations in health contexts have found no evidence of significant hypothetical bias[73]. Also, as the survey was only distributed by the EANS and the CNS, fewer responses were collected from Asia, South America and Africa. It remains up to debate if the inclusion of more respondents from these continents would have affected the results. The continent of employment of the 641 respondents (of which 16% not from Europe or North America) was not associated with a preference profile. Furthermore, we were not able to calculate a response rate as the survey was distributed by multiple manners by two organizations. For instance, the EANS distributed the survey by email and social media. It is unknown how many non-members were able to see the survey request through social media. Furthermore, some surgeons may be member of both organizations. The number of respondents (N=641), however, seems to representative for neurosurgeons worldwide and was substantially larger than the prior calculated sample size so that the statistical power would also suffice to address the heterogeneity in preferences. Furthermore, previous research has shown that the response rate of a survey may not be reflective of a survey's quality or bias by itself [74].

The current study is the first to quantify preferences for specifically offering lumbar disk surgery among surgeons. The results of this DCE can help clinicians and policy makers understand why some certain surgical techniques may or may not be offered by surgeons, especially as lumbar discectomy is an elective procedure and multiple techniques are available to treat sciatica. A prior DCE measured preferences of patients for the treatment of low back pain [75]. In this DCE among 348 patients referred to a regional spine center, most of the patients prefer nonsurgical interventions to treat their low back pain. In another previously conducted DCE among surgeons, family physicians and patients, the relative importance of presenting symptoms when considering surgery for degenerative lumbar surgery was investigated[76]. Surgeons placed the highest importance on the location of pain such as leg versus back, while patients placed the highest importance on the severity of the pain, walking tolerance and duration of the pain. Similarly, in the current study surgeons gave less importance to the effectiveness on pain or the duration of the (postoperative) pain. These differences in preference profiles between patients and surgeons justify further research to study specific patient preferences for lumbar disk surgery. Such research may further facilitate shared decision making and tailored communication in lumbar disk surgery between patients and surgeons.

CONCLUSION

This study shows that surgeons consider the risk of complications as most important when a surgical technique is offered to treat sciatica, while the risk of recurrent disk herniation and effectiveness are also important factors. Surgeons were prepared to trade-off substantial amounts of effectiveness to achieve lower complication rates.



6

Chapter

PATIENT PREFERENCES FOR THE TREATMENT OF SCIATICA: A DISCRETE CHOICE EXPERIMENT

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J Neurosurg Spine. 2021 Nov 26:1-9.

ABSTRACT

Introduction

Lumbar discectomy is a frequently performed procedure to treat sciatica caused by LDH. Multiple surgical techniques are available, and the popularity of minimally invasive surgical techniques is increasing worldwide. Clinical outcomes between these techniques may not show any substantial differences. As lumbar discectomy is an elective procedure, patients' own preferences play an important role in determining the procedure they will undergo. The aims of the current study were to determine the relative preference weights patients apply to various attributes of lumbar discectomy, determine if patient preferences change after surgery, identify preference heterogeneity for choosing surgery for sciatica, and calculate patient willingness to pay for other attributes.

Methods

A DCE was conducted among patients with sciatica caused by lumbar disk herniation. A questionnaire was administered to patients before they underwent surgery and to an independent sample of patients who had already undergone surgery. The DCE required patients to choose between two surgical techniques or to opt out from 12 choice sets with alternating characteristic levels: waiting time for surgery, out-of-pocket costs, size of the scar, need of general anesthesia, need for hospitalization, effect on leg pain, and duration of the recovery period.

Results

A total of 287 patients were included in the DCE analysis. All attributes, except scar size, had a significant influence on the overall preferences of patients. The effect on leg pain was the most important characteristic in the decision for a surgical procedure (by 44.8%). The potential out-of-pocket costs for the procedure (28.8%), the wait time (12.8%), need for general anesthesia (7.5%), need for hospitalization (4.3%), and the recovery period (1.8%) followed. Preferences were independent of the scores on patient-reported outcome measures and baseline characteristics. Three latent classes could be identified with specific preference patterns. Willingness-to-pay was the highest for effectiveness on leg pain, with patients willing to pay €3133 for a treatment that has a 90% effectiveness instead of 70%.

Conclusion

Effect on leg pain is the most important factor for patients in deciding to undergo surgery for sciatica. Not all proposed advantages of minimally invasive spine surgery (e.g., size of the scar, no need of general anesthesia) are necessarily perceived as advantages by patients. Spine surgeons should propose surgical techniques for

sciatica, not only based on own ability and proposed eligibility, but also based on patient preferences as is part of shared decision making.

INTRODUCTION

Even though sciatica caused by LDH has a favorable prognosis with conservative treatment, lumbar discectomy remains a frequently performed procedure by spine surgeons[3,68]. Annually, over 480,000 lumbar discectomies are performed in the US[77]. The current surgical procedure of choice is conventional open microdiscectomy[5,6]. During microdiscectomy, the herniation is removed through a transflaval approach with or without the use of magnification by loupes or microscope.

Throughout the years multiple surgical techniques have become part of the surgical armamentarium, mainly due to the refinement of surgical instruments and the development of endoscopes[10]. Therefore, less-invasive techniques were introduced. The aim of these more recent surgical techniques is to reduce the surgical invasiveness of microdiscectomy and improve patient outcomes, such as leg pain, back pain, and recovery time. Examples of surgical techniques that were intended to be less invasive are MTD and percutaneous transforaminal endoscopic discectomy (PTED)[12,14]. During MTD, the disk herniation is removed by using a tubular retractor system that splits the back muscles. During PTED, which is performed by using instruments through an incision of approximately 8 mm with the patient under local anesthesia, the disk herniation is removed through the neuroforamen. In recently reported meta-analyses authors have analyzed and pooled the outcomes of studies comparing MTD and PTED with conventional microdiscectomy[17,19] and concluded that the results of MTD and microdiscectomy are largely comparable and that endoscopic discectomy might have some advantages in outcomes compared to microdiscectomy, such as blood loss, duration of hospitalization, and time until return to work. These advantages, however, were of uncertain clinical relevance and the evidence in favor for these advantages might be hampered by a high risk of bias. Therefore, high-quality studies comparing PTED and microdiscectomy are warranted.

Because outcomes of patients undergoing different surgical techniques for disk herniation are comparable, the application of these techniques is subject to practice variation. A recent survey among 817 spine surgeons employed worldwide showed that in the treatment of sciatica more than 80% of the surgeons usually performed microdiscectomy[47]. MTD was only performed routinely by 14% of the surgeons while PELD was routinely performed by less than 5% of the surgeons. Aside from the lack of evidence in favor of MTD and PELD, previous research has shown that the risk of complications, the risk of recurrent disk herniation, and the effect on leg pain were the most important factors in deciding which surgical procedure is offered by surgeons[78]. Aside from the surgeons' preferences in offering certain techniques to treat sciatica, patients' own preferences might also play an important role in determining the procedure they will undergo. Currently it is unknown which characteristics of the different surgical techniques (e.g., size of the scar, ability to undergo surgery under local anesthesia) determine the preferences patients have for elective surgery for sciatica. Therefore, the aims of the current study were to 1) determine the relative weights of preference patients give to various attributes of lumbar discectomy, 2) determine the trade-offs patients were willing to make between these various attributes, 3) determine if patients' preferences change after surgery, and 4) identify preference heterogeneity for choosing surgery for sciatica.

METHODS

Discrete Choice Experiment

A DCE was developed. A DCE is a survey method that is most often used to elicit preferences by analyzing how patients weigh and trade off characteristics of treatments[70]. The theoretical foundation of a DCE is that when choices are made for different treatment modalities, characteristics (i.e., attributes) of the treatment options are traded off against each other. For instance, back surgery interventions can be characterized by whether general anesthesia is required or not and by the size of the scar (e.g., 1, 2, or 5 cm). By making choices based on these treatment attributes or their alternative levels, preferences can be measured.

Attributes and Attribute Levels

Based on the literature, a list of potential attributes with their potential levels was made[18,36]. Subsequently, interviews were held with patients at the outpatient clinic to evaluate these potential attributes and identify any additional attributes. In the next stage, a focus group session was held with a neurosurgeon and a senior and a junior researcher in spine surgery. During this focus group session, all potential attributes were discussed and ranked. Eventually, a list of seven attributes with two to four levels was finalized (Table 1). These attributes were 1) waiting time for surgery, 2) out-of-pocket costs, 3) size of the scar, 4) use of general anesthesia, 5) need for hospitalization, 6) effect on leg pain, and 7) duration of the recovery period. It was hypothesized that patients would prefer surgery with no waiting time, no out-of-pocket costs, small size of the scar, no use of general anesthesia, the largest effect on leg pain, and the shortest recovery period.

Table 1: Attributes and levels of the surgical options used in the DCE

Attribute	Levels
Waiting time for surgery	2 weeks
The time patients must wait till surgery.	4 weeks
	8 weeks
Out-of-pocket costs	None
The amount of money patients have to pay for the procedure.	€ 500
	€ 1000
	€ 2000
Size of the scar	1 cm
The size of the scar on the back after surgery.	2 cm
	5 cm
General anesthesia	Yes
Whether surgery is performed under local or general anesthesia.	No
Hospitalization	Yes
Defined as 1 to 2 days of postoperative hospitalization. No hospitalization indicates that the patient is treated on an outpatient basis.	No
Pain reduction	70%
The reduction of leg pain after surgery.	80%
	90%
Recovery period	1 week
Period after surgery, until patients can fully return to their normal daily activities (e.g., sports, work etc.).	4 weeks
	12 weeks

Questionnaire Design

Based on the seven attributes and the two to four levels, 1296 treatment profiles ($2^2 \times 3^4 \times 4^1$) were possible. Because it would not be feasible to present patients with all potential treatment profiles, a Bayesian efficient design maximizing D-efficiency was used to estimate all coefficients[71]. Eventually 24 choice sets were created which were divided in two versions with 12 choice sets to further reduce the response burden to patients. An unlabeled DCE design was applied to avoid bias that may be associated with the name of an intervention. For example, asking patients to choose between procedure A, open discectomy, and procedure B, endoscopic discectomy, may already evoke a preference aside from the attributes. Therefore, the procedures were described as "back surgery A" and "back surgery B." Because lumbar discectomy is an elective procedure, an opt-out option was added. If, based on the attributes of option A and option B, patients would decide to rather not undergo surgery, they could choose to opt out. Both versions with 12 choice sets were randomly distributed to the patients.

After pilot testing these two versions, the design was updated to increase the statistical efficiency of the DCE. It was estimated that at least 84 respondents were required to perform reliable preference analyses[72].

Both versions of the DCE were accompanied with an extensive instruction and the COMI-back[79]. The COMI-back is a 7-question patient-reported outcome questionnaire used to measure the severity of back disorders on a scale ranging from 0 (best status) to 10 (worst status). The COMI-back is based on the domains function, symptom-specific well-being, quality of life, disability, and both back and leg pain. Back and leg pain were measured on a NRS ranging from 0 (no pain) to 10 (worst pain that I can imagine). The version of the questionnaire for the post-surgery group contained two 7-point Likert scales on satisfaction with treatment and recovery and symptoms. The current study incorporated a pilot design which required at least 10% of the attempted sample size to complete the DCE. Based on the pilot testing, the data would be analyzed to optimize the efficiency of the design.

Study Sample

To estimate patient preferences before and after surgery, two independent patient groups were approached for inclusion: a presurgery and a post-surgery group. Subsamples of both groups participated at the study pilot. The presurgery group consisted of patients with sciatica scheduled for surgery who were prospectively included at two clinics during a 3-year period. Patients would receive surgery within 1 to 2 weeks after their consultation with the neurosurgeon. The post-surgery group consisted of patients who underwent discectomy at one of those two clinics during a 3-year period prior to the start of the study. In general, patients were considered candidates for surgery when they had the following indications: 1) at least 6 weeks of radiating leg pain, 2) an MRI-confirmed lumbar disk herniation, and 3) sciatica that was unresponsive or insufficiently responsive to conservative treatment with or without motor loss. All patients were approached through regular mail and returned the questionnaires by using included prestamped return envelopes. All patients gave their written informed consent prior to study inclusion. The local IRB gave approval for the conduction of this study.

Surgical Techniques

Patients in the post-surgery arm underwent surgery either by microdiscectomy or PTED, based on preferences of both the surgeon and the patient. Surgery was performed by surgeons that had extensive experience in PTED and microdiscectomy[66].

The PTED technique has been described previously[14]. In brief, PTED was performed with the patient under local anesthesia. With the use of anteroposterior and lateral fluoroscopy, a needle and subsequently a guidewire was placed to the superior articular process of the lower involved disk level. After introduction of conical rods and enlarging the neuroforamen with a drill, an endoscope and forceps were introduced via a working channel. After removal of the disk fragments, all instruments were removed, and the skin was closed.

General anesthesia was used for conducting microdiscectomy. After verification of the disk level with fluoroscopy, a paramedian incision was performed and indications of the lamina, ligamentum flavum, and optional parts of the lamina were removed. After identification of the nerve root, the disk herniation was removed. The wound was closed in layers.

Patients were discharged as soon as medically responsible, which was usually a few hours after PTED and 1 day after microdiscectomy.

Statistical Analyses

Descriptive statistics were used to demonstrate demographics and patient-reported outcomes with mean and SD for continuous variables. Categorical variables were encoded by effects coding and presented using valid percentages[80]. The two 7-point Likert scales were analyzed by dichotomizing the options of fully recovered/satisfied and almost fully recovered/satisfied as a good outcome and the remaining options as a bad outcome. Only questionnaires with all 12 DCE choice sets completed were included in the DCE analysis. Biogeme 3.2.6 was used to estimate two discrete choice models, namely 1) a multinomial logit model and 2) a latent class logit model. Whereas the multinomial logit model allows estimation of the average preferences across the patient groups, the latent class logit model takes preference heterogeneity into account by identifying (latent) groups with identical preference patterns. In this case the optimal number of latent classes in latent class logit model was determined by the best model fit based on the Bayesian information criterion.

The optimal utility function was derived by estimating the multinomial logit model first. Based on the likelihood ratio test, the most parsimonious multinomial logit model was selected, which led to this optimal utility function:

$$V_{nsj|c} = \beta_{0|c} + \beta_{1|c}\text{waiting time(4 wks)}_{nsj|c} + \beta_{2|c}\text{waiting time(8 wks)}_{nsj|c} + \beta_{3|c}\text{costs}_{nsj|c} + \beta_{4|c}\text{scar size}_{nsj|c} + \beta_{5|c}\text{general anaesthesia(no)}_{nsj|c} + \beta_{6|c}\text{hospitalization(no)}_{nsj|c} + \beta_{7|c}\text{effectiveness(80\%)}_{nsj} + \beta_{8|c}\text{effectiveness(90\%)}_{nsj} + \beta_{9|c}\text{recovery period}_{nsj|c}$$

where

$V_{nsj|c}$ represents the observable utility that respondent *n* belonging to class segment *c* has for alternative *j* in choice set *s;*

$\beta_{0|c}$ represents an alternative specific constant for a certain class; and

$\beta_{1\text{-}9|c}$ are class specific parameter weights (coefficients) associated with each attribute(level) of the DCE

In this model, costs (scaled per €100), scar size (scaled per cm) and recovery period (scaled per week) were included as linear variables. All other variables were included as categorical variables.

The probability of belonging to one of the identified latent classes in association with the respondents' demographic characteristics and score on the COMI-back, NRS for leg pain and NRS for back pain were estimated. The cutoff value for the COMI-back score and NRS for back and leg pain was 6.0, indicating that patients who scored higher than 6.0 had a functional impairment or disabling pain.

Coefficients were calculated. Coefficients with a p-value < 0.05 indicated that an attribute had a significant effect on the choice for a treatment modality or opt out. Positive coefficients indicated a positive effect of the attribute on the preferences for a treatment, while a negative coefficient indicated a negative effect on the preferences for a treatment.

For all latent classes and these classes combined, importance scores were calculated for the attributes. An importance score of 1 indicated the highest ranked attribute, and a score of 7 indicated the lowest ranked attribute. To compare the preference weights of the different attributes between the pre- and postsurgery patient groups, a prespecified subgroup analysis was conducted. Last, as PTED was not reimbursed in the Netherlands, patient willingness to pay out of pocket was calculated[67]. To calculate these trade-offs, the ratio of one of the coefficients of the other attributes was taken as the numerator with willingness to pay as the denominator.

RESULTS

Patient Enrollment

Figure 1 gives an overview of the study procedures. During the actual study's enrollment period, 150 patients scheduled for lumbar discectomy were recruited. Adding the questionnaires of the 24 patients that were included in the pilot study led to a total of 174 patients in the "pre-surgery group." Of the 434 patients in the post-surgery group, 148 patients replied (34%). Eleven of these replies were received during the pilot study. Combining both the pre- and post-surgery patient groups resulted in 322 patients that filled in questionnaires with 287 being suitable for the DCE analysis because they had no missing data in the DCE tasks.

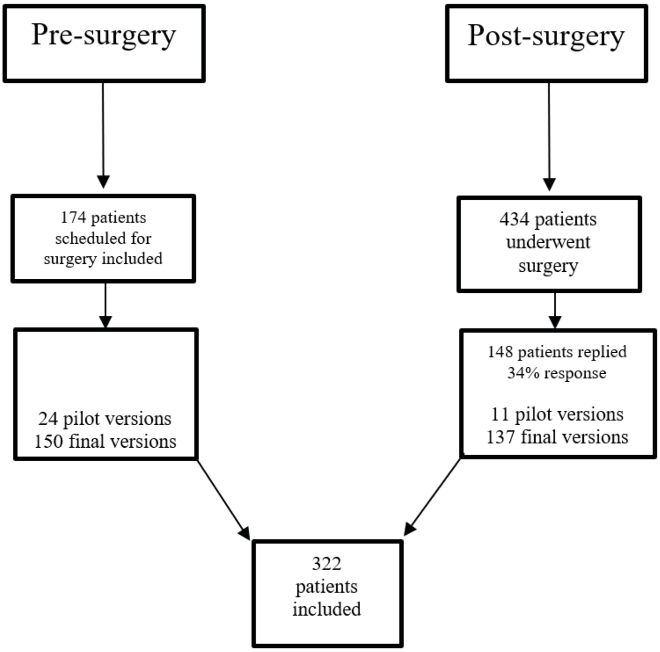

Figure 1: overview of the study procedures

Demographics and Patient-Reported Outcome Measures

Table 2 gives an overview of the demographics and patient-reported outcome measures at the time of measurement. Except for the use of analgesics and for the patient-reported outcome measures, data were comparable between the pre- and post-surgery patient groups. Overall, patients (n = 322) had a mean age of 49.4 ± 13.7 years. Among all patients, 64.3% had a paid job and 36.7% had a high level of education.

Characteristic	Pre-surgery (N=174)	Post-surgery (N=148)
Age (mean ± SD)	48.2 ± 14.6	50.8 ± 12.5
Civil class	173	147
Married/partnered	125 (72.3%)	127 (86.4%)
Single	48 (27.7%)	20 (13.6%)
Paid job	104 (60.1%)	103 (70.1%)
Level of education	172	147
Low	47 (27.3%)	39 (26.5%)
Intermediate	73 (42.4%)	43 (29.3%)
High	52 (30.2%)	65 (44.2%)
Smokers	57 (32.8%)	37 (25.2%)
Use of medication	174	147
Antidepressants	20 (11.5%)	14 (9.5%)
Muscle relaxants	12 (6.9%)	11 (7.5%)
Analgesics	123 (70.7%)	38 (25.9%)
Patient-reported outcome (mean ± SD)		
COMI-summary*	7.4 ± 1.6	2.7 ± 2.6
NRS leg pain*	7.4 ± 1.8	2.4 ± 2.8
NRS back pain*	5.8 ± 2.7	2.7 ± 2.8
Surgical procedure	-	148
OM	-	102 (68.9%)
PTED	-	46 (31.1%)
Clinical condition at follow-up	-	133,135
Satisfied with treatment‡	-	129 (95.6%)
Recovered from symptoms‡	-	110 (82.7%)

In the presurgery patient group, the mean summary scores were 7.4 ± 1.6 on the COMI-back, 7.4 ± 1.8 on the NRS for leg pain, and 5.8 ± 2.7 on the NRS for back pain. In the post-surgery group, the mean summary scores were 2.7 ± 2.6 on the COMI-back, 2.4 ± 2.8 on the NRS for leg pain, and 2.7 ± 2.8 on the NRS for back pain. Of the 148 patients in the post-surgery group, 68.9% underwent microdiscectomy and 31.1%

PTED. At follow-up in the post-surgery group, 95.6% of the patients were satisfied with the treatment and 82.7% were fully recovered from symptoms.

Mean Preference Weights and Importance Score

Except for the size of the scar ($p = 0.09$), all attributes had a statistically significant effect ($p < 0.05$) on the preference for lumbar disk surgery. Figure 3A gives an overview of the mean preference weight of the different attributes among all patients. In general, patients opted for a surgical procedure with a short waiting time, no out-of-pocket costs, a small scar size (albeit not statistically significant), the requirement for general anesthesia and hospitalization, a high effect on leg pain, and a short recovery period.

Figure 2: Mean preference weights for patients before and after surgery. Figure 3a depicts the preference weights for all patients and 3b for the latent classes.

Table 3: Results of the latent class analysis among all patients (N=287). *p-value<0.05, **p-value<0.001

	Latent Class I (probability 51.2%)		Latent Class II (probability 26.3%)		Latent Class III (probability 22.5%)		Overall
	Coefficient	**Importance % (rank)**	**Coefficient**	**Importance % (rank)**	**Coefficient**	**Importance % (rank)**	**Importance % (rank)**
Wait time to surgery		13.4 (3)		10.9 (2)		7.4 (4)	12.8 (3)
2 weeks	0.295		0.147		-0.711		
4 weeks	0.064		0.329*		-0.168*		
8 weeks	-0.359**		-0.476		0.879**		
Out-of-pocket costs (per €100)	-0.085**	34.9 (1)	-0.044		-0.148**	53.2 (1)	28.8 (2)
Scar size (per 1 cm)	-0.084**	6.9 (5)	-0.089		-0.048		
General anesthesia		11.9 (4)				9.6 (3)	7.5 (4)
Yes	0.289		-0.058		0.267		
No	-0.289**		0.058		-0.267**		
Hospitalization							4.3 (5)
Yes	0.033		0.121		0.021		
No	-0.033		-0.121		-0.021		
Effectiveness		30.8 (2)		89.1 (1)		28.6 (2)	44.8 (1)
70%	-0.685		-3.249		-0.711		
80%	-0.146*		-0.123		-0.168*		
90%	0.831**		3.373**		0.879**		
Recovery period (per 1 week)	-0.009**	2.0 (6)	-0.007		-0.006**	1.2 (5)	1.8 (6)
Alternative specific constant	-5.217**		-6.230**		-0.979**		

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Overall, effect on leg pain was ranked to be of the highest importance as it determined the choice for a procedure by 44.8% (Table 3). Out-of-pockets costs followed as the second most important, determining the preference by 28.8%. The waiting time to surgery, necessity of general anesthesia, necessity for hospitalization, and length of the recovery period were ranked third (12.8%), fourth (7.5%), fifth (4.3%), and sixth (1.8%), respectively.

Preference weights were not affected by any of the baseline characteristics (e.g., relationship status, job, education level, patient-reported outcome measures, etc.). Furthermore, preferences did not differ between patients who still had to undergo surgery and those who already had undergone surgery.

Latent Classes

Table 3 gives an overview of the results of the latent class analysis. Based on the DCE analysis, 3 latent classes were identified. 1) Class I with a probability of 51.2% for belonging to this class. For patients in this class, their decision was determined 34.9% by the costs, 30.8% by effectiveness, 13.4% by the waiting time to surgery, 11.9% for the necessity of general anesthesia, 6.9% for the size of the scar, and 2.0% for the recovery period. The necessity for hospitalization did not affect the preference pattern in this class. 2) Class II with a probability of 26.3%. Preferences were determined 89.1% by effectiveness and 10.9% by waiting time for surgery. None of the other attributes influenced the preferences for this class. 3) Class III with a probability of 22.5%. Preferences were mainly determined by the out-of-pocket costs (53.2%) and effectiveness (28.6%). The necessity of general anesthesia (9.6%), wait time to surgery (7.4%), and the recovery period (1.2%) determined the preference to a lesser extent, while the necessity for hospitalization did not affect the preference pattern. Figure 3B presents a graphic overview of the preference patterns of the 3 latent classes.

Trade-Offs Affecting Patient Decisions

Table 4 gives an overview of patients' willingness to pay out of pocket for different attributes of lumbar disk surgery. For instance, patients were willing to pay €894 to receive a treatment with a waiting time of 2 weeks instead of 8 weeks. The most substantial willingness to pay was for pain reduction; on average patients were willing to pay €1764 to receive a treatment with 90% reduction of leg pain instead of a treatment with 80% pain reduction, while they were willing to pay €3133 to receive a treatment with 90% compared to 70% pain reduction.

Table 4: Results of the linear trade-offs in willingness-to-pay for other attributes.

Characteristics	The patient is willing to pay €...	.. to get a treatment that
Waiting time to surgery	29	… has 2 weeks waiting time compared to 4 weeks.
	894	… has 2 weeks waiting time compared to 8 weeks.
Pain reduction	1764	… has 90% effectiveness on leg pain compared to 80%.
	3133	… has 90% effectiveness on leg pain compared to 70%.
Size of the scar	48	… has a 1 cm scar compared to 2 cm.
	191	… has a 1 cm scar compared to 5 cm.
General anesthesia	522	… is performed under general anesthesia instead of local anesthesia.
Hospitalization	302	… is performed in a clinical setting instead of an outpatient setting.
Recovery period	35	… has a recovery period of 1 week compared to 4 weeks.
	105	… has a recovery period of 1 week compared to 12 weeks.

DISCUSSION

The results of this study show that all the investigated attributes, except for the scar size, had a statistically significant influence on the overall treatment preferences of patients. The effect on leg pain was the most important characteristic in the patients' decision for a surgical procedure, followed by out-of-pocket costs, wait time, need for general anesthesia, need for hospitalization, and the recovery period. Preferences did not appear to differ between patients before and after surgery and seemed not to differ based on scores on patient-reported outcome measures. Three latent classes could be identified with specific preference patterns. The results of the willingness-to-pay analysis show that patients were prepared to pay substantial amounts (e.g., €1764) to receive a treatment with a 10% higher effect on leg pain.

Comparison With Other Studies

In a previous DCE among 641 surgeons, preferences in offering lumbar discectomy were measured[78]. In that analysis, surgeons deemed the risk of complications to be of the most importance, followed by the risk of recurrent disk herniation, effect on leg pain, postoperative back pain duration, and length of the recovery period. In the DCE study reported here, risk of complications, risk of recurrent disk herniation, and the postoperative duration of back pain did not receive a high enough ranking by patients to be included as attributes. Furthermore, in the current study the effect on leg pain determined patient preferences by 38.5%, whereas it determined surgeon preference by 18.8%. This discrepancy can be explained by the differences in perspectives of patients and surgeons. On one hand, patients are suffering from disabling leg pain and want to recover from it, preferably without spending out-of-pocket costs. On the other hand, surgeons think from the "first do no harm" perspective and prefer to offer a surgical option with a low complication rate and low recurrence risk, before preferring a procedure with high effectiveness and a short recovery period.

Study Strengths and Limitations

Some limitations of this study must be acknowledged. First is the 34% response rate of the retrospective patient group, which can be deemed average. Low response rates may have a higher risk of introducing selection bias, e.g., specific groups of patients replying. However, as the retrospective group covers a time span of 3 years and the patient preferences for this group were our main outcome, selection bias may only be of limited concern. Furthermore, the clinical outcome data of the retrospective group seem to be comparable to those reported in the literature, with higher follow-up rates[66]. Another form of selection bias may have been introduced due to the change in reimbursement of fully endoscopic procedures in the Netherlands. In the retrospective patient group, PTED was not reimbursed and therefore selection bias may have played a role as patients who could afford the procedure would be more likely to undergo PTED. In contrast to this, PTED was reimbursed for the group of prospective patients, and this form of bias may not have been introduced in this group. Nevertheless, no differences in preferences were detected between the two patient groups, which suggests that this form of selection bias may have had only limited impact on the results.

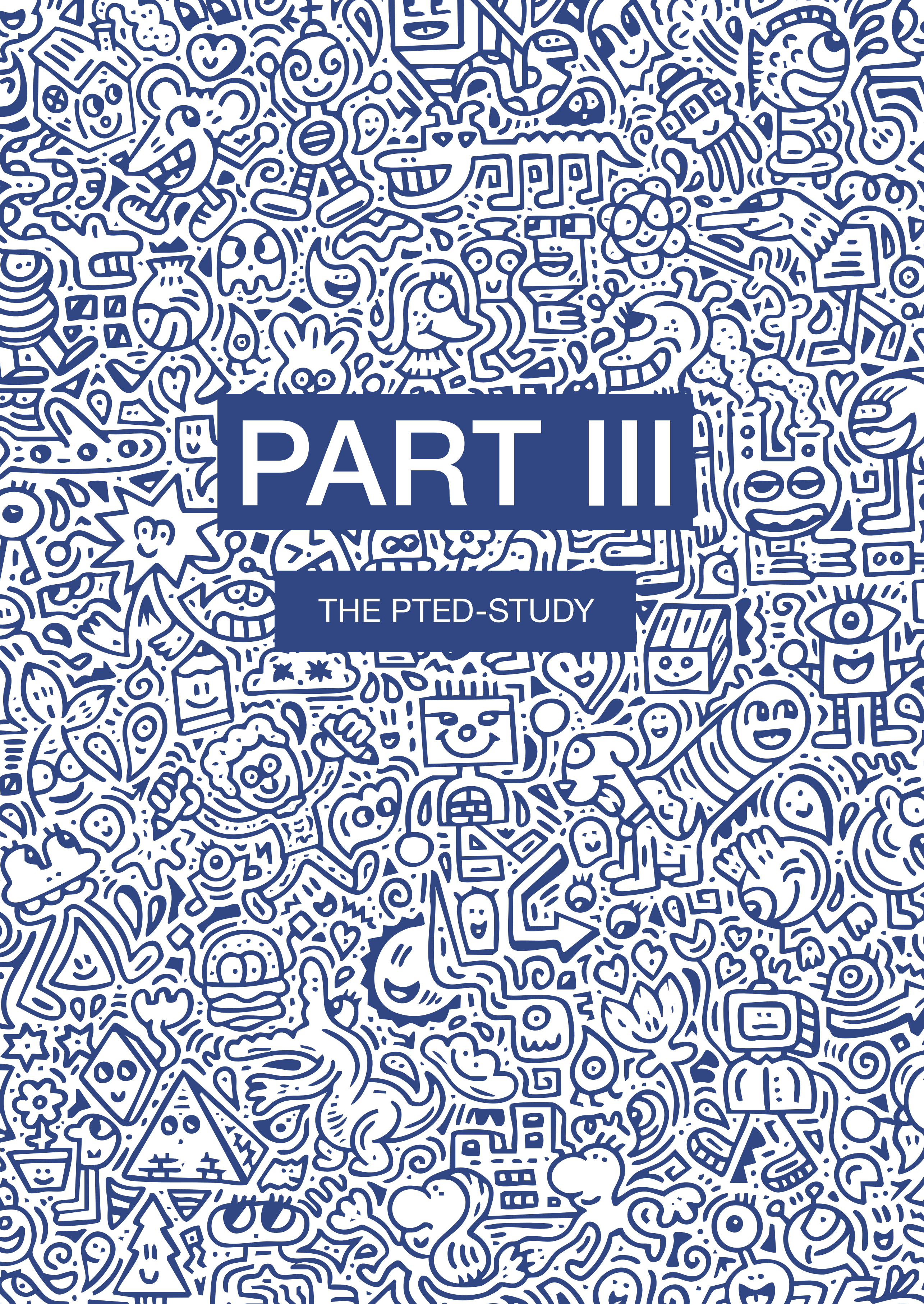
Another limitation may be the introduction of recall bias due to the inclusion of a retrospective patient group. Furthermore, there may also be some concerns regarding the national or international generalizability of the study results. This study was conducted at two Dutch hospitals and was therefore conducted based on the Dutch healthcare system, in which fully endoscopic procedures for sciatica were previously not reimbursed. Both clinics treated patients with similar indications for surgery based on national guidelines, which included at least 6 weeks of treatment-resistant sciatica or progressive motor loss. From an international perspective, between-country differences in policies for reimbursement of endoscopic procedures and cultural differences may limit the generalizability. Another limitation may be that not all presented DCE scenarios reflect actual scenarios in clinical practice. Previous research, however, has shown that most DCEs in health research have not shown significant hypothetical bias[73]. Another potential area of improvement for this study is the use of a within-group design, in which the patients in the prospective group answered the DCE again after surgery. The option to include a second questionnaire was omitted, however, to reduce the burden on patients. Strengths of this study include the use of a pilot design, the attainment of the calculated sample size, the unlabeled design of the DCE, and the inclusion of both patients who underwent open surgical procedures and patients who underwent endoscopic procedures.

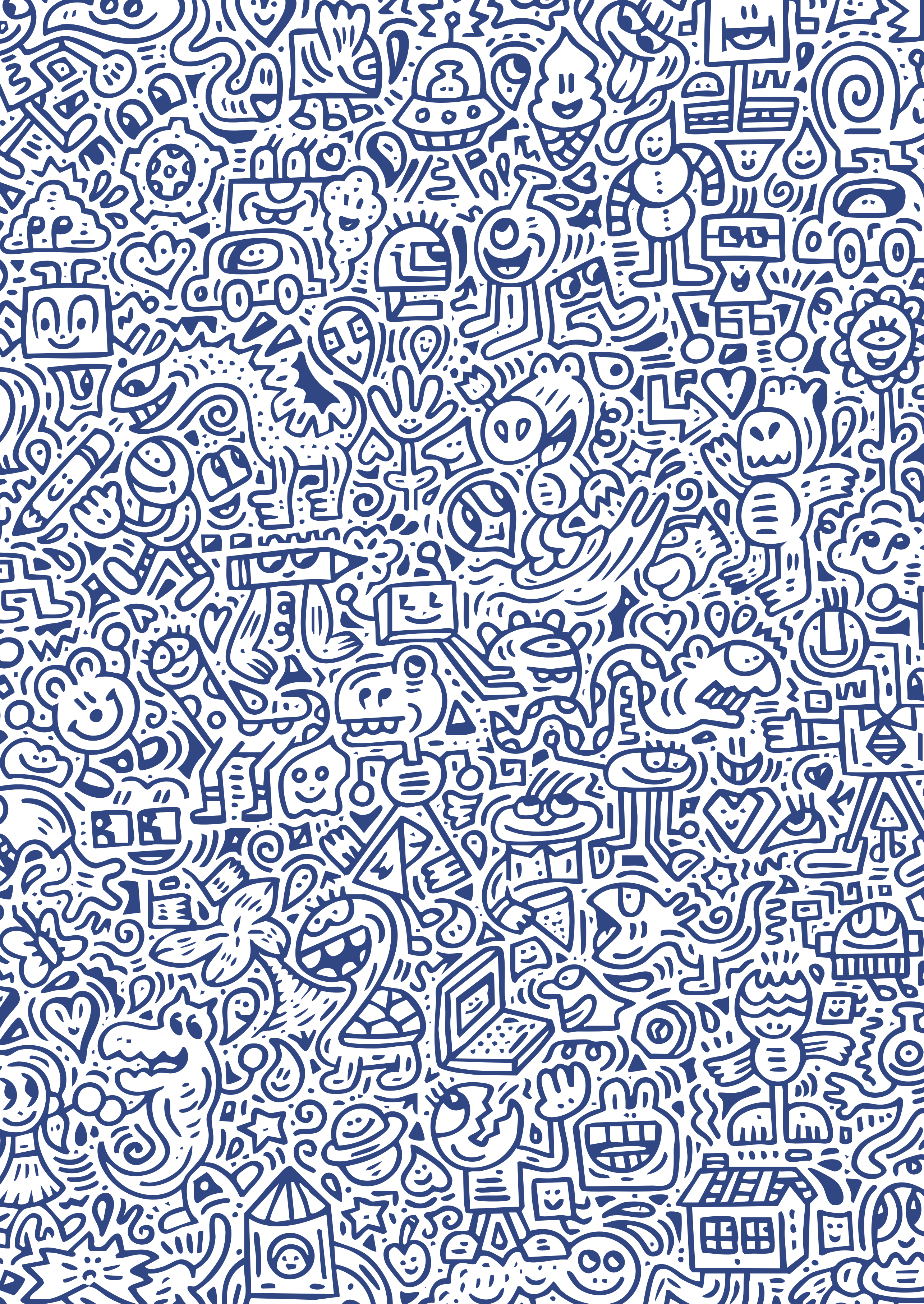
CONCLUSION

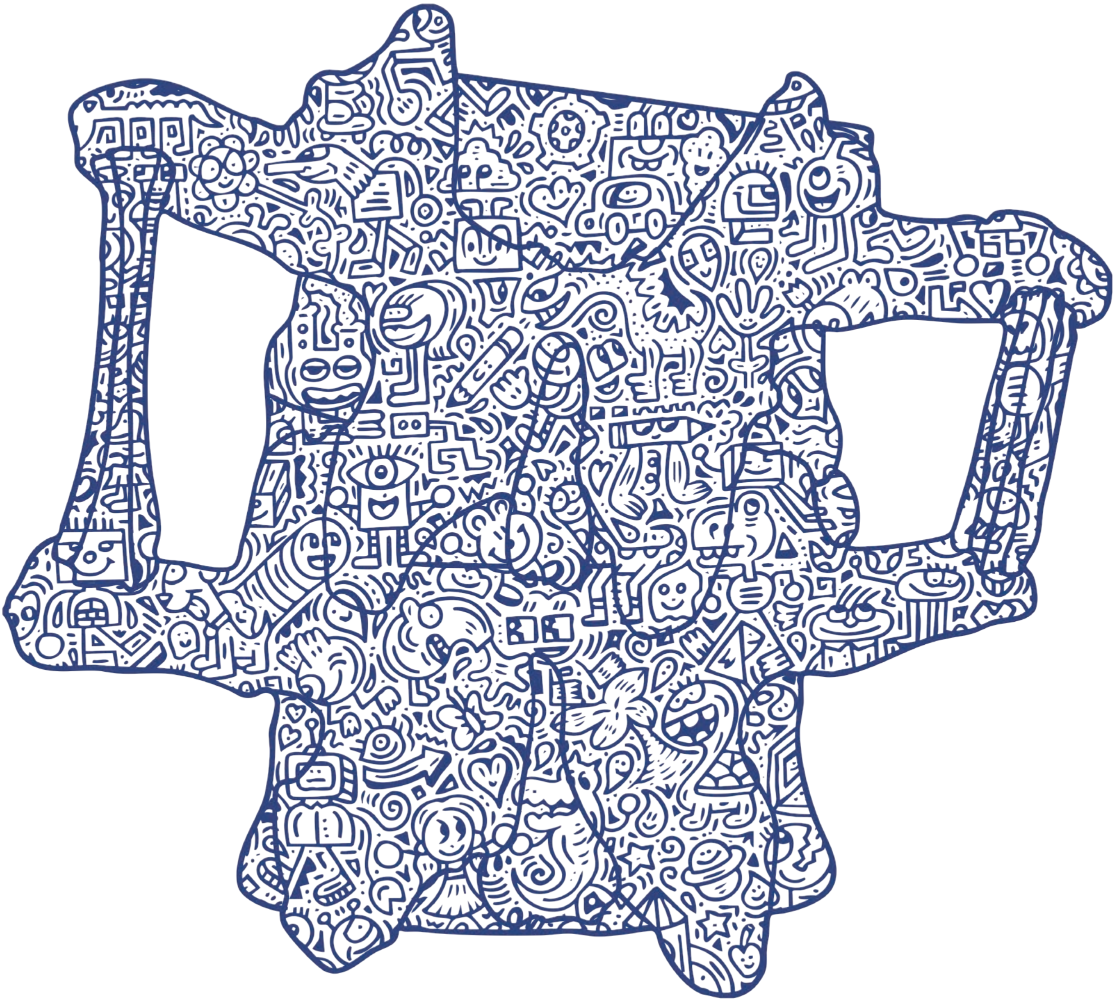
The findings of the current study further illustrate patient perceptions of the benefits of minimally invasive spine surgery. For instance, in general proposed advantages of minimally invasive surgery are the ability to perform the technique on an outpatient basis and the increased likelihood of a shorter recovery period, smaller scar size, and lower rate of postoperative back pain compared with open surgery, among others. In this study, patients preferred hospitalization and did not necessarily seem to be influenced in their choices by the size of the scar. The effect on leg pain is of the most importance for patients in deciding to undergo surgery for sciatica. Furthermore, this study shows that not all proposed advantages of minimally invasive spine surgery (e.g., size of the scar, no need of general anesthesia) are necessarily perceived as advantages by all patients and that surgical techniques for sciatica should be offered, not only based on own ability and proposed eligibility by spine surgeons, but also based on specific patient preferences.

PART III

THE PTED-STUDY







7

Chapter

FULL-ENDOSCOPIC VERSUS OPEN DISCECTOMY FOR SCIATICA: A NONINFERIORITY RANDOMIZED CONTROLLED TRIAL

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BMJ. 2022 Feb 21;376:e065846.

ABSTRACT

Introduction

Open microdiscectomy is the standard procedure for the treatment of sciatica caused by LDH. PTED is an alternative procedure which is performed under conscious sedation. The objective of the current study was to assess if PTED is non-inferior to microdiscectomy in leg pain reduction in patients with sciatica.

Methods

A pragmatic, multicenter, non-inferiority, randomized controlled trial was conducted in which patients were randomized between PTED or microdiscectomy in a 1:1 ratio. The primary outcome is self-reported leg pain measured by the 0-100 VAS with a non-inferiority margin of 5. Secondary outcomes include self-reported functionality, back pain, costs, QALYs, health-related quality of life and self-perceived recovery. Outcomes were measured the day following surgery, at 2, 4, and 6 weeks, and at 3, 6, 9, and 12 months

Results

At 12 months, patients who were randomised to PTED had a statistically significantly lower VAS leg pain (median 7.0, IQR 1.0 to 30.0) compared with patients randomised to microdiscectomy (16.0, 2.0 to 53.5) (between group difference of 7.1, 95% confidence interval 2.8 to 11.3). Blood loss was less, length of hospital admission was shorter, and timing of postoperative mobilisation was earlier in the PTED group than in the open microdiscectomy group. Secondary patient reported outcomes such as functionality, visual analogue scale for back pain, health related quality of life, and self-perceived recovery, were similarly in favour of PTED as the primary outcome. Within one year, nine (5%) in the PTED group compared with 14 (6%) in the open microdiscectomy group had repeated surgery. Per protocol analysis and sensitivity analyses including the patients of the learning curve resulted in similar outcomes to the primary analysis.

Conclusion

PTED was non-inferior to open microdiscectomy in reduction of leg pain. PTED resulted in more favourable results for self-reported leg pain, back pain, functional status, quality of life, and recovery. These differences, however, were small and may not reach clinical relevance. PTED can be considered as an effective alternative to open microdiscectomy in treating sciatica.

INTRODUCTION

With a lifetime prevalence of up to 43%, sciatica is a common health problem in the general population[1]. Sciatica is typically characterized by radiating leg pain starting from the low back, at times accompanied by sensory or motor deficits, and most frequently caused by lumbar disk herniation[2]. Sciatica has a favorable natural course in most people; however, surgery may be indicated when conservative treatment fails or progressive neurological deficits develop[68]. Previous studies have shown the short-term benefits of surgery for pain relief, function, and perceived recovery, with similar long-term outcomes to prolonged conservative management for people with sciatica lasting from six to 12 weeks. Recent studies showed that surgery led to a greater reduction in leg pain on long term follow-up compared with conservative management for sciatica lasting from four to 12 months[7,8].

Following publication of initial reports on surgery for lumbar disk herniation in 1934, attempts were made to reduce the surgical invasiveness of this procedure[28]. These modifications have led to conventional transflaval open microdiscectomy becoming the standard procedure for treating lumbar disk herniation[5,6]. Owing to the development of surgical endoscopes and their application to the lateral transforaminal “safe” entry zone as described by Kambin and Brager, other surgical techniques were developed with the intention to be less invasive[48]. PTED is one of these proposed less invasive techniques. PTED is expected to lead to less postoperative back pain, shorter hospital admission, and a faster recovery because paraspinal muscles are not detached from their insertion, bony anatomy is not changed, and general anesthesia is not used[14]. Some concerns exist, however, in the scientific literature about the effectiveness for leg pain and recovery of function after PTED compared with open microdiscectomy, and previously published studies may have been influenced by commercial enterprises[17-19]. Furthermore, as PTED has a learning curve and exposes surgeons and patients to a higher radiation dose, these concerns need to be overcome with high quality evidence before PTED can be widely implemented[21,22,81].

Previous studies that have compared PTED with open microdiscectomy found either no differences in outcomes or small differences of uncertain clinical relevance[17,19,23,24,44]. However, these studies were of small sample size, were not randomized, or involved only one surgeon[23,44,60]. Therefore, a randomized controlled trial with adequate sample size and low risk of bias is warranted. Advantages adherent to minimally invasive surgery are claimed for PTED, such as less postoperative back pain and shorter hospital admission, so we hypothesized that PTED should not be worse than open microdiscectomy in treating leg pain to be offered as a treatment alternative. Therefore, the aim of the PTED-study was to investigate whether the effect of PTED was non-inferior to conventional open microdiscectomy in terms of reduction in leg pain in patients having surgery for sciatica caused by lumbar disk herniation.

METHODS

Trial design

This multicenter, non-inferiority randomized controlled trial was conducted at four general hospitals in the Netherlands in patients with sciatica caused by lumbar disk herniation. Details of the protocol and study design have been published previously[67]. The study was funded by ZonMw, the Netherlands Organization for Health Research and Development, without involvement of the medical technology industry. The research protocol was approved by the research ethics board of all participating hospitals and registered at ClinicalTrials.gov (NCT02602093). All patients provided written informed consent before enrolment.

Enrolment and randomization

From February 2016 to April 2019, neurosurgeons and orthopedic surgeons screened and enrolled patients with sciatica during outpatient clinic visits. Patients were eligible for the PTED-study if they had an indication for surgery according to Dutch consensus, which means that patients should have at least six weeks of excessive radiating leg pain with no tendency for any clinical improvement despite conservative therapy. Aside from leg pain, patients could be included with or without motor or sensory loss, as is part of daily practice. Furthermore, patients should be between 18 and 70 years of age; have a nerve root compression by a lumbar disk herniation proven by magnetic resonance imaging, corresponding to the clinical dermatomal area; and have sufficient knowledge of the Dutch language to complete forms and follow instructions independently. Exclusion criteria were previous surgery at the same or adjacent disk level; cauda equina syndrome; isthmic or degenerative spondylolisthesis; pregnancy; severe comorbid medical or psychiatric disorder (ASA-classification >2); severe caudal or cranial sequestration of disk fragments, defined as sequestration towards more than half of the adjacent vertebra; contraindication for surgery, and moving abroad on short notice.

We randomized patients in a one-to-one ratio to PTED or open microdiscectomy by using computer generated variable block sizes (four, six, or eight), stratified by enrolling center. Blinding of patients was not feasible because of the substantial differences between the two procedures (for example, PTED being performed under conscious sedation and having an 8 mm incision 8-12 cm lateral of the spine midline and open microdiscectomy being performed under general anesthesia with a 2-4 cm dorsal incision in the spine midline). Both surgical techniques were presented to patients as equal in effectiveness during enrolment.

Study interventions

All surgeons were spine dedicated with eight to 11 years of experience in degenerative lumbar spine surgery. One of the primary reasons for conducting this study was the opinion that PTED did not meet scientific criteria inherent in reimbursement within the Dutch public healthcare system[66]. Therefore, PTED was temporarily reimbursed by insurance companies on the condition that patients were enrolled in the PTED-study. Furthermore, only one of the participating surgeons was proficient in doing PTED in the Netherlands; therefore, three surgeons (one per hospital) were trained to do PTED. Each surgeon attended an accredited postgraduate hands-on workshop and did 10-15 procedures under the supervision of a senior surgeon with ample experience in PTED. After these supervised procedures, the surgeons did PTED independently. Their first 50 cases (including the supervised cases) would be deemed learning curve cases.

PTED

The full procedure has been described previously[14]. Local anesthesia was administered, and surgery was performed under conscious sedation[15]. The site was verified by fluoroscopy, after which a line was drawn from the center of the herniation. The needle was placed, and the position was checked. After the needle had reached the correct position, a guidewire was inserted. After that, a series of conical rods were introduced, and subsequently a drill was introduced through the cannula. By drilling, the neuroforamen was enlarged. Hereafter, the instruments were removed with the guidewire remaining in place. Then, the endoscope with the working channels was introduced via the cannula. Following removal of the loose disk fragments, the cannula and endoscope were removed. Patients were treated on an outpatient basis.

Open microdiscectomy

Open microdiscectomy was conducted under general anaesthesia[6]. The disk level was verified using fluoroscopy, and a paramedian incision was made. The use of loupes or a microscope was optional. After identification of the lamina, the yellow ligament was removed to identify the nerve root and disk herniation. The amount of degenerative disk material removed was at the discretion of the surgeon. Laminotomy, as well as foraminotomy, was done if necessary. A partial medial facetectomy was used for the foraminal herniated disk, and an approach alongside the facet joints was used for the extraforaminal herniated disk. The patient was discharged as soon as medically responsible, which is usually one day after surgery.

Patients in both groups were discharged as soon as medically responsible. Pain medication was offered to all patients if necessary and included paracetamol and optionally non-steroidal anti-inflammatory drugs, short acting opioids, or both. We used questionnaires to monitor the use of pain medication and of co-interventions.

Outcome measures

The primary outcome was the improvement in leg pain at one year, as measured with VAS ranging from 0 to 100 with higher scores indicating more leg pain[38]. We chose the VAS for leg pain as the primary outcome because the goal of surgery is to reduce leg pain, so PTED should be non-inferior in reduction of leg pain to be considered as a treatment alternative to microdiscectomy. The VAS for leg pain was measured at baseline; one day; two, four, and six weeks; and three, six, nine, and 12 months postoperatively. Secondary outcomes were functional status as measured with the ODI (ranging from 0 to 100, with higher scores indicating more disability)[82]; VAS for back pain (ranging from 0 to 100, with higher scores indicating more back pain)[38]; VAS for quality of life (ranging from 0 to 100, with higher scores indicating a higher quality of life)[83]; the physical component summary and mental component summary of the SF-36, with higher scores indicating better perceived health[84]; and seven point Likert-type scales measuring self-perceived recovery from symptoms, recovery from leg pain, satisfaction with treatment, and change in symptoms[83]. We defined recovery and satisfaction by combining “complete” and “nearly complete” recovery or satisfaction. We added an 11-point numerical rating scale for leg pain, back pain, and quality of life for internal validation of the study results in a protocol amendment[85]. All secondary outcome measures were assessed at the same time points as the primary outcome except for one day postoperatively, when only functional disability, quality of life, back pain, self-perceived recovery, and satisfaction were measured. Questionnaires were sent to patients by email or regular mail. At six weeks, three months, and 12 months after surgery, patients visited the clinic for a neurological examination by a research nurse who was aware of the treatment allocation. In addition to the patient reported outcome measures, data on the surgical procedure, complications, discharge, and reoperations were collected.

Statistical analysis

The expected mean difference between the groups in visual analogue scale for leg pain was 5 with a standard deviation of 14.9[13]. With a margin of non-inferiority set at 5.0 (expected difference), a one-sided α of 0.05, and a β of 0.10, we estimated that a sample size of 306 patients would show non-inferiority with 90% power. Considering an attrition rate of 20%, we set the sample size at 382. We planned to recruit an additional 150 patients (50 per surgeon) for the learning curve in the PTED arm. We based this decision to include 50 learning curve cases per surgeon on the literature and consensus of the research group[20]. We excluded these learning curve cases from the primary analyses. In total, we included an additional 300 patients (150 randomized to PTED as learning curve cases and 150 randomized to open microdiscectomy) above the sample size calculation because reimbursement of PTED was dependent on participation in the trial. Thus, the goal was to recruit 682 participants.

We did the primary analyses according to the intention-to-treat principle. We did per protocol analyses as sensitivity analyses, including only patients who received the intervention to which they were randomized. Furthermore, we did sensitivity analyses including the learning curve patients and sensitivity analyses using the numerical rating scale to test the robustness and validity of the results. We presented baseline characteristics by using percentages for categorical variables and means and SDs or medians and IQRs, when appropriate, for continuous variables. We used mixed model analyses with random intercepts on the patient level to account for dependency of measurements over time within patients. We used linear mixed models to analyze leg pain, functional disability, back pain, quality of life, physical component summary, and mental component summary. We used logistic mixed models to analyze the dichotomized Likert-type scales. In addition to the adjusted models in which we corrected for the baseline score and center, fully adjusted models for the primary analyses are shown in the supplementary material. Fully adjusted models included adjustment for factors such as the baseline score, center, age, sex, duration of complaints, smoking status, body mass index, employment status, site of disk protrusion, treatment preference of the patient, and psychopathology as measured on the four-dimensional symptom questionnaire[86]. Finally, we added a linear and logistic regression analysis adjusting for baseline and hospital for the outcomes at 12 months as an alternative analysis. Mean differences and odds ratios are presented with their 95% confidence intervals. We estimated confidence intervals from linear mixed model analyses by using 1000 bootstrap samples according to the bias accelerated procedure to consider skewness of residuals. We used SPSS version 27.0 for all analyses.

As follow-up data were collected using electronic questionnaires, all patients who had data available had complete data available at that follow-up point. We handled data missing owing to missed visits or patients' withdrawal from the study at follow-up time points by using the mixed model analysis using the maximum likelihood estimation.

Patient involvement

Before the start of the PTED study, members of the patients' organization "de Wervelkolom" ("the Spine") were involved in the study design. Furthermore, this organization was also part of the half yearly board meetings during which recruitment, implementation, and results of the study were discussed.

RESULTS

Patients

In the period between February 2016 and April 2019, 711 patients were assessed for eligibility, of whom 613 patients were enrolled into the PTED study (Figure 1). The baseline characteristics of the patients were similar in both groups (Table 1). The trial was finalized before the estimated sample size of 682 participants was reached, because the end of the enrolment period of the study was reached. Of the 304 patients randomized to PTED, 286 (94%) received the intervention; of the 309 patients randomized to open microdiscectomy, 244 (79%) had microdiscectomy as assigned; ten of these were tube assisted. At 12 months of follow-up, the primary outcome was available for 532 (87%) of the randomized patients.

Learning curve

The estimated learning curve of 150 learning curve cases was not reached. Of the 304 patients randomized to the PTED group, 125 were learning curve cases. During the learning curve, the PTED procedure was converted to microdiscectomy in four patients. Four complications occurred, and 14 (11%) patients had repeated surgery within one year because of recurrent disk herniation. All patient reported outcome measures showed significant improvement after 12 months compared with baseline.

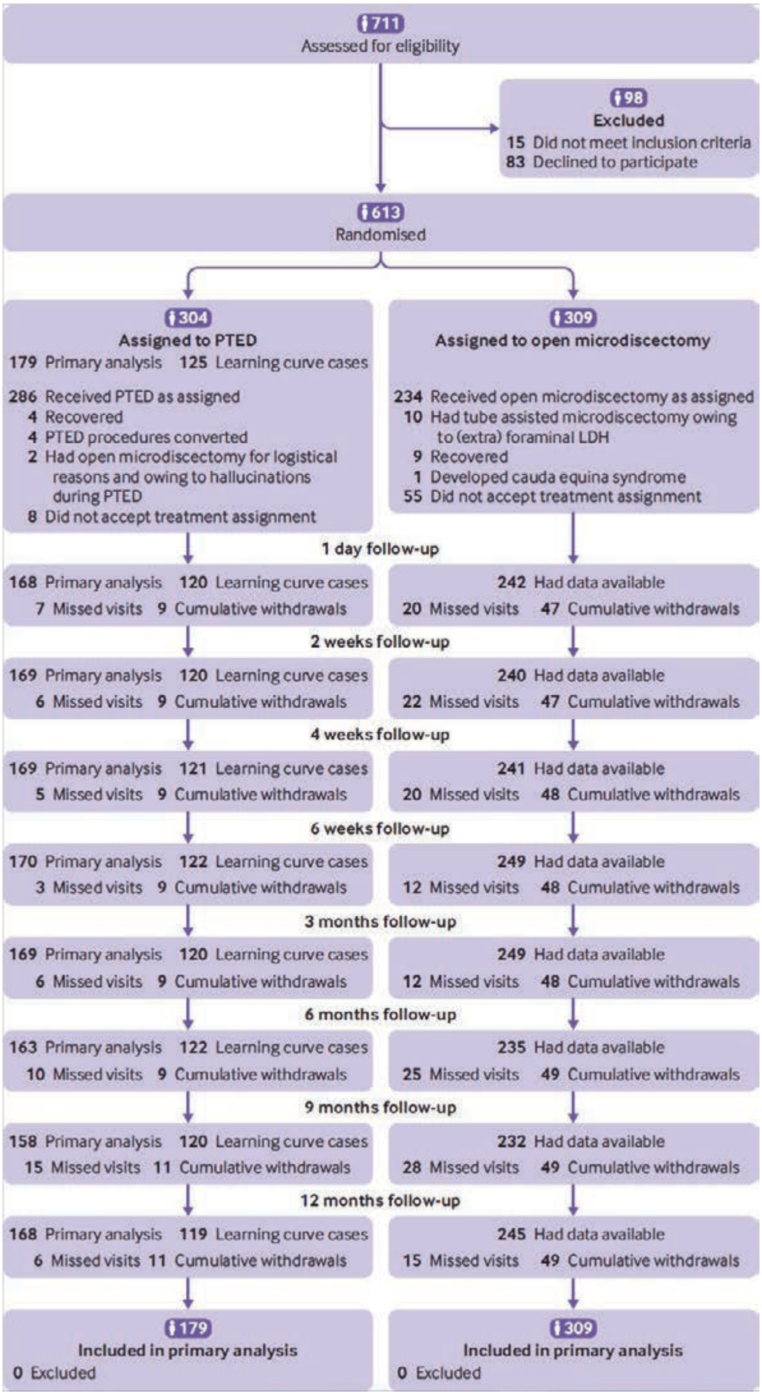

Figure 1: Flowchart of study eligibility, enrolment, procedures, and outcomes.

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Table 1 Characteristics of participants. Values are numbers (percentages) unless stated otherwise

Characteristic	PTED (n=179)	Open microdiscectomy (n=309)
Mean (SD) age, years	45.3 (12.4)	45.7 (11.3)
Male sex	99 (55)	180 (58)
Current smoker	43 (24)	91 (29)
Median (IQR) body mass index	25.8 (23.8-28.7)	25.8 (23.3-29.4)
Paid employment	151 (84)	242 (78)
Median (IQR) duration of leg pain*, months	4.0 (2.0-6.0)	4.0 (2.0-6.0)
Radiating pain in right leg	84 (47)	155 (50)
Sensory disturbances†	161 (90)	290 (94)
Muscle weakness†	92 (51)	183 (59)
Difference in deep tendon reflexes in knees	48 (27)	81 (26)
Difference in deep tendon reflexes in ankles	42 (23)	77 (25)
Level of disk herniation causing sciatica:		
L2-L3	2 (1)	7 (2)
L3-L4	15 (8)	13 (4)
L4-L5	68 (38)	137 (44)
L5-L6	1 (<1)	2 (<1)
L5-S1	93 (52)	148 (48)
L6-S1	0	2 (<1)
Median (IQR) score on VAS for pain‡:		
Leg pain	71.0 (58.0-82.0)	74.0 (61.0-83.5)
Back pain	51.0 (26.0-71.0)	51.0 (18.0-71.0)
Median (IQR) Oswestry Disability Index§	44.0 (32.0-58.0)	44.0 (34.0-57.8)
Median (IQR) score on VAS for quality of life¶	48.0 (31.0-62.0)	51 (33.0-65.0)
Median (IQR) SF-36 score**:		
Physical component summary	30.5 (24.7-36.3)	30.0 (23.5-35.1)
Mental component summary	49.4 (40.1-56.9)	48.4 (37.3-56.2)
Median (IQR) four-dimensional symptom questionnaire score††:		
Distress	7.0 (4.0-14.0)	7.0 (3.0-14.0)
Depression	0.0 (0-1.0)	0.0 (0-1.0)
Anxiety	0.0 (0-2.0)	0.0 (0-2.0)
Somatisation	6.0 (4.0-9.0)	6.0 (4.0-10.0)
Preference for PTED	153 (85)	240 (78)

*Self-reported duration of radiating leg pain from onset until inclusion in trial.
†Patient reported.
‡Scores intensity of leg and back pain from 0 to 100, with higher scores indicating more pain.
§Measures functional disability from 0 to 100, with higher scores indicating more functional disability.
¶Scores general quality of life from 0 to 100, with higher scores indicating better quality of life.
**SF-36 score can be summarised in physical component summary and mental component summary using normative data; higher scores indicate better quality of life.
††Measures distress in four categories.

Primary outcome

The median visual analogue scale for leg pain showed a similar improvement in leg pain in both groups following surgery (Figure 2). In the first three months, mean differences in reduction of leg pain between the groups were small. At six, nine, and 12 months, mean differences in favor of PTED increased. At 12 months' follow-up, the mean between group difference in leg pain was 7.1 (95% confidence interval 2.8 to 11.3, Table 2) in favor of PTED. This between group difference indicates that PTED was non-inferior, because the between group difference in leg pain was not worse than 5.0 at 12 months for PTED compared with open microdiscectomy.

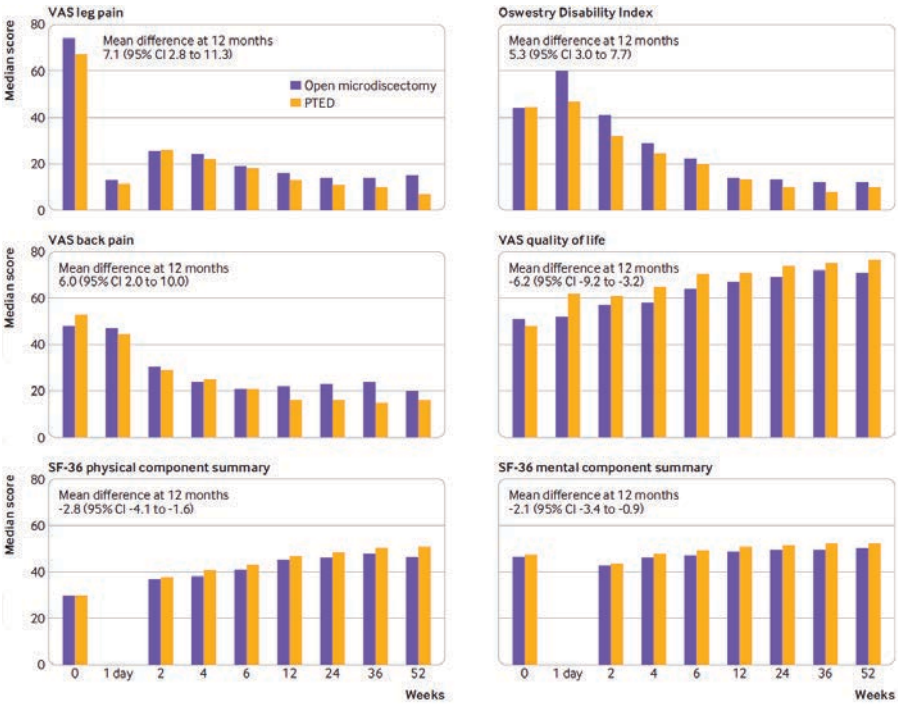


Figure 2: Median scores on VAS for leg pain, ODI, VAS for back pain, VAS for quality of life, SF-36 physical component summary, and SF-36 mental component summary.

Table 2 Primary and secondary outcomes according to treatment and timing of treatment after surgery

Outcome	2 weeks			6 weeks	
	PTED (n=169)	OM (n=240)	Between group difference (95% CI)	PTED (n=170)	OM (n=249)
Primary outcome					
VAS for leg pain*	24.5 (7.0-53.5)	25.0 (8.0-54.8)	−0.5 (−4.5 to 3.8)	18 (4.8-47.3)	21.0 (6.5-48.5)
Secondary outcomes					
Oswestry Disability Index†	32.0 (18.0-48.0)	41.0 (24.4-53.3)	6.5 (4.0 to 8.9)	20.0 (8.0-32.0)	24.0 (12.0-36.0)
VAS for back pain†	28.0 (11.5-48.0)	29.5 (12.3-50.8)	1.8 (−1.9 to 5.4)	21.0 (7.8-46.3)	22.0 (9.0-49.0)
VAS for quality of life‡	61.0 (48.0-75.0)	56.5 (36.3-73.0)	−6.8 (−9.8 to −3.9)	70.0 (55.8-81.3)	64.0 (47.0-75.5)
SF-36 physical component summary§	37.8 (33.0-44.1)	36.9 (32.4-41.6)	−1.3 (−2.7 to −0.1)	43.1 (36.4-48.7)	41.0 (33.6-46.8)
SF-36 mental component summary§	45.8 (34.3-53.2)	42.7 (42.9-53.4)	−1.3 (−3.1 to 0.5)	53.8 (41.5-57.1)	50.1 (39.3-55.0)
Proportion recovered from symptoms¶	89 (53%)	118 (49%)	1.2 (0.7 to 2.2)	113 (66%)	148 (59%)
Proportion recovered from leg pain¶	98 (58%)	144 (60%)	0.8 (0.5 to 1.5)	119 (70%)	168 (67%)
Proportion satisfied with change in symptoms¶	97 (57%)	124 (52%)	1.3 (0.7 to 2.4)	112 (66%)	149 (60%)
Proportion satisfied with result of treatment¶	106 (63%)	140 (58%)	1.2 (0.7 to 2.2)	121 (71%)	155 (62%)

*Scores intensity of leg and back pain from 0 to 100, with higher scores indicating more pain.
†Measures functional disability from 0 to 100, with higher scores indicating more functional disability.
‡Scores general quality of life from 0 to 100, with higher scores indicating better quality of life.
§ SF-36 score can be summarised in physical component summary and mental component summary using normative data. Higher scores indicate better quality of life.
¶Measured by dichotomising Likert scales with recovered or satisfied defined as complete or nearly complete recovery/satisfaction.

Secondary outcomes

In general, mean differences in secondary outcomes between both groups were small in the first three months and increased in favor of PTED at six, nine, and 12 months (Figure 2; Table 2). At 12 months, the median score on the ODI was 10.0 (IQR 2.0-17.8) in the PTED group and 12.7 (2.2-28.4) in the microdiscectomy group (mean difference of 5.3, 3.0 to 7.7). At 12 months, back pain intensity was 16.0 (IQR 3.0-38.8) in the PTED group compared with 21.0 (5.0-55.0) in the microdiscectomy group (mean difference 6.0, 2.0 to 10.0). Furthermore, at 12 months the median VAS score for quality of life was 76.5 (IQR 61.8-86.8) in the PTED group compared with 70.5 (54.3-83.0) in the microdiscectomy group (mean difference of −6.2, −9.2 to −3.2). The mean differences for the SF-36 physical component summary and mental component summary at 12 months were in

	6 months			12 months		
Between group difference (95% CI)	**PTED (n=163)**	**OM (n=235)**	**Between group difference (95% CI)**	**PTED (n=168)**	**OM (n=245)**	**Between group difference (95% CI)**
0.2 (–3.6 to 3.6)	11.5 (1.0-28.0)	14.5 (3.0-46.0)	4.9 (1.2 to 8.5)	7.0 (1.0-30.0)	16.0 (2.0-53.5)	7.1 (2.8 to 11.3)
3.4 (1.6 to 5.4)	11.1 (4.0-20.0)	14.0 (4.0-26.5)	3.1 (0.9 to 5.2)	10.0 (2.0-17.8)	12.7 (2.2-28.4)	5.3 (3.0 to 7.7)
0.9 (–2.2 to 4.1)	15.5 (4.0-42.0)	24.5 (10.0-53.0)	6.2 (2.8 to 10.0)	16.0 (3.0-38.8)	21.0 (5.0-55.0)	6.0 (2.0 to 10.0)
–7.8 (–10.3 to 5.4)	73.0 (61.0-82.0)	68.0 (56.0-81.0)	–4.3 (–7.2 to –1.3)	76.5 (61.8-68.8)	70.5 (54.3-83.0)	–6.2 (–9.2 to –3.2)
–1.9 (–3.0 to –0.7)	48.4 (41.3-54.6)	46.1 (38.2-53.5)	–1.8 (–3.0 to –0.6)	50.8 (42.3-56.5)	46.4 (38.7-53.8)	–2.8 (–4.1 to –1.6)
–2.3 (–3.5 to –1.0)	54.3 (48.4-57.3)	53.8 (44.4-57.2)	–2.1 (–3.4 to –0.7)	54.6 (50.1-57.1)	53.8 (46.3-56.8)	–2.1 (–3.4 to –0.9)
1.5 (0.8 to 2.6)	120 (74%)	154 (66%)	1.6 (0.9 to 3.0)	133 (79%)	157 (64%)	2.7 (1.4 to 5.2)
1.1 (0.6 to 2.0)	125 (77%)	165 (70%)	1.5 (0.8 to 2.9)	133 (79%)	169 (69%)	2.0 (1.0 to 3.7)
1.3 (0.7 to 2.4)	119 (73%)	143 (61%)	2.1 (1.1 to 4.0)	127 (76%)	150 (61%)	2.6 (1.4 to 4.8)
1.7 (0.9 to 3.1)	124 (76%)	155 (66%)	2.0 (1.0 to 3.8)	133 (79%)	161 (66%)	2.6 (1.3 to 5.0)

the same direction as the other secondary outcomes: –2.8 (–4.1 to –1.6) and –2.1 (–3.4 to –0.9), respectively. At 12 months, the odds ratio for recovery of symptoms was 2.7 (1.4 to 5.2), and the odds ratio for recovery of leg pain was 2.0 (1.0 to 3.7). Furthermore, the odds ratio for satisfaction with change in symptoms and satisfaction with the result of treatment were 2.6 (1.4 to 4.8) and 2.6 (1.3 to 5.0), respectively.

Table 3 Surgical outcomes and complications of patients who had surgery, according to intention-to-treat analysis. Values are numbers (percentages) unless stated otherwise

Outcome/complication	PTED (n=171)	Open microdiscectomy (n=249)
Median (IQR) duration of surgery, minutes	30.0 (23.0-43.0)	30.0 (23.0-40.0)
Estimated blood loss <10 mL	125 (73)	68 (27)
Position of disk herniation†:		
Median	15 (9)	19 (8)
Paramedian	125 (73)	178 (71)
Intraforaminal	20 (12)	33 (13)
Extraforaminal	11 (6)	20 (8)
Total intraoperative complications:		
Dural tear	0	8 (3)
Nerve root injury	0	1 (<1)
Exploration on wrong level	1 (<1)	0
Had procedure other than assigned:		
PTED	0	5 (2)
Open microdiscectomy	3 (2)	0
Tubular discectomy	0	10 (4)
Total postoperative complications:		
Wound haematoma	0	1 (<1)
Wound infection	0	3 (1)
Cerebrospinal fluid leakage	0	2 (<1)
Micturition disturbances	0	1 (<1)
Deep venous thrombosis in the leg	0	1 (<1)
Transient increase in neurological deficit	2 (1)	0
Timing of mobilisation:		
Day of surgery	171 (100)	209 (84)
Day 1 after surgery	0	39 (16)
Day 2 after surgery	0	1 (<1)
Day of discharge:		
Day of surgery	161 (94)	14 (6)
Day 1 after surgery	10 (6)	229 (92)
Day 2 or later	0	6 (2)
Mean (SD)length of scar at 6 weeks§, mm	11.7 (9.2)	38.4 (15.0)
Repeated surgery within 1 year:	9 (5)	14 (6)¶
Re-discectomy for disk herniation	9 (5)	12 (5)
Disk herniation on other level	0	0
Stenosis	0	0

Outcome/complication	PTED (n=171)	Open microdiscectomy (n=249)
Instrumented fusion for recurrent disk herniation	0	2 (<1)
Analgesic use after discharge:		
Two weeks after surgery	(n=169)	(n=241)
Non-opioid analgesics	84 (50)	133 (55)
Opioid analgesics	22 (13)	70 (29)
Six months after surgery	(n=163)	(n=236)
Non-opioid analgesics	41 (25)	50 (21)
Opioid analgesics	8 (5)	21 (9)
Twelve months after surgery	(n=168)	(n=244)
Non-opioid analgesics	23 (14)	52 (21)
Opioid analgesics	9 (5)	24 (10)

†One disk herniation was both intraforaminal and extraforaminal.
§Data on scar size was available for 162 patients in PTED group and 224 in open microdiscectomy group.
¶One patient had two re-discectomies within one year, and one patient had instrumented fusion after re-discectomy within one year.

Complications and surgical outcomes

Both procedures were of similar duration, but less perioperative blood loss occurred in the PTED group (Table 3). Eight (3%) dural tears and three (1%) wound infections were reported in the open microdiscectomy group compared with none in the PTED group. One (0.4%) nerve root injury and one (0.4%) deep vein thrombosis occurred in the open microdiscectomy group. Of the patients in the PTED group, 94% could be discharged on the day of surgery compared with 6% in the microdiscectomy group. Measured at six weeks, the mean length of the scar was 11.7 (SD 9.2) mm in the PTED group and 38.4 (SD 15.0) mm in the microdiscectomy group. The rate of repeated surgery within one year was 5.3% in the PTED group compared with 5.6% in the microdiscectomy group. At two weeks and six months of follow-up, the use of non-opioid analgesics seemed to be similar between both groups, whereas patients in the PTED group seemed to use less non-opioid analgesics at 12 months than did patients in the microdiscectomy group. Furthermore, patients from the PTED group used fewer opioid analgesics than did patients from the microdiscectomy group at two weeks, six months, and 12 months of follow-up.

Alternative, per-protocol, and sensitivity analyses

Figure 3 gives an overview of all analyses conducted. In general, all alternative analyses did not significantly affect the main results. The results of the alternative analyses using linear regression shows a between group difference of 7.9 (1.8 to 13.4) in favor of PTED on the VAS for leg pain at 12 months. The per-protocol analysis included 168 patients who had PTED and 244 patients who had microdiscectomy. At 12 months, the mean between group difference in improvement of leg pain for PTED compared with microdiscectomy was 8.3 (4.1 to 12.8). Secondary outcomes were also comparable to the results according to the intention-to-treat analysis. In addition, we did sensitivity analyses including the 125 learning curve cases of all three surgeons who did not do PTED before the study. These analyses resulted in comparable outcomes to the primary analysis.

Population	No/total No (%) PTED group	No/total No (%) Open microdiscectomy group	Mean difference (95% CI) in VAS leg pain
Modified intention-to-treat population, using mixed models	168/179 (94)	245/309 (79)	7.1 (2.8 to 11.3)
Modified intention-to-treat population, using regression analysis	168/179 (94)	245/309 (79)	7.9 (1.8 to 13.4)
Fully adjusted modified intention-to-treat population, using mixed models	168/179 (94)	245/309 (79)	7.1 (2.3 to 11.3)
Per protocol population, using mixed models	164/168 (98)	227/244 (93)	8.3 (4.1 to 12.8)
Modified intention-to-treat population with learning curve cases, using mixed models	287/304 (94)	245/309 (79)	4.5 (0.6 to 8.4)

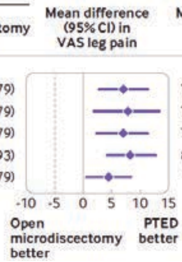


Figure 3: Results of primary outcome in primary and secondary analyses. Mean difference between groups is shown on VAS for leg pain at 12 months, together with 95% CI. Modified intention-to-treat population included all patients randomized to PTED or microdiscectomy without learning curve cases. Per-protocol population included all patients randomized to PTED or microdiscectomy who received allocated treatment. Learning curve cases were also omitted for these analyses. Results of modified intention-to-treat population are also presented including learning curve cases. Crude analyses were adjusted for baseline and center. Fully adjusted analysis included adjustment for baseline score, center, age, sex, duration of complaints, smoking status, body mass index, employment status, site of disk protrusion, treatment preference of patient, and psychopathology as measured on four-dimensional symptom questionnaire.

DISCUSSION

In this multicenter trial among patients with sciatica caused by LDH, we found PTED to be non-inferior to microdiscectomy in reduction of leg pain at 12 months. Mean differences in leg pain reduction between the groups were small in the first three months, but they increased in favor of PTED at six, nine, and 12 months. Different hypotheses can be formulated to explain this difference. An explanation may be that three months after surgery the formation of scar tissue may limit the patients in the microdiscectomy group more than those in the PTED group, as a less invasive surgical route was used to access the disk herniation. Eventually at 12 months, patients in the PTED group experienced a larger reduction in leg pain than did patients in the microdiscectomy group, which is a larger difference than expected and clearly within the non-inferiority margin. One can argue as to whether this difference of 7.1 on a 0-100 VAS be clinically relevant, as it is below commonly recognized minimally clinically important difference thresholds[87]. Similarly, the secondary patient reported outcomes showed more favorable results for the patients in PTED group—namely, in functional disability, back pain, quality of life, and self-perceived recovery. These effect sizes, however, were also small and may also not reach clinical relevance[87]. Further results show that the rate of repeated surgery within one year due to sciatica was similar. Analysis of the learning curve cases showed that PTED can safely be adopted by surgeons in different centers under initial supervision of a surgeon proficient in PTED.

Comparison with other studies

A recently published meta-analysis compared PTED with open microdiscectomy in the treatment of sciatica[19]. This meta-analysis included 14 prospective studies, of which nine were (quasi)randomized, and eventually concluded that moderate quality evidence existed for no difference in leg pain reduction or functional status at long term follow-up. The results of our study are in line with these findings. Most of the studies in the meta-analysis did not have an adequate randomization procedure. Three of the identified studies in the meta-analysis had a low risk of selection bias but had some form of attrition or reporting bias[23,44,57]. These studies, however, were either underpowered to detect small differences between groups or were conducted by a single surgeon or in single center. Furthermore, these studies did not show the feasibility of implementing PTED among surgeons naïve to the procedure.

Strengths and limitations of study

Some limitations have to be acknowledged. Firstly, participation bias cannot be ruled out because a proportion of patients with a strong preference for PTED who were randomized to open microdiscectomy dropped out of the study immediately. Secondly, blinding of patients was not possible owing to the substantial differences between PTED and microdiscectomy. Thirdly, the pre-estimated sample size of 682 patients was not reached. Of the 382 patients calculated as being necessary in the final sample size of the trial (that is, excluding learning curve cases), we were able to include 179 instead of 191 of the patients who would have PTED. However, the sensitivity analysis including the learning curve patients (n=613) confirms the robustness of our findings. Another point of discussion could be the use of mixed models for our primary analysis. Mixed model analyses adjust the primary outcome at 12 months for leg pain measured at earlier time points and may lead to a subtly different outcome than our defined primary outcome of improvement in leg pain at 12 months. Both methods of analyzing the data (linear regression and mixed model) suggest similar outcomes (Figure 3) and support the conclusion that PTED is non-inferior to open microdiscectomy in leg pain reduction.

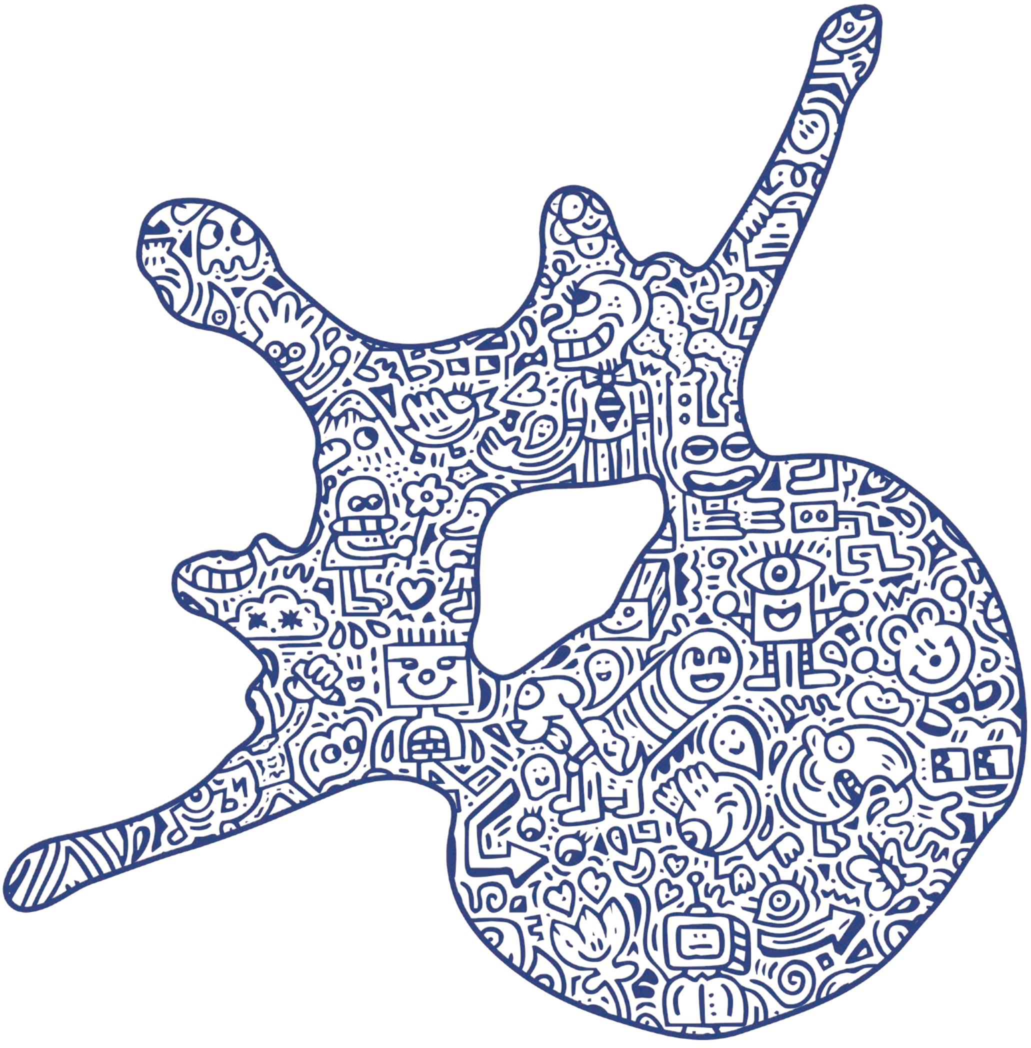
Strengths of this study include the multicenter, randomized design and the inclusion of learning curve cases in the sample size. An additional strength is the generalizability. We chose the study's inclusion and exclusion criteria to reflect current neurosurgical practice for sciatica. This is also underlined by the proportion of patients that were enrolled after screening. Another strength is the signed agreement on the non-inferiority margin by the research group, patients' organization, professional organizations, and the Dutch Health Care Institute, before the trial started. Furthermore, clinical outcomes, complications, and adverse events were structurally documented between short time intervals.

Policy implications

Before this study, PTED was not reimbursed by various insurance companies because of the lack of evidence on the benefits of PTED compared with open microdiscectomy in the treatment of sciatica. The results of the study show that PTED is non-inferior to microdiscectomy in the treatment of leg pain but also that no meaningful clinical differences in patient reported outcomes exist between the procedures. Therefore, future decisions on doing lumbar discectomy should consider patients' preferences for a treatment, the burden of the treatment to the patient, and the costs of the treatment. Aside from the lack of clinically relevant differences between the procedures, PTED comes with advantages of facilitating outpatient surgery, less estimated blood loss, a low complication rate, lower use of opioids, and a smaller scar, as well as a comparable rate of repeated surgery within one year. Furthermore, 81% of the patients included preferred PTED, indicating the popularity of this procedure among patients. PTED, however, has a learning curve with a higher rate of repeated surgery within one year, more exposure to perioperative radiation, and possibly greater costs[19,20,81]. Whether the small differences in clinical outcomes and the advantages of PTED will outweigh the potential higher costs of the procedure remains open for debate. To answer these remaining questions, an economic evaluation has been conducted alongside the PTED study and is published concomitantly[88]. As a result of this study, the Dutch government now reimburses PTED, and patients are able to have PTED outside of the experimental setting. This reimbursement also comes with the need for an implementation plan to ensure that the PTED technique is performed by surgeons who have received proper training.

Conclusions

PTED is non-inferior to microdiscectomy in reduction of leg pain. PTED resulted in more favorable results for patients' self-reported leg pain, back pain, functional status, quality of life, and recovery. These differences, however, were small and may not reach clinical relevance. PTED can be considered as an effective alternative to open microdiscectomy in treating sciatica.



8.1

Chapter

COST-EFFECTIVENESS OF FULL-ENDOSCOPIC VERSUS OPEN DISCECTOMY FOR SCIATICA: ECONOMIC EVALUATION OF A RANDOMIZED CONTROLLED TRIAL

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Br J Sports Med. 2022 Feb 20:bjsports-2021-104808

ABSTRACT

Introduction

PTED appears to be non-inferior to open microdiscectomy in leg pain reduction as treatment of sciatica. An economic evaluation of both techniques has not been performed yet. Therefore, the aim was to assess the costs and cost-effectiveness of PTED compared with microdiscectomy among patients with sciatica.

Methods

This economic evaluation was conducted alongside a 12-month multi-center randomized controlled trial with a non-inferiority design, in which patients were randomized to PTED or microdiscectomy. Patients were aged from 18 to 70 years and had at least 6 weeks of radiating leg pain caused by lumbar disk herniation. Effect measures included leg pain and QALYs, as derived using the EQ-5D-5L. Costs were measured from a societal perspective. Missing data were multiply imputed, bootstrapping was used to estimate statistical uncertainty, and various sensitivity analyses were conducted to determine the robustness.

Results

Of the 613 patients enrolled, 304 were randomized to PTED and 309 to microdiscectomy. Statistically significant differences in leg pain and QALYs were found in favor of PTED at 12-months follow-up (leg pain: 6.9; 95%CI: 1.3 to 12.6; QALYs: 0.040; 95%CI: 0.007 to 0.074). Surgery costs were higher for PTED than for microdiscectomy (i.e., €4,500/patient versus €4,095/patient). All other disaggregate costs as well as total societal costs were lower for PTED than for open microdiscectomy. Cost-effectiveness acceptability curves indicated that the probability of PTED being less costly and more effective (i.e., dominant) compared with open microdiscectomy was 99.4% for leg pain and 99.2% for QALYs

Conclusion

Our results suggest that PTED is more cost-effective from the societal perspective compared with microdiscectomy for patients with sciatica.

INTRODUCTION

As sciatica has a lifetime prevalence of up to 43% in the general population, it has a high disease burden at the individual level as the societal level[1]. At the individual level patients can suffer from leg pain which can be accompanied by sensory or motor loss, possibly leading to disability and a poor health-related quality of life[2,89]. As so, sciatica can severely impact the lives of active adults, especially as sciatica mostly affects individuals aged between 30 and 50 years[2]. At societal level sciatica comes with a major financial burden mainly because of sick leave and hospital costs[90].

Fortunately, the natural course of sciatica is favorable as majority of the cases resolve with conservative treatment[3]. Due to the high prevalence of sciatica, however, surgery for lumbar disk herniation is a frequently performed procedure[47,91]. The current standard surgical procedure for the treatment of lumbar disk herniation is microdiscectomy. PTED was introduced as a less invasive alternative. In contrast to microdiscectomy, PTED is performed under local anesthesia and is offered as outpatient surgery[15]. Furthermore, PTED is performed from a far lateral approach and requires surgeons to operate from a two-dimensional view, which makes performing PTED more challenging even for experienced surgeons. Because of this challenging learning curve, the unclear merits of PTED over conventional microdiscectomy and possible issues associated with reimbursement, PTED is offered by only a few surgeons worldwide[20,47].

Previous research has compared various outcomes between PTED and microdiscectomy and suggested no differences between both procedures for leg pain and functional status[17-19]. PTED, however, had the advantage of less intraoperative blood loss and shorter hospital stays compared with microdiscectomy. Some prior research has examined the direct costs of both procedures[60,65]. One study assessed the costs of the operating theater, hospitalization, endoscopes, and sterilization of the surgical equipment and found significantly higher costs for PTED than for microdiscectomy. Among these costs, endoscopes were identified to be the biggest cost driver and made up 66% of the costs of PTED[60]. The other study found the cost of hospitalization to be significantly lower for PTED by 27% compared to microdiscectomy[65]. No studies performed a large, full trial-based economic evaluation, in which both the costs and effects of PTED and open microdiscectomy were assessed and compared to one another.

The PTED-study aimed to assess the effectiveness and cost-effectiveness of PTED compared to open microdiscectomy in patients with lumbar disk herniation. Results of the effectiveness analyses suggest that PTED is non–inferior to open microdiscectomy in leg pain reduction at 12 months after surgery[92]. Furthermore, PTED had more favorable results for patient-reported leg pain and health-related quality of life as compared to open microdiscectomy. It is unknown, however, how the difference in costs between both procedures is related to the corresponding differences in leg pain and health-related quality of life. Furthermore, as PTED is not covered by all insurance providers, an economic evaluation comparing PTED with microdiscectomy is warranted. Therefore, this study aimed to explore the cost-effectiveness of PTED compared with microdiscectomy among patients with lumbar disk herniation from a societal perspective at 12 months after surgery.

METHODS

Patients and setting

This economic evaluation was conducted alongside the PTED-study, a large multi-center randomized controlled trial with a non-inferiority design. The PTED-study was approved by the Medical Ethical Committee of the VU Medical Centre Amsterdam (NL50951.029.14) and was prospectively registered at ClinicalTrials.gov (NCT02602093).

A detailed description of the PTED-study, including its sample size calculation, has previously been published[67]. In brief, participants were recruited between February 2016 and April 2019 from three hospitals and one private health clinic in the Netherlands. To be eligible, patients had to meet the following inclusion criteria: age between 18–70 years; >10 weeks of radiating pain with or without motor or sensory loss in the leg or with >6 weeks of excessive radiating pain and no tendency for any clinical improvement; indication for surgery; MRI-confirmed lumbar disk herniation with nerve compression with or without concomitant spinal or lateral recess stenosis; sufficient knowledge of the Dutch language. Exclusion criteria were previous surgery on the same or adjacent disk level; cauda equina syndrome; spondylitis or degenerative spondylolisthesis; pregnancy; severe comorbid medical or psychiatric disorder (ASA >2); severe caudal or cranial sequestration; contraindication for surgery; moving abroad at short notice.

Patients with lumbar disk herniation were screened for eligibility during their outpatient consultation by one of the participating surgeons. Eligible patients received written information about the study and were given at least two days to consider participation. After that period, a trained research nurse further screened patients who were willing to participate, informed consent was obtained, and baseline measurements were performed. Then, patients were randomized in a 1:1 ratio to PTED or microdiscectomy, using a computer-generated, random-number tables with variable block sizes (i.e., 4, 6, 8), stratified by treatment center. Treatment allocation was concealed and was performed by an independent research nurse. Blinding of patients was not possible due to the fundamentally different nature of both procedures. Outcome assessors were not blinded either, because all outcomes were self-reported.

Learning curve

Prior to this study, only two surgeons in the Netherlands were proficient in PTED. During this study, one of these surgeons provided PTED training to the other participating surgeons, all of whom had between 8-11 years of surgical experience. It was expected that about 50 patients per surgeon were needed for them to become proficient in PTED (i.e., 'learning curve'). These patients were registered as learning curve patients and were excluded from the primary analysis.

Effect measures

The primary effect measures for the economic evaluation were intensity of leg pain measured on the VAS ranging from 0 (no pain) to 100 (worst imaginable pain) and QALYs, derived from the EQ-5D-5L[67,83]. QALYs, a commonly used outcome in economic evaluation, are a generic measure which provides a common outcome metric across clinical areas enabling comparisons across conditions. We also included pain intensity because it was the primary clinical outcome of the effectiveness trial and facilitates comparison of the results within the Spine field. Both measures were assessed at baseline, the day after surgery, at 2, 4 and 6 weeks, and 3, 6, 9, 12 months. The EQ-5D-5L measures health-related quality of life in five health dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. The Dutch EQ-5D-5L tariff was used to convert the patients' EQ-5D-5L health states into utility scores, anchored by the health states of death (0) and perfect health (1.00)[93]. QALYs were estimated using the 'area under the curve', meaning that QALYs were calculated by multiplying the patients` health state utility scores with the time spent in that health state. A linear relationship between the patients' health state utility scores at the various time points was assumed. The total QALY of the one-year follow-up period was calculated by adding up the QALYs for each follow-up period (0-2 weeks, 2-4 weeks, 4-6 weeks etc.) assuming a linear increase in QALY within each period.

Cost measures

Resource use was assessed using cost questionnaires administered at baseline and at 2, 4 and 6 weeks, and 3, 6, 9, 12 months. Since this study adopted a social perspective, both direct and indirect costs were included. Direct costs included costs of the intervention, primary healthcare use, secondary healthcare use, and the use of medication. Intervention costs were estimated using hospital accounting records, while all other healthcare utilization was valued according to the Dutch guidelines and medication use using prices of the Dutch Health Care Institute[94]. Costs of the interventions include the time of the operating room used, the costs of the medications used during the surgery and for microdiscectomy also the cost for one overnight hospital stay. Indirect costs consisted of absenteeism, presenteeism, unpaid productivity, and informal care costs. Absenteeism was assessed by asking patients to report their number of sick days and valuing them using the friction cost method (friction period=12 weeks) with wages adjusted for gender[94]. Presenteeism (i.e., reduced productivity at work) was assessed using the WHO-HPQ and valued using the same gender-specific wages. Unpaid productivity losses (i.e., losses due to being unable to perform unpaid activities, such as volunteer work) and informal care (i.e., care by family and friends) were valued using a recommended Dutch shadow price (15 euros). All costs were converted to euros (2019) using consumer price indices. Discounting of costs was not necessary.

Confounding variables

Based on the literature, clinical experience, and consensus among the project team, the following potential confounders were identified[95]: age, gender, smoking status, BMI, employment status, duration of complaints, morphological location of disk herniation, Four-Dimensional Symptom Questionnaire, and treatment preferences[86].

Statistical analyses

A cost-effectiveness analysis and a cost-utility analysis were conducted. In the cost-effectiveness analysis, total costs were related to improvement of leg pain during 12-month follow-up. In the cost-utility analysis, total costs were related to QALYs gained during follow-up. The primary analysis was conducted according to the intention-to-treat approach. All missing data were imputed using Multivariate Imputation by Chained Equations[96]. The imputation was stratified by treatment group to account for association of the treatment group with missingness[97]. To deal with the association between being part of the learning curve group and the missingness of data, data from learning curve patients were excluded before imputing data for the main analysis and five sensitivity analyses. Predictive Mean Matching was used to create ten complete datasets. Disaggregate cost differences were analyzed using linear regression models, both adjusted and unadjusted for confounders. Differences in total costs and effects between treatment groups were obtained from a system of Seemingly Unrelated Regressions that accounted for the potential correlation between costs and effects[98]. These total cost and effect differences were adjusted for baseline and confounders. Incremental cost-effectiveness ratios (ICER) were calculated by dividing incremental costs by incremental effects. Uncertainty surrounding ICERs and cost differences were estimated by bias corrected and accelerated bootstrapping with 5,000 repetitions.

Uncertainty was presented using cost-effectiveness planes and cost-effectiveness acceptability curves[99,100]. Results were pooled over the imputed datasets using Rubin's rules[101]. Analyses were performed in R statistical programming language, version 3.6.1.

Sensitivity analyses

To assess the robustness of the results, six sensitivity analyses were performed for both effect measures. First, a crude analysis was run (unadjusted for potential confounders). Second, only complete cases were used. Third, two scenarios of PTED intervention costs were considered. In the high-cost scenario, the cost of PTED was €5,000/patient, i.e., €500 more than in the main analysis. In the low-cost scenario, the cost of PTED and OM were equal, i.e., €4,095/patient. Fourth, productivity losses were measured according to the human capital approach. Fifth, the healthcare perspective was adopted. Sixth, learning curve patients were included. Except for the high- and low-cost scenario`s, all sensitivity analyses were planned a priori.

Patient involvement

Prior to the start of the PTED-study, the proposed study design and study procedures were presented to the relevant physician organizations, members of the Dutch Health Insurance board and members of the patient organization *"de Wervelkolom"* (translated: the Spine). Based on the input of these organizations on aspects such as feasibility, patient friendliness and patient safety, the study design would be updated if necessary. Furthermore, the organizations such as the patient organization were invited to be part of the half-yearly board meetings during which recruitment, implementation and results of the study were discussed.

RESULTS

Patients

Between February 2016 and April 2019, 711 patients were assessed for eligibility. Of them, 613 met the inclusion criteria and agreed to participate. The trial was finalized before reaching the estimated sample size of 682 participants, because the inclusion term of the study was reached. These patients were randomized to PTED (n=304) or open microdiscectomy (n=309). In the PTED group, 125 patients were considered learning curve patients and were excluded from the primary analysis. The final study sample counted 488 patients and consisted of 179 and 309 patients in the PTED and open microdiscectomy group, respectively. Patient characteristics were similar in both groups (Table 1 of chapter 7). All follow-up questionnaires were completed by 313 patients, whereas 49 patients in the PTED group and 126 in the microdiscectomy group missed at least one questionnaire. In total, 16% of follow-up data was missing. Participants with complete and incomplete data differed in terms of gender, employment status, treatment preference, depression, anxiety, duration of symptoms, probability of second surgery and baseline utility. All these variables were included in the imputation model.

Clinical outcomes

Statistically significant differences in leg pain and QALYs were found. In comparison to the microdiscectomy group, patients in the PTED group experienced a 6.9 larger VAS score reduction in leg pain (95%CI: 1.3 to 12.6) and gained 0.040 more QALYs (95%CI: 0.007 to 0.074) at 12 months follow-up. Of the patients in the PTED-group 94.2% could be discharged on the day of surgery compared to 5.6% in the microdiscectomy group. The rate of repeated surgery within one year was 5.3% in the PTED-group vs. 5.6% in the microdiscectomy group.

Costs

Surgery costs were higher for PTED than for open microdiscectomy, i.e., €4,500/patient versus €4,095/patient. All other disaggregate costs were lower for PTED than for microdiscectomy. The differences in primary healthcare, informal care, absenteeism, and presenteeism costs were statistically significant. Total societal costs were significantly lower for PTED than for open microdiscectomy by €2,787 (95%CI: -4,401 to -1,181). Total healthcare costs were lower for PTED than for open microdiscectomy as well, but the difference was not statistically significant. Presenteeism and absenteeism were the biggest cost drivers (Table 2).

Cost-effectiveness

At 12 months, PTED was found to be a cost-effective and even a dominant treatment strategy over open microdiscectomy for leg pain and QALYs, i.e., PTED was on average both less costly and more effective than microdiscectomy (Table 3). Cost-effectiveness-planes show that the probability of PTED being dominant over microdiscectomy in about 99.4% for leg pain and 99.2% for QALYs (i.e., the proportion of pairs located in the south-east quadrant; Figure 1a, 1c). In line with these findings, both cost-effectiveness acceptability curves show that the probability of PTED being cost-effective compared with open microdiscectomy was 99.4% for leg pain and 99.2% for QALYs, for all willingness-to-pay thresholds (Figure 1b, 1d).

Table 2: Mean cost (in euros) per patient receiving PTED and microdiscectomy (OM) and mean cost differences between groups during follow-up

Cost category	PTED n=179, mean (SEM)	OM n=309, mean (SEM)	Cost difference, crude mean (95%CI)	Cost difference, adjusted mean (95%CI)
Direct costs				
Surgery	4500	4095	405	405
Primary care	632 (77)	918 (78)	-287 (-476 to -67)	-307 (-497 to -102)
Secondary care	725 (186)	1061 (222)	-336 (-948 to 140)	-245 (-773 to 243)
Medication	8 (2)	38 (23)	-30 (-93 to -11)	-11 (-26 to 0)
Indirect costs				
Informal care	172 (43)	334 (63)	-162 (-306 to -28)	-152 (-283 to -18)
Absenteeism	4774 (389)	5820 (361)	-1047 (-2050 to -14)	-924 (-1808 to -37)
Presenteeism	3183 (396)	3738 (435)	-555 (-1629 to 503)	-1007 (-1757 to -313)
Unpaid productivity loss	1097 (220)	1629 (180)	-532 (-1019 to 65)	-518 (-1011 to 61)
Total healthcare costs	**5865 (215)**	**6112 (248)**	**-248 (-901 to 316)**	**-138 (-711 to 415)**
Total societal costs	**15090 (719)**	**17633 (700)**	**-2543 (-4380 to -686)**	**-2787 (-4401 to -1181)**

Please note that the difference in total societal costs of this table slightly differs from that of Table 3. This is given by the fact that in the current table, linear regression was used for estimating cost differences, whereas for Table 3 a system of Seemingly Unrelated Regressions was used.

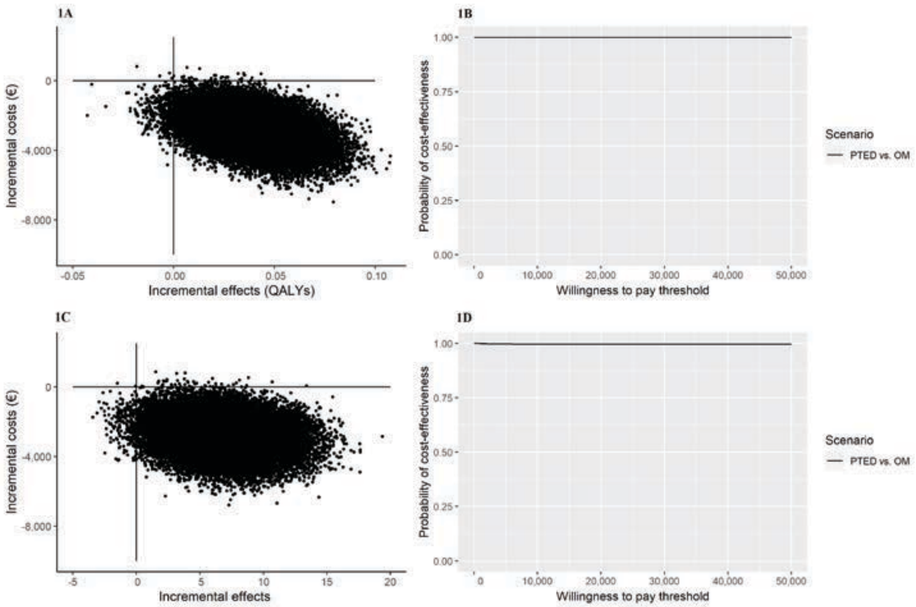


Figure 1: cost-effectiveness planes for QALYs and leg pain.

Sensitivity analyses

In all six sensitivity analyses (Table 3), PTED was found a cost-effective and oftentimes even a dominant treatment strategy, compared with microdiscectomy for both leg pain and QALYs. The dominance was least profound when the healthcare perspective was adopted in which no productivity losses were considered. In this sensitivity analysis, however, the probability of PTED being cost-effective compared with microdiscectomy remained high at reasonable values of willingness to pay for both outcomes.

Table 3: Differences in pooled mean costs and effects (95% Confidence intervals), incremental cost-effectiveness ratios, and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness planes for PTED compared to microdiscectomy

	Sample size		Outcome measure
	PTED	OM	
Main analysis - Imputed dataset	179	309	Leg pain (Range: 0 – 100, lower is better)
	179	309	QALYs (Range: 0 - 1)
SA1 - Unadjusted outcomes	179	309	Leg pain (Range: 0 – 100, lower is better)
	179	309	QALYs (Range: 0 - 1)
SA2 - Complete cases**	130	183	Leg pain (Range: 0 – 100, lower is better)
	130	183	QALYs (Range: 0 - 1)
SA3a - Cost of PTED = 5000	179	309	Leg pain (Range: 0 – 100, lower is better)
	179	309	QALYs (Range: 0 - 1)
SA3b - Cost of PTED = Cost of OM	179	309	Leg pain (Range: 0 – 100, lower is better)
	179	309	QALYs (Range: 0 - 1)
SA4 - Human capital approach	179	309	Leg pain (Range: 0 – 100, lower is better)
	179	309	QALYs (Range: 0 - 1)
SA5 - Healthcare perspective	179	309	Leg pain (Range: 0 – 100, lower is better)
	179	309	QALYs (Range: 0 - 1)
SA6 - Including learning curve patients	304	309	Leg pain (Range: 0 – 100, lower is better)
	304	309	QALYs (Range: 0 - 1)

* The difference measures improvement in leg pain symptoms, i.e., positive number signalizes a decrease in symptoms.
** Variable indicating preference for treatment was left out because it was constant in some of the bootstrapped samples

ΔC (95% CI)	ΔE (95% CI)	ICER	Distribution CE-plane (%)			
€	Points	€/point	NE	SE	SW	NW
-2786 (-4399 to -1181)	6.9* (1.3 to 12.6)	-402 Dominant	0.1	99.4	0.5	0.0
-2825 (-4400 to -1222)	0.040 (0.007 to 0.074)	-70235 Dominant	0.1	99.2	0.7	0.0
-2543 (-4380 to -686)	8.2* (2.5 to 13.9)	-310 Dominant	0.6	99.2	0.1	0.0
-2543 (-4380 to -686)	0.052 (0.016 to 0.088)	-48496 Dominant	0.6	99.2	0.2	0.0
-2083 (-3991 to -234)	7.8* (1.5 to 14.0)	-267 Dominant	1.5	98.0	0.5	0.0
-2133 (-4029 to -280)	0.031 (-0.008 to 0.070)	-68014 Dominant	1.0	93.3	5.4	0.3
-2260 (-3876 to -650)	6.9* (1.3 to 12.6)	-326 Dominant	0.6	98.9	0.5	0.0
-2300 (-3916 to -693)	0.040 (0.007 to 0.074)	-57167 Dominant	0.5	98.8	0.7	0.0
-3212 (-4824 to -1610)	6.9* (1.3 to 12.6)	-464 Dominant	0.0	99.5	0.5	0.0
-3251 (-4863 to -1651)	0.040 (0.007 to 0.074)	-80820 Dominant	0.0	99.3	0.7	0.0
-4111 (-6384 to -1919)	6.9* (1.3 to 12.5)	-594 Dominant	0.0	99.5	0.5	0.0
-4179 (-6466 to -1983)	0.040 (0.007 to 0.074)	-103256 Dominant	0.0	99.3	0.7	0.0
-144 (-724 to 406)	6.9* (1.3 to 12.6)	-21 Dominant	30.3	69.3	0.2	0.3
-152 (-731 to 398)	0.040 (0.007 to 0.074)	-3773 Dominant	29.2	70.1	0.3	0.5
-2573 (-3995 to -1192)	5.4 (0.7 to 10.1)	-476 Dominant	0.0	98.9	1.0	0.0
-2602 (-4028 to -1226)	0.040 (0.012 to 0.068)	-65097 Dominant	0 .0	99.7	0.3	0.0

DISCUSSION

Results of this study suggest that PTED is cost-effective compared with open microdiscectomy for patients with a lumbar disk herniation from the societal perspective within the first year of surgery. That is, PTED was found to be dominant (i.e., more effective, and less costly) compared with open microdiscectomy for leg pain and QALYs. Cost-effectiveness-planes indicated that the probability of PTED being dominant over open microdiscectomy was 99.4% for leg pain and 99.2% for QALYs. Sensitivity analyses confirmed the results were robust to the handling of measured confounding, the applied method for handling missing data, the unit price of PTED, the applied method for valuing productivity losses, and the applied perspective.

Comparison with other studies

Other randomized controlled trials assessing the cost-effectiveness of PTED compared with open microdiscectomy, or another surgical technique for patients with lumbar disk herniation, are lacking. A recent non-randomized study assessed the cost-effectiveness of microdiscectomy compared to three different endoscopic techniques, one of which was PTED[102]. They showed that both (direct and indirect) costs and QALYs gained were in favor of endoscopic surgery, which is in line with our findings. The previous study, however, was limited by its non-randomized and retrospective design and was conducted from a healthcare perspective only.

Strengths and limitations

Strengths of this study are its high response rate, its large sample size, its design as a randomized controlled trial, and its low number of missing values and lost to follow-up. Moreover, a wide range of sensitivity analyses was performed to determine the robustness of the results. All these attributes support the validity of the findings observed in this study. We also consider it a strength that a covenant was signed prior to commencement of the study by the researchers, the participating clinics, the Dutch spine patient association, the Dutch association of orthopedic surgeons, the Dutch association of neurosurgeons, and the Dutch spine society. Amongst others, the covenant included commitment to conduct the study as described in the study protocol, and to monitoring, communication, and implementation. The main limitation of the study was that we failed in recruiting the desired number of 682 patients (382 without learning curve). Recruitment was slower than expected, mainly because only four of the six clinics that had expressed an intention to participate included patients for this trial. Furthermore, some potential participants decided to undergo PTED in a private clinic at their own cost, because they did not accept the 50% chance of getting randomized to open microdiscectomy. However, the final number of 179 (instead of 191) participants randomized to PTED seems sufficient for a precise estimate of the difference in effect between PTED and open microdiscectomy, which is underscored by the relatively narrow confidence intervals around the cost and effect estimates. Furthermore, the sensitivity analysis that included the patients of the learning curve (total 304 patients in the PTED-group) did not alter the results. Another limitation is the follow-up period of 12 months. Even though this is customary in trials investigating surgery for sciatica, long-term follow-up of the PTED-study may clarify long-term cost-effectiveness.

Implications

The findings of the PTED-study are expected to have implications, both for patients at an individual level as for society. At an individual level it has been shown that PTED is non-inferior to open microdiscectomy in the treatment of leg pain and that PTED has more favourable patient-reported outcomes such as less low back pain, less functional disability due to low back pain and a higher health-related quality of life at 12 months after surgery[92]. These differences in outcomes between PTED and microdiscectomy, however, were relatively small. Nonetheless, PTED requires no general anaesthesia, is performed as an outpatient procedure, has less intraoperative blood loss, leaves a smaller scar and does not require the back muscles to be removed from their insertion during surgery. By inducing less surgical trauma to the lumbar spine, PTED facilitates patients to mobilize earlier but also to return earlier to daily activities such as sport and work. The earlier resumption of daily activities is underlined by current finding that absenteeism, presenteeism, and unpaid productivity costs were lower among patients receiving PTED compared with those receiving microdiscectomy. These findings warrant implementation of PTED as a treatment alternative to treat sciatica, not only for older patients who may be less suitable for receiving general anesthesia, but also for younger active patients.

Aside from these clinical implications, there are also financial implications. When the PTED-study started, microdiscectomy was included in the Dutch basic health insurance package and consequently reimbursed for all patients, but PTED was not. The Dutch Ministry of Health had classified PTED as an important, new, and experimental technique to examine and decided that PTED would be conditionally admitted to the Dutch basic health insurance package for patients participating in this study. Based on the results, the Dutch Ministry of Health made the decision to include PTED in the basic health insurance package with a reimbursement rate like microdiscectomy. As the actual reimbursement rate in the Netherlands is lower than the rate calculated in the primary analysis of this study, and as the health care market process will possibly lead to PTED becoming cheaper as it will be performed more frequently, it is to be expected that PTED will even be more likely to be cost-effective than the primary analysis suggests.

Even though PTED is now reimbursed in the Netherlands, internationally, multiple health insurances still don't reimburse endoscopic techniques with the argument that these techniques have not been proven effective and should be considered experimental. This study suggests that this argument might need to be reconsidered. Challenges for the implementation of PTED are to ensure that it will be used for the right indication and that spine surgeons that are willing to start using PTED, get an adequate training and that the patients' safety is ensured during the learning curve by close monitoring of the results.

CONCLUSION

Results suggest that PTED is less costly and more effective and therefore cost-effective compared with microdiscectomy for patients with lumbar disk herniation from the societal perspective. Therefore, PTED deserves to be included in the treatment armamentarium of sciatica.

8.2

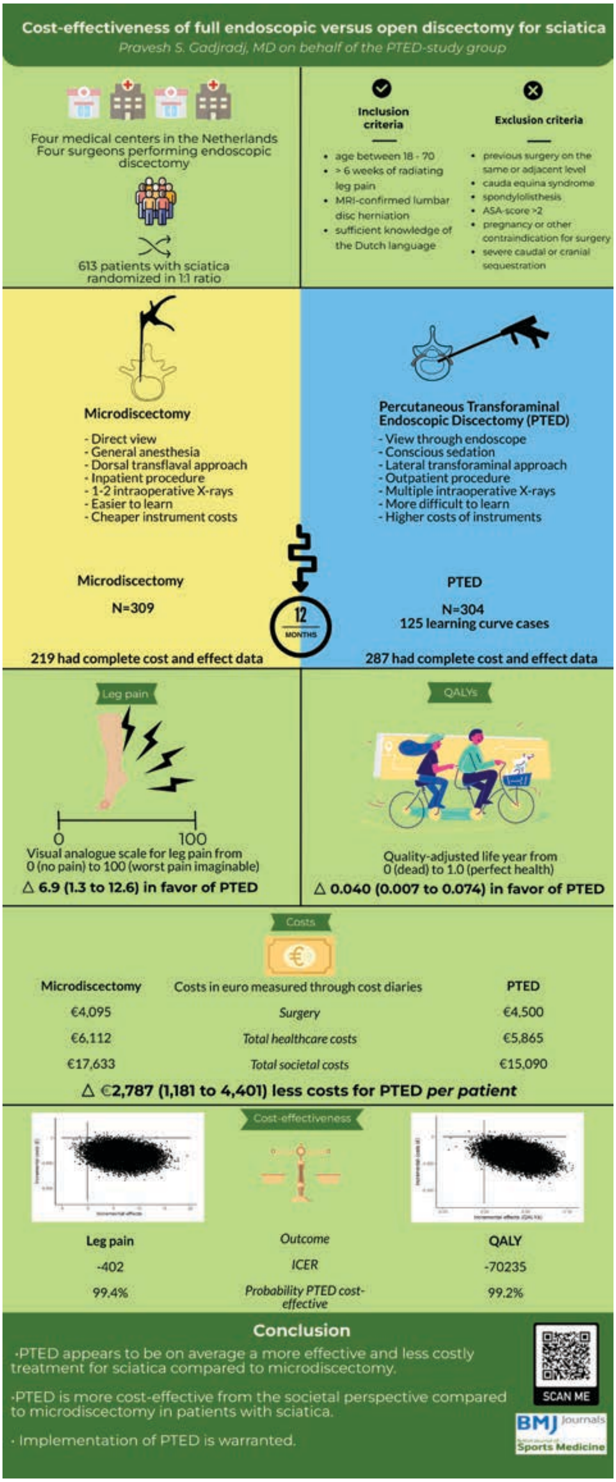
Chapter

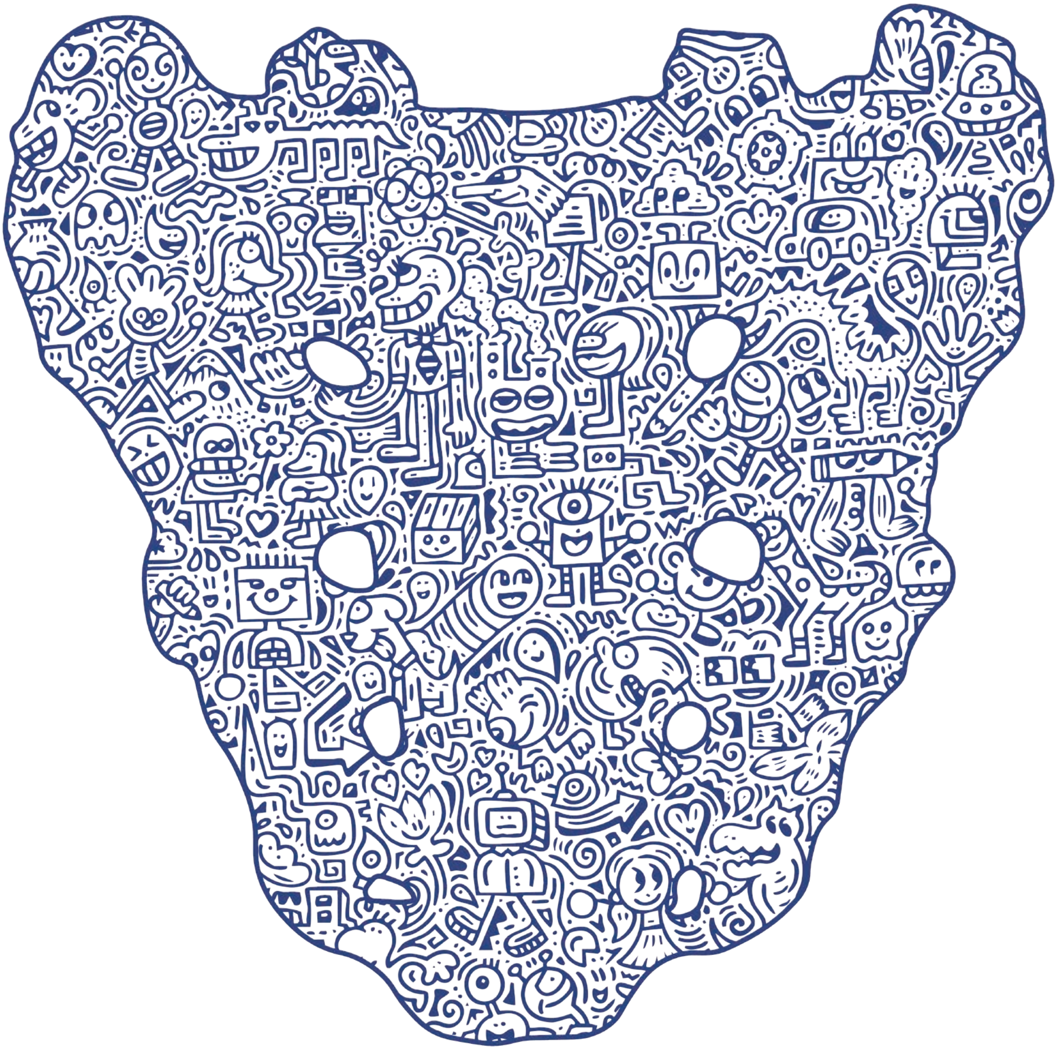
ENDOSCOPIC VS OPEN DISCECTOMY FOR SCIATICA

Infographic

Pravesh S. Gadjradj

Br J Sports Med. 2022 May 18:bjsports-2022-105766.


Cost-effectiveness of full endoscopic versus open discectomy for sciatica
Pravesh S. Gadjradj, MD on behalf of the PTED-study group
Four medical centers in the Netherlands
Four surgeons performing endoscopic discectomy
613 patients with sciatica randomized in 1:1 ratio
Inclusion criteria
• age between 18 - 70
• > 6 weeks of radiating leg pain
• MRI-confirmed lumbar disc herniation
• sufficient knowledge of the Dutch language
Exclusion criteria
• previous surgery on the same or adjacent level
• cauda equina syndrome
• spondylolisthesis
• ASA-score >2
• pregnancy or other contraindication for surgery
• severe caudal or cranial sequestration
Microdiscectomy
- Direct view
- General anesthesia
- Dorsal transflaval approach
- Inpatient procedure
- 1-2 intraoperative X-rays
- Easier to learn
- Cheaper instrument costs
Percutaneous Transforaminal Endoscopic Discectomy (PTED)
- View through endoscope
- Conscious sedation
- Lateral transforaminal approach
- Outpatient procedure
- Multiple intraoperative X-rays
- More difficult to learn
- Higher costs of instruments
Microdiscectomy
N=309
12 MONTHS
PTED
N=304
125 learning curve cases
219 had complete cost and effect data
287 had complete cost and effect data
Leg pain
0
100
Visual analogue scale for leg pain from 0 (no pain) to 100 (worst pain imaginable)
△ 6.9 (1.3 to 12.6) in favor of PTED
QALYs
Quality-adjusted life year from 0 (dead) to 1.0 (perfect health)
△ 0.040 (0.007 to 0.074) in favor of PTED
Costs
Microdiscectomy
Costs in euro measured through cost diaries
PTED
€4,095
Surgery
€4,500
€6,112
Total healthcare costs
€5,865
€17,633
Total societal costs
€15,090
△ €2,787 (1,181 to 4,401) less costs for PTED per patient
Cost-effectiveness
Leg pain
Outcome
QALY
-402
ICER
-70235
99.4%
Probability PTED cost-effective
99.2%
Conclusion
·PTED appears to be on average a more effective and less costly treatment for sciatica compared to microdiscectomy.
·PTED is more cost-effective from the societal perspective compared to microdiscectomy in patients with sciatica.
· Implementation of PTED is warranted.
SCAN ME
BMJ Journals
Sports Medicine



9

Chapter

GENERAL DISCUSSION
BJSM PhD-ACADEMY AWARD

Pravesh S. Gadjradj

Br J Sports Med. 2022 May 19:bjsports-2022-105434
Spine (Phila Pa 1976). 2022 Sep 15;47(18):E591-E594

SUMMARY OF THE MOST IMPORTANT FINDINGS

What did I do?

The main aim of my PhD-project was to provide high-quality evidence regarding the effectiveness and cost-effectiveness of PTED compared to open microdiscectomy in patients with sciatica caused by LDH.

Why did I do it?

Sciatica is common health care problem and leads to high costs both at the individual as at the societal level. The current standard surgical procedure to treat sciatica caused by lumbar disk herniation, is microdiscectomy[6,47]. Microdiscectomy is a relatively common procedure during which the disk herniation can be removed safely through a posterior approach. A relatively new, surgical procedure is PTED during which the disk herniation is removed through a smaller incision at the lateral side from the spine[14]. Aside from the difference in incision size, PTED is performed under local anesthesia, allowing outpatient surgery and does not require detachment of the back muscles. PTED, however, seems to be more challenging to be performed and requires patients to be exposed to a higher dose of radiation due to use of intraoperative fluoroscopy. Preliminary results of PTED were promising, but the consensus in the literature was that there was moderate quality of evidence suggesting no differences in leg pain reduction or functional status between PTED and microdiscectomy[19,66]. Furthermore, as the past had shown that innovative, less-invasive techniques appeared to have no merits over conventional techniques, PTED faced skepticism from the professional organizations[13]. Consequently, PTED was not reimbursed in the Netherlands. This led to disappointment among both patients and surgeons. In order to determine whether PTED should be included in the healthcare system, the PTED-study was initiated, which was funded by The Netherlands Organization for Health Research and Development[67].

How did I do it?

From 2016 to 2019, a randomized controlled non-inferiority trial was conducted at four centers in the Netherlands. Patients with at least 6 weeks of radiating leg pain due to an MRI-confirmed lumbar disk herniation were eligible for inclusion[67,103]. Patients were randomized between PTED and microdiscectomy and were followed for 12 months after surgery. The primary outcome was leg pain as measured on a VAS ranging from 0 to 100. The non-inferiority margin was set at 5, meaning that if patients that were randomized to PTED would have a difference in VAS of less than 5 compared to patients randomized to microdiscectomy, PTED would be deemed to be non-inferior. Consequently, it was decided in an agreement between the Dutch Health Care Institute and the research team that PTED would become reimbursed care if it would be non-inferior. Other outcomes of the PTED-study were costs, functional status, back pain, quality of life and self-reported recovery and satisfaction with treatment.

What did I find?

In total, 613 patients were included in the trial, of which 304 were randomized to PTED and 309 to microdiscectomy. Twelve months after surgery, patients of the PTED-arm had statistically significant less leg pain, less back pain, a better functional status, a higher quality of life and higher rates of self-received recovery and satisfaction with treatment[92]. Furthermore, patients of the PTED-arm had less intraoperative blood loss, less complications, a shorter length of hospital stay, less analgesics use and a similar rate of recurrent disk herniation. These differences in patient-reported outcomes, however, were small and questionable whether they fulfill established minimal clinically important difference thresholds. Given the PTED-arm had slightly better clinical outcomes, the economic evaluation would determine cost-effectiveness. The economic evaluation demonstrated that aside from the direct costs for the surgery (including primary care, medication), all other indirect costs (informal care, absenteeism and presenteeism) were lower in the PTED-arm[88]. Overall, the probability of PTED being cost-effective compared to microdiscectomy in leg pain reduction, was 99.4% regardless of the willingness-to-pay.

What is the most important clinical impact of this thesis?

The most important clinical impact is that PTED is now part of the Dutch healthcare system, meaning that the PTED technique is among those procedures that is financially fully covered. We hope that these findings will help resolve reimbursement issues with endoscopic procedure abroad. Furthermore, as we showed dominance of PTED in our economic evaluation, we expect that widespread implementation of PTED to treat sciatica will lead to less societal costs.

DISCUSSION OF INDIVIDUAL CHAPTERS

How do surgeons worldwide treat sciatica?

The results of the survey as conducted in chapter 2, showed that unilateral transflaval discectomy was the standard procedure to surgically treat LDH by most of the surgeons. Only around a fifth of the surgeons offered full-endoscopic techniques. PELD was expected to result in the lowest back pain compared to other techniques, but a higher rate of recurrent disk herniation. Due to further implementation of PTED, the number of surgeons that can perform PTED should be increased in order to make PTED more accessible to patients. Furthermore, the expectations for a lower intensity of low back pain after PELD seem to be proven, even if the differences in back pain intensity as shown in the PTED-study are small. A follow-up survey, several years after publication of the PTED-study could show if PELD would be more widely implemented and if expectations on clinical merits were altered.

What are the clinical outcomes of PTED for sciatica?

The results of the prospective case series presented in chapter 3, show that PTED is safe and effective and has a low rate of reoperations 1-year after surgery in experienced hands. These results would become a benchmark of the results obtained from the RCT. Interestingly, the results of the RCT regarding complications showed even less complications than the prospective case series, as no clinical dural tears or (transient) motor weakness occurred in the PTED-arm. Furthermore, the rate of repeated surgery at 1-year in the case series, appears similar to the reoperation rate of the trial. An explanation for these slightly improved results in the PTED-study may be that even after a learning curve of 166 cases, the more frequent performance of PTED as during the PTED-study, leads to better outcomes.

What is the evidence of PTED as a treatment for sciatica caused by lumbar disk herniation?

As chapter 4 shows, the literature up to April 2020 showed there is moderate quality evidence suggesting no difference in leg pain or functional status at intermediate and long-term follow-up between PTED and microdiscectomy in the treatment of sciatica. Therefore, the conduction of the PTED-study was warranted. Between the conduction of the literature review (April 2020) and publication of the PTED-study (February 2022), no RCTs have been performed regarding this subject. Therefore, table 1 was constructed based on the data of table 3 of chapter 4 to assess if the level of evidence was impacted by the results of the PTED-study. As shown in table 1, the level of evidence of five out of six of the clinical outcome domains were improved to a high level of evidence.

What are surgeons' preferences for lumbar disk surgery?

Chapter 5 shows the results of the DCE among surgeons and showed that the risk of complications was most important when a surgical technique is offered to treat sciatica, while the risk of recurrent disk herniation and effectiveness are also important factors. Results of the PTED study showed that PTED is to be preferred among these surgeons as the rate of complications was lower, the risk of recurrent disk herniation was similar, and effectiveness was slightly more favorable in the PTED-arm compared to the microdiscectomy-arm.

What are patients' preferences for lumbar disk surgery?

The results of the DCE conducted among patients (chapter 6). The effect on leg pain is the most important factor for patients in deciding to undergo surgery for sciatica. The potential out-of-pocket costs and wait time followed. Effectiveness on leg pain was slightly higher in the PTED-arm of the PTED-study. Furthermore, as PTED was reimbursed during the PTED-study and has become part of the Dutch Health Care Insurance package. Therefore, out-of-pocket costs would not be an issue anymore for Dutch patients. Wait time tended to be shorter among patients undergoing PTED as it was mostly performed in private clinics before the PTED-study. However, as this study has shown the benefits of PTED and as the out-of-pockets costs have been removed, the wait time to undergo PTED in the Netherlands, increased. Due to increase in demand, training of additional surgeons in PTED is warranted.

STRENGTHS AND WEAKNESSES OF THE PTED-STUDY

The biggest strength is the inclusion of multiple centers across the Netherlands. Three surgeons were trained in performing PTED and their first 50 cases were regarded as a learning curve. Therefore, the PTED-study has incorporated an "additional implementation study". This demonstrated that PTED can also be performed safely during the learning curve phase, but with an additional risk of recurrent disk herniation of approximately 5%. Additionally, the broad inclusion criteria and the type of disk herniations at all lumbar levels of the spine, reflect common practice. In the literature, there seems to be a preference to treat LDHs at the L5-S1 level from an interlaminar approach due to possible conflict of the iliac crest with the working trajectory [41]. In those cases, often interlaminar PELD is used to remove the LDH. In a similar fashion, lateral (foraminal) LDHs are less popularly treated by a conventional transflaval approach. In the study demographics of the PTED-study, all these disk herniations appear to be evenly distributed and reflect real world demographics; therefore, the results of this study should be considered generalizable. Another strength is the low level of attrition . At one year follow-up, 87% of the patients had data available. Furthermore, due to the use of an online questionnaire system, all patients with data available, had complete data available. Finally, the large sample size ensures robustness of the results. All sensitivity analyses performed, did not impact the results and therefore the conclusion.

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An important limitation is that it was not possible to blind patients, surgeons, or outcome assessors for the allocated treatment. This was due to the fundamental differences between both procedures, such as scar size, scar position, type of anesthesia and moment of discharge. Further research may control for the scar size, type of anesthesia used or the moment of discharge, but such kind of studies would not reflect practice and therefore, have poor generalizability. Given patients were not 'blinded' to the intervention, it is important to consider patient preference. In our study, 81% of the included patients preferred PTED, which was not unexpected. This preference rate might have influenced the self-reported PROMs, which we attempted to adjust for. Results adjusted for patient preferences, however, did not differ from unadjusted results.

Lastly, we were not able to include the estimated 682 patients as determined by our power calculation (including learning curve cases or 382 without the learning curve). The impact of this, however, was thought to be limited because of the low rate of missing data and the small Cis of the study results had small CIs demonstrating a high degree of precision.

CURRENT STATUS AND FUTURE PERSPECTIVE

Based upon the results of the PTED-study, PTED became part of the Dutch health care package and is consequently reimbursed for all patients that have an indication for PTED and undergo surgery by an experienced surgeon. Scientifically, the results of the PTED-study have also led to an increase in the level of evidence for PTED as presented in chapter 4. Table 1 shows that except for functional outcomes at the intermediate term, all other outcomes were upgraded in evidence level and now have a high-quality of evidence level. It is to be expected that PTED and other endoscopic techniques to treat pathology of the spine, will be applied more frequently in the Netherlands and internationally. This will also go accompanied with challenges. One of these challenges is patient safety. The results of the PTED-study show that adoption of PTED is safe by surgeons naïve to the procedure. However, these surgeons were spine-dedicated with already substantial experience in spine surgery. Furthermore, these surgeons received a training program consisting of a cadaver workshop and supervision during the first cases. The results of the learning curve underline safety but patient that were learning curve cases had a higher rate of reoperations.

Further studies should explore implementation strategies for PTED. Should every spine dedicated surgeon perform endoscopic spine surgery? Or should only a few centers provide endoscopic spine surgery in high volumes? Another challenge in patient care may be the extrapolation of the results to other pathology or minimally invasive spinal surgery techniques. This thesis only evaluated full-endoscopic transforaminal spine surgery to treat a symptomatic LDH. Therefore, no conclusions can be drawn for the application of other PELD techniques such as the full-endoscopic interlaminar surgery, or for other pathologies such as lumbar spinal stenosis, cervical radiculopathy or even a recurrent disk herniation. Further studies could explore these fields. Finally, this thesis only reported the outcomes of PTED at 1-year follow-up. Two-year and 5-year results have also been collected and will address concerns on the long-term (cost) effectiveness.

CONCLUSION

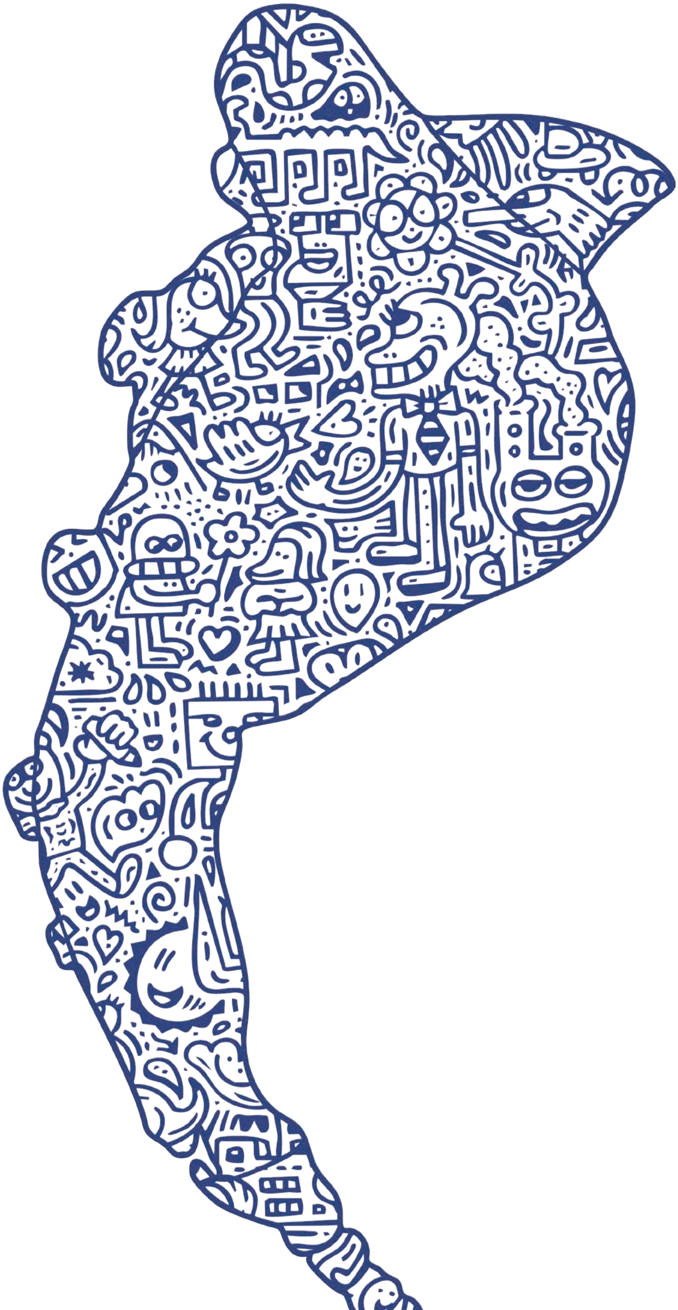
The current thesis was aimed at assessing whether PTED is non-inferior to microdiscectomy in leg pain reduction. Prior to this thesis, only a minority of the spine surgeons worldwide performed full-endoscopic surgery to treat sciatica. PTED appeared to be safe and effective, but it was questionable whether the technique resulted in differences in leg pain or functional status at short, intermediate, and long-term follow-up between PTED and microdiscectomy. Conjoint analyses showed that surgeons prefer to offer a procedure that has a low complication risk, had a low rate of recurrent disk herniation, and had a high effectiveness on leg pain. Patients preferred a procedure with a high effectiveness on leg pain, no out-of-pocket costs and short wait time. Results of the PTED-study showed that PTED is non-inferior to microdiscectomy in leg pain reduction and has a lower complication rate. Furthermore, PTED was dominant over microdiscectomy in the economic evaluation, independent of the levels chosen for willingness-to-pay.

In short, there is high-quality evidence of no difference in leg pain reduction at the intermediate or long-term between PTED and microdiscectomy. There is moderate evidence for a better functional outcome at the intermediate-term and high-quality evidence for a better functional outcome at long-term after PTED. Finally, there is high-quality evidence of no difference in back pain at the intermediate and long-term between both procedures. It is uncertain if PTED will result in a paradigm shift. This thesis may be regarded as a first step towards that end.

Table 1: GRADE-assessment of the evidence including the results of the PTED-study. Bold indicates a change compared to the GRADE-assessment as presented in chapter 4.

Quality assessment					
	No. of studies	Design	Limitations	Inconsistency	Indirectness
Leg pain (intermediate term)	**5**	RCT	**No** serious limitations	No serious inconsistency	No serious indirectness
Leg pain (long term)	**4**	RCT	No serious limitations	No serious inconsistency	No serious indirectness
Functional outcome (intermediate term)	**4**	RCT	Serious limitations	No serious inconsistency	No serious indirectness
Functional outcome (long term)	**3**	RCT	No serious limitations	No serious inconsistency	No serious indirectness
Back pain (intermediate term)	**2**	RCT	No serious limitations	**No** serious inconsistency	No serious indirectness
Back pain (long term)	**2**	RCT	No serious limitations	**No** serious inconsistency	No serious indirectness

		No. of patients		Effect (95% CI)	Quality of evidence
Imprecision	**Other**	**PTED**	**OM**		
No serious imprecision	No serious considerations	**498**	**570**	**SMD 0.80 (-1.69 to 0.08)**	**High**
No serious imprecision	No serious considerations	**268**	**356**	**SMD -0.07 (-0.43 to 0.28)**	**High**
No serious imprecision	No serious considerations	**472**	**546**	**SMD -0.17 (-0.29 to -0.04)**	Moderate
No serious imprecision	No serious considerations	**237**	**326**	**SMD -0.24 (-0.45 to -0.04)**	**High**
No serious imprecision	No serious considerations	**224**	**295**	**SMD -0.23 (-0.53 to 0.07)**	**High**
No serious imprecision	No serious considerations	**219**	**306**	**SMD -0.20 (-0.52 to 0.11)**	**High**



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Chapter

SUMMARY

ENGLISH SUMMARY

Sciatica has a high prevalence in the general population and therefore causes a high burden on the individual patient and on society. Most cases of sciatica caused by lumbar disk herniation resolve with conservative treatment. For the cases that don't resolve with conservative treatment or cases with progression of neurological deficits, surgery is indicated. Conventional transflaval microdiscectomy is regarded to be the standard procedure to treat sciatica. Endoscopic techniques were introduced as a less invasive treatment option but uncertainties on its effectiveness remain. The main objective of this thesis was to assess whether PTED was non-inferior to conventional microdiscectomy in the treatment of sciatica.

This thesis can be divided in three parts after the general introduction in **chapter 1**.

Part I of this thesis, focusses on the contemporary management of sciatica and the application of PTED before the PTED-study.

Chapter 2 presents the results of a survey on the management of sciatica that received responses from 817 surgeons from 89 countries. Among these surgeons, the severity of pain and/or disability and failure of conservative therapy were the most important indications for surgery. Surgery would be considered after a period of 1 to 2 months of conservative therapy. Unilateral transflaval discectomy was the procedure of choice among the majority and was expected to be the most effective technique with the lowest complication risk. Around 20% of the surgeons offered full-endoscopic surgery. Surgeons performing more lumbar discectomies, with more clinical experience and those located in Asia, were more likely to offer minimally invasive surgical techniques.

Chapter 3 reports on the clinical results of a prospective case series of 166 patients that underwent PTED from 2009 to 2012. This was the period that PTED was covered by Dutch Insurance. All cases were performed by a single surgeon who had already overcame the learning curve. These preliminary results showed that PTED is a safe and effective treatment to treat sciatica during the first year of follow-up. There were four complications of which three were transient and most patients had a good experience with the local anesthesia used during surgery. At 1-year, patients had a statistically significant and clinically relevant decrease in disability and leg pain, and furthermore, most patients would recommend PTED in similar cases or would undergo it again under similar circumstances. The recurrence rate was 6.6% at 1 year.

Chapter 4 is a systematic review and meta-analysis of the published literature up to April 2020 on the effectiveness of PTED compared to microdiscectomy. Multiple online databases were systematically searched for randomized controlled trials and prospective studies comparing PTED with microdiscectomy in clinical outcomes. Eventually 14 studies were included, with 9 of them being (quasi)randomized. Summarizing the evidence shows that there is moderate quality evidence suggesting no difference in leg pain or functional status at intermediate and long-term follow-up between PTED and microdiscectomy. High quality, robust studies reporting on clinical outcomes and cost-effectiveness on the long term are lacking.

Part II focusses on the preferences of surgeons and patients to surgically treat sciatica. To objectively measure the preferences, two discrete choice experiments were designed and conducted. In a discrete choice experiment, surgical treatments were presented as neutral treatment options with different characteristics (e.g., leg pain reduction) varying in level (e.g., 80% vs. 90%).

Chapter 5 presents the results of the discrete choice experiment conducted among 641 surgeons treating sciatica. Overall, the risk of complications was the most important characteristic in opting-in or -out for surgery. This was followed by the risk of recurrent disk herniation, the effectiveness on leg pain, the duration of postoperative back pain and the length of recovery period. Preference heterogeneity was partially explained by the tenure of the surgeon. Surgeons were willing to trade-off 57.8% of effectiveness on leg pain to offer a treatment that has a 1% complication risk instead of 10%.

Chapter 6 reports the results of the discrete choice experiment conducted among 287 patients that had either undergone surgery or were on the waiting list for surgery. Except for the size of the scar, all attributes tested had a significant influence on the overall preferences of patients. These attributes were (ranged from highest to lowest importance): effect on leg pain, out-of-pocket costs, wait time, need for general anesthesia, need for hospitalization and the recovery period. Willingness-to-pay was the highest for effectiveness on leg pain, with patients willing to pay €3,133 for a treatment that has a 90% effectiveness instead of 70%.

Part III focusses on the first results of the PTED-study, a multicenter randomized controlled, non-inferiority trial that included patients with sciatica caused by a lumbar disk herniation and an indication for surgery. The main objective of the PTED-study was to assess the non-inferiority in effectiveness and the cost-effectiveness of PTED compared to microdiscectomy with as primary outcome the visual analogue scale of leg pain at 12 months ranging from 0 to 100. The non-inferiority margin was set at 5.

Patients were randomized in a 1:1 ratio between PTED and microdiscectomy. Other outcomes measured were functionality, back pain, quality of life, health-related quality of life, self-perceived recovery, satisfaction with treatment, utilities, costs, and scar-related outcomes among others. Measurements were conducted at baseline and 1 day, 2, 4 and 6 weeks, and 3, 6, 9, and 12 months postoperative.

Chapter 7 reports the 1-year clinical data of the PTED-study. At 12 months, patients that were randomized to PTED had statistically significant less leg pain compared to patients that were randomized to microdiscectomy. Blood loss was less, duration of hospitalization was shorter, and timing of postoperative mobilization was earlier in the PTED-group compared to the microdiscectomy-group. Secondary patient-reported outcomes such as functionality, back pain, health-related quality of life and self-perceived recovery, were similarly in favor of PTED as the primary outcome. The reoperation rate was similar. Therefore, it is to be concluded that PTED is non-inferior to microdiscectomy in leg pain reduction. Even though, PTED resulted in more favorable results, these differences may not reach clinical relevance. PTED can be considered as an effective alternative to microdiscectomy in treating sciatica.

Chapter 8 presents the results of the economic evaluation of the PTED-study at 1-year follow-up. Statistically significant differences in leg pain and quality adjusted life years were found in favor of PTED at 12-months follow-up. Surgery costs were higher for PTED than for microdiscectomy. All other disaggregate costs as well as total societal costs were lower for PTED than for microdiscectomy. Cost-effectiveness acceptability curves indicated that the probability of PTED being less costly and more effective (i.e., dominant) compared with microdiscectomy was 99.4% for leg pain and 99.2% for QALYs. Therefore, it is to be concluded that PTED is more cost-effective from the societal perspective compared with microdiscectomy for patients with sciatica.

Chapter 9 describes a secondary analysis of the PTED-study concerning scar-related outcomes of PTED compared to those of microdiscectomy. Mean scar size was shorter after PTED compared to microdiscectomy. There were 3 wound infections in the microdiscectomy group, compared to none in the PTED-group. At 12 months, patients that underwent PTED had a higher score on the body image scale, and the cosmesis scale compared to patients that underwent microdiscectomy. Furthermore, patients scored their scar esthetic better in the PTED-group compared to the microdiscectomy-group. Based on these results, it can be concluded that both PTED and microdiscectomy have favorable scar-related outcomes. However, from an esthetic point of view, PTED seems to be the preferred technique to treat lumbar disk herniation.

CONCLUSION

To reduce the invasiveness of conventional microdiscectomy, minimally invasive procedures such as PTED have been developed and are becoming increasingly popular in practice. The objective of the current thesis was to assess non-inferiority of PTED compared to microdiscectomy, which is shown by the results of the PTED-study. PTED resulted in more favorable results for patient self-reported leg pain, back pain, functional status, quality of life and recovery. These differences were small, however, and may not reach clinical relevance. As both procedures seem to have comparable results, the economic evaluation is of importance as a potential tiebreaker. As PTED is on average less costly and more effective, albeit with small effect size, PTED is dominant over microdiscectomy in terms of cost-effectiveness. At this point it is uncertain if PTED will become the new gold standard, but the results of this thesis have shown that PTED is an important alternative to microdiscectomy that warrants implementation.

NEDERLANDSE SAMENVATTING

Het lumbosacraal radiculair syndroom (LSRS) heeft een hoge prevalentie in de algemene bevolking en veroorzaakt daardoor een hoge belasting op zowel de individuele patiënt als op de maatschappij. De meeste gevallen van LSRS veroorzaakt door een lumbale hernia, herstellen met een conservatieve behandeling. Voor de gevallen die niet herstellen met een conservatieve behandeling, of die gevallen waarbij er sprake is van progressieve neurologische uitval, is chirurgie gëindiceerd. De chirurgische techniek die beschouwd wordt als de gouden standaard, is de conventionele transflavale (micro)discectomie. Alhoewel endoscopische technieken werden geïntroduceerd als een minder invasieve behandelingsoptie om een hernia te behandelen, is er veel onzekerheid omtrent de effectiviteit van deze technieken. Het hoofddoel van dit proefschrift was om te onderzoeken of de volledig percutane transforaminale endoscopische discectomie (PTED) non-inferior (“ niet slechter”) is aan microdiscectomie in de behandeling van het LSRS.

Dit proefschrift kan in drie delen verdeeld worden na de algemene inleiding in **Hoofdstuk 1**.

Deel I van dit proefschrift richt zich op de hedendaagse behandeling van het LSRS en de toepassing van PTED vóór de uitvoer van de PTED-studie.

Hoofdstuk 2 beschrijft de resultaten van een enquête over de behandeling van het LSRS. De enquête werd ingevuld door 817 chirurgen afkomstig uit 89 landen. Deze chirurgen vonden de hevigheid van de pijn en/of de functionele beperkingen, en het falen van een conservatieve behandeling, de belangrijkste indicaties voor een operatieve ingreep. Chirurgie werd het vaakst overwogen na een periode van 1 tot 2 maanden waarbij een conservatieve behadeling werd gegeven. De unilaterale transflavale discectomie werd beschouwd als de standaard ingreep onder de meeste chirurgen. Deze techniek werd verwacht het meest effectief te zijn met tevens ook de laagste complicatie risico. Rond één op de vijf chirurgen biedt volledig endoscopische chirurgie aan. Chirurgen die frequenter minimaal invasieve chirurgie aanbieden, hebben vaak grotere volume aantallen, meer klinische ervaring en praktiseren veelal in Azië.

Hoofdstuk 3 beschrijft de klinische uitkomsten van een prospectieve *case series* bestaande uit 166 patiënten die PTED ondergingen gedurende 2009 to en met 2012, toen PTED nog vergoed werd in Nederland. De operaties werden uitgevoerd door één chirurg die al een zekere leercurve had doorlopen. Deze eerste uitkomsten lieten zien dat PTED een veilige en effectieve behandeling is om het LSRS te behandelen, gemeten tot 1 jaar de na operatie. Er waren vier complicaties waarvan er drie spontaan herstelden. Daarnaast hadden de meeste patiënten een goede ervaring onder sedatie. Eén jaar na de ingreep hadden patiënten een statistisch significant én een klinisch relevante verbetering van de functionele berperkingen en van de beenpijn. Daarnaast zou een grote meerderheid PTED aanbevelen in vergelijkbare gevallen of het opnieuw ondergaan onder gelijke omstandigheden. Na 1 jaar had 6.6% van de patiënten een heroperatie ondergaan.

Hoofdstuk 4 betreft een systematische review en meta-analyse van studies gepubliceerd tot en met April 2020 omtrent de effectiviteit van PTED vergeleken met microdiscectomie. Meerdere online databases werden systematisch doorzocht om prospectieve studies te identificeren die PTED met microdiscectomie vergeleken. Uiteindelijk werden 14 studies geïncludeerd waarvan 9 enige vorm van randomisatie hadden. Samenvattend, is er matig bewijs dat er geen verschil in beenpijn reductie of functionele status is tussen PTED een microdiscectomie op de middellange en lange termijn. Studies van hoge methodologische kwaliteit en voldoende steekproefgrootte zijn nodig, om uitspraken te kunnen doen over de klinische uitkomsten en kosteneffectiveit van deze procedures op de lange termijn.

Deel II van dit proefschrift concentreert zich op voorkeuren; voorkeuren van chirurgen en voorkeuren van patiënten om het LSRS chirurgisch te behandelen. Om dit objectief te meten werden twee discrete keuze-experimenten ontwikkeld en uitgevoerd. In zo`n discrete keuze-experiment werden chirurgische behandelingen gepresenteerd als neutrale opties omschreven door verschillende karakteristieken (zoals beenpijnreductie) met alternerende niveaus (bijvoorbeeld 80% vs. 90%).

Hoofdstuk 5 rapporteert de resultaten van de discrete keuze-experiment onder 641 chirurgen die het LSRS behandelen. Gemiddeld genomen, was het risico op complicaties de belangrijkste karakteristiek om voor een ingreep te kiezen. Hierna volgden het risico op een recidief, effectiviteit op beenpijn, duur van postoperatieve rugpijn en de herstelperiode. Heterogeniteit in voorkeuren werd deels verklaard door de klinische ervaring van de chirurg. Chirurgen waren bereid om 57.8% in beenpijn reductie in te willen ruilen om een ingreep aan te bieden met een complicatie risico van 1% ten opzichte van een ingreep met een complicatie risico van 10%.

Hoofdstuk 6 beschrijft de resultaten van de discrete keuze-experiment die onder 287 patiënten is uitgevoerd. Deze patiënten hadden óf een operatie in het verleden ondergaan, óf stonden op de wachtlijst voor een operatie. Behoudens de grootte van het litteken, waren alle onderzochte karakteristieken statistisch significant van invloed op de keuzes. Deze karakteristieken waren, van meest naar minst belangrijk; effectiviteit op beenpijn, eigen kosten, wachttijd, noodzaak voor algehele anesthesie, noodzaak voor opname en de herstelperiode. Patiënten waren bereid het meest te betalen voor beenpijnreductie, namelijk €3,133 voor een ingreep met 90% effectiviteit in plaats van 70%.

Deel III bevat de eerste resultaten van de PTED-studie: een multicenter gerandomiseerde *non-inferiority* studie waarbij patiënten met het LSRS door een lumbale hernia en een indicatie voor een operatie, werden geïncludeerd. Het hoofddoel van de PTED-studie was om de *non-inferiority* in effectiviteit en kosteneffectiviteit van PTED in vergelijking met microdiscectomie te onderzoeken, met als primaire uitkomstmaat de visueel analoge schaal voor beenpijn welke van 0 tot 100 loopt. De *non-inferiority* marge was 5. Patiënten werden geloot voor PTED of microdiscectomie in een 1:1 ratio. Andere gemeten uitkomsten waren functionaliteit, rugpijn, kwaliteit van leven, algemene gezondheidstoestand, zelf waargenomen herstel, tevredenheid met de behandeling, QALYs, kosten en littekenuitkomsten. Metingen werden verricht vóór de operatie en 1 dag, 2, 4, 6 weken, 3, 6, 9, en 12 maanden na de operatie.

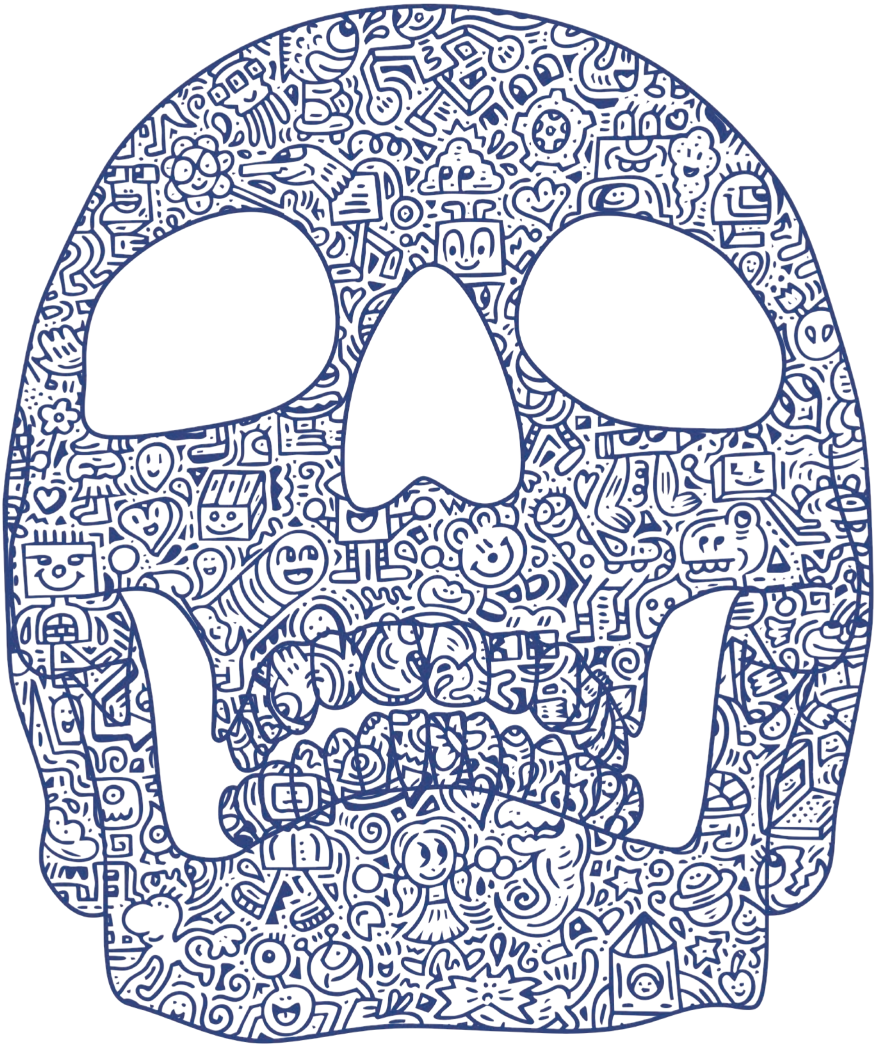
Hoofdstuk 7 beschrijft de 1-jaar resultaten van de PTED-studie. Twaalf maanden na de ingreep, hadden patiënten uit de PTED-groep statistisch significant minder beenpijn in vergelijking met patiënten uit de microdiscectomie-groep. Het bloedverlies was minder, patiënten lagen korter in het ziekenhuis en konden eerder mobiliseren, ten opzichte van de microdiscectomie-groep. De secundaire uitkomstmaten, zoals functionaliteit, rugpijn, kwaliteit van leven, algemene gezondheidstoestand, zelf waargenomen herstel en tevredenheid met de behandeling, waren net zoals de beenpijnreductie, gunstiger in de PTED-groep. De percentages heroperaties na een jaar waren vergelijkbaar. Ook al waren deze resultaten statistisch gezien gunstiger in de PTED-groep, toch lijken ze geen klinische relevantie te bereiken. Desalniettemin kan PTED als een effectieve alternatief voor de behandeling van het LSRS worden beschouwd.

Hoofdstuk 8 rapporteert de resultaten van de economische evaluatie van de PTED-studie gedurende de eerste jaar na operatie. Er waren statistisch significante verschillen ten voordele van PTED voor zowel beenpijn als QALYs, 12 maanden na de operatie. Kosten voor de operatie lagen hoger in de PTED-groep dan in de microdiscectomie groep. Alle andere kosten waren minder voor de PTED-groep. Kosteneffectiviteits curves lieten zien dat de kans dat PTED goedkoper en tevens effectiever dan microdiscectomie (oftewel dominant) is, bijna 100% waren voor beenpijn en QALYs. Derhalve toont dit onderzoek aan dat PTED kosteneffectiever is dan microdiscectomy in de behandeling van LSRS.

Hoofdstuk 9 beschrijft de secundaire analyse van de PTED-studie betreffende de litteken uitkomsten. Gemiddelde lengte van het litteken was korter na PTED in vergelijking met microdiscectomie. Er waren drie wondinfecties na microdiscectomie in vergelijking met geen na PTED. Twaalf maanden na de operatie hadden patiënten na een PTED een betere scores voor lichaamsbeeld en lichaamsesthetiek dan patiënten na een microdiscectomie. Daarnaast werd de esthetiek van het litteken beter gescoord na een PTED. Op grond van deze resultaten kan geconcludeerd worden dat beide ingrepen goede litteken-gerelateerde uitkomsten hebben. Echter, vanuit een esthetisch oogpunt, heeft PTED de voorkeur om het LSRS te behandelen.

CONCLUSIE

Minimaal invasieve ingrepen zoals PTED, werden geïntroduceerd als minder invasief vergeleken met microdiscectomie. Deze ingrepen werden steeds populairder onder zowel chirurgen als patiënten. Het doel van dit proefschrift was om de non-inferiority in beenpijnreductie van PTED aan te tonen ten opzichte van microdiscectomie. De PTED-studie heeft dit aangetoond. PTED resulteerde in gunstigere uitkomsten aangaande beenpijn rugpijn, functionaliteit, kwaliteit van leven en herstel. Deze verschillen tussen PTED en microdiscectomie waren echter klein en lijken niet klinisch relevant te zijn. Aangezien beide procedures vergelijkbare klinische uitkomsten hebben, is een economische evaluatie des te meer van belang om meerwaarde van PTED aan te kunnen tonen. Vanuit een sociale perspectief gezien blijkt PTED gemiddeld minder kosten met zich mee te dragen dan microdiscectomie. Aangezien PTED ook enigzins gunstere resultaten heeft, is PTED dominant ten opzichte van microdiscectomie in termen van kosteneffectiviteit. Op dit moment is het niet te voorspellen of PTED de nieuwe gouden standaard wordt om een lumbale hernia te behandelen. De resultaten gepresenteerd in dit proefschrift, echter, hebben aangetoond dat PTED een belangrijk alternatief is om een lumbale hernia te behandelen en ook derhalve implementatie verdient.



A

Appendix

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PhD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Pravesh Shankar Gadjradj

Promotor(s): Prof.dr. F.J. Huygen
Supervisor: dr. B.S. Harhangi

	Year	Workload (Hours/ECTS)
1. PhD training		
General courses		
CPO-course	2016	0.3
BROK-cursus	2021	1.5
Specific courses		
MSc in Epidemiology (Amsterdam UMC)	2023	30.0
Epidemiological research: basic principles	2020	4.0
Principles of epidemiological data-analysis	2020	3.0
Regression techniques	2020	5.0
Clinimetrics	2021	3.0
Epidemiological research in depth	2021	4.0
Missing data: consequences and solutions	2022	2.0
Casual inference and propensity scoring methods	2022	2.0
Multilevel models and longitudinal data-analysis	2022	4.0
Clinical prediction models and machine learning	2022	2.0
Epidemiological Consultation	2023	3.0
MSc in Medicine (Erasmus MC)	2018	180.0
Seminars and workshops		
Max-More Spine Workshop, Rotterdam, the Netherlands	2019	1.0
AOSpine: Managing complications, New Orleans, LA, USA	2021	1.0
AOSpine: Endoscopy Course, Davos, Switzerland	2021	2.0
Medtronic Spine Tech Summit, Austin, TX, USA	2022	1.0
NYCMISS, New York, NY, USA	2022	1.0

	Year	Workload (Hours/ECTS)
Presentations		
Global Spine Congress, Milan, Italy	2017	2.0
North American Spine Society, Boston, MA, USA	2021	2.0
EANS, Hamburg, Germany	2021	1.0
SMISS, Las Vegas, NV, USA	2021	2.0
NYCMISS, New York, NY, USA	2021	1.0
Back and Neck Pain Forum, Sidney, Australia	2021	1.0
Joint Section Spine Summit, Las Vegas, NV, USA	2022	2.0
AANS, Philadelphia, PA, USA	2022	2.0
AOSpine Fellow, Banff, Canada	2022	1.0
North American Spine Society, Chicago, IL, USA	2022	1.0
ISSLS, Boston, USA	2022	1.0
ISASS, Nassau, Bahamas	2022	1.0
EANS, Serbia	2022	1.0
Joint Section Spine Summit, Miami, FL, USA	2023	2.0
Global Spine Congress, Prague, Czech Republic	2023	3.0
(Inter)national conferences		
Global Neurosurgery Summit, New York, NY, U.S.A.	2021	1.0
Other		
Grants and awards		
Baltimore Grant	2016	
Expedition van Beek	2016	
MRace	2017	
SMISS Young Surgeon Grant	2021	
Charlie Kuntz Award	2022	
Sanford Larson Award	2022	
BJSM PhD-academy Award	2022	
ISASS Young Surgeon Grant	2022	
ISSLS Travel Grant	2022	
NASS Value Award	2022	
EANS Best Spine Abstract	2022	
Dutch Spine Society Annual Award	2022	
Journal of Spine Surgery Reviewer of the Month	2022	
Fessler Award for Best Research	2023	
Forbes 30-under-30	2023	
Elsevier Magazine 30-under-30	2023	

	Year	Workload (Hours/ECTS)
2. Teaching		
Lecturing		
Max-More Spine Workshop	2019	1.0
Supervising Master's theses		
Timothy Chin-See-Chong 4th year medical student (Erasmus MC)	2016	1.0
Mamta Jalimsing, 3rd year student Health Care Management (EUR)	2016	1.0
Busra Kayapa, 4th year medical student (Erasmus MC)	2018	1.0
Laura Willemsz, nurse practioner in training (Erasmus MC)	2020	1.0
Istifari Voigt, 4th year medical student (Erasmus MC)	2021	1.0
Savina Booi, 6th year medical student (LUMC)	2021	1.0
Najillah Damee, 6th year medical student (Erasmus MC)	2021	1.0
Other		
Education Commission MSc Epidemiology (Amsterdam UMC)	2020-22	2.0

CURRICULUM VITÆ

Pravesh Shankar Gadjradj was born on April 22nd 1993, in Rotterdam. After graduating cum laude from secondary school (Gymnasium, Melanchthon Schiebroek), he started to study Medicine at the Erasmus University Rotterdam. Because his grades belonged to the top 5% of his cohort, he was invited to participate in the Erasmus MC Honours Class. This sparked his interest in medical research. In 2014 he started doing research at the Department of Neurosurgery under supervision of dr. B.S. Harhangi. In 2016, before starting his clinical rotations, he was able to continue this research project as a PhD-candidate for 6 months. In 2023, he completed both his post-initial MSc-program in Epidemiology at the Vu University Amsterdam as well as a postdoctoral fellowship in Spine Surgery at Weill Cornell Medicine/New York Presbytarian Hospital. Throughout the years he received numerous awards for his research on endoscopic spine surgery, including the Charlie Kuntz award of the CNS, the Sanford Larson award of the AANS, the NASS Value award in 2022, and the Fessler award of the CNS/AANS joint spine section. In 2023, he was selected as one of the members of the Forbes 30-under-30 list.

A

PUBLICATIONS OF THIS THESIS

Chapter 2
Gadjradj PS, Arts MP, van Tulder MW, Rietdijk WJR, Peul WC, Harhangi BS. Management of Symptomatic Lumbar Disk Herniation: An International Perspective. **Spine (Phila Pa 1976).** 2017 Dec 1;42(23):1826-1834. doi: 10.1097/BRS.0000000000002294. PMID: 28632645.
Impact factor (2017): 2.8
Citations (October 2025): 78

Chapter 3
Gadjradj PS, van Tulder MW, Dirven CM, Peul WC, Harhangi BS. Clinical outcomes after percutaneous transforaminal endoscopic discectomy for lumbar disc herniation: a prospective case series. **Neurosurg Focus.** 2016 Feb;40(2):E3. doi: 10.3171/2015.10. FOCUS15484. PMID: 26828884.
Impact factor (2016): 3.1
Citations (October 2025): 134

Chapter 4
Gadjradj PS, Harhangi BS, Amelink J, van Susante J, Kamper S, van Tulder M, Peul WC, Vleggeert-Lankamp C, Rubinstein SM. Percutaneous Transforaminal Endoscopic Discectomy Versus Open Microdiscectomy for Lumbar Disc Herniation: A Systematic Review and Meta-analysis. **Spine (Phila Pa 1976).** 2021 Apr 15;46(8):538-549. doi: 10.1097/BRS.0000000000003843. PMID: 33290374.
Impact factor (2022): 3.2
Citations (October 2025): 166

Chapter 5
Gadjradj PS, Harhangi BS, van Tulder MW, Peul WC, de Bekker-Grob EW. Surgeons preference for lumbar disk surgery: a discrete choice experiment. **Eur Spine J.** 2022 Feb;31(2):380-388. doi: 10.1007/s00586-021-06838-9. Epub 2021 Apr 19. PMID: 33876280.
Impact factor (2022): 2.8
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Chapter 6
Gadjradj PS, Smeele NVR, de Jong M, Depauw PRAM, van Tulder MW, de Bekker-Grob EW, Harhangi BS. Patient preferences for treatment of lumbar disc herniation: a discrete choice experiment. **J Neurosurg Spine.** 2021 Nov 26:1-9. doi: 10.3171/2021.8.SPINE21995. Epub ahead of print. PMID: 34826818.
Impact factor (2022): 3.5
Citations (October 2025): 18

Chapter 7

Gadjradj PS, Rubinstein SM, Peul WC, Depauw PR, Vleggeert-Lankamp CL, van Susante JL, de Boer MR, van Tulder MW, Harhangi BS. Full endoscopic versus open discectomy for sciatica: randomised controlled non-inferiority trial. **BMJ.** 2022 Feb 21;376:e065846. doi: 10.1136/bmj-2021-065846. PMID: 35190388.
Impact factor (2022): 105.7
Citations (October 2025): 128

Chapter 8.1

Gadjradj PS, Broulikova HM, van Dongen JM, Rubinstein SM, Depauw PR, Vleggeert C, Peul WC, van Susante JL, van Tulder MW, Harhangi BS. Cost-effectiveness of full endoscopic versus open discectomy for sciatica. **Br J Sports Med.** 2022 Feb 20:bjsports-2021-104808. doi: 10.1136/bjsports-2021-104808. Epub ahead of print. PMID: 35185010.
Impact factor (2022): 18.4
Citations (October 2025): 58

Chapter 8.2

Gadjradj PS; PTED-study group. Infographic. Endoscopic versus open discectomy for sciatica?
Which is more cost-effective? **Br J Sports Med.** 2022 May 18:bjsports-2022-105766. doi: 10.1136/bjsports-2022-105766. Epub ahead of print. PMID: 35584887.
Impact factor (2022): 18.4
Citations (October 2025): 3

Chapter 9

Gadjradj PS. Full-endoscopic lumbar disc surgery: the new gold standard? (PhD Academy Award). **Br J Sports Med.** 2022 May 19:bjsports-2022-105434. doi: 10.1136/bjsports-2022-105434. Epub ahead of print. PMID: 35589376.
Impact factor (2022): 18.4
Citations (October 2025): 5

Gadjradj PS, Harhangi BS. Full-endoscopic Transforaminal Discectomy versus Open Microdiscectomy for Sciatica: Update of a Systematic Review and Meta-analysis. **Spine (Phila Pa 1976)**. Spine (Phila Pa 1976). 2022 Sep 15;47(18):E591-E594 doi: 10.1097/BRS.0000000000004421. Epub 2022 Jul 15. PMID: 35867477.
Impact factor (2022): 3.0
Citations (October 2025): 11

AKNOWLEDGEMENTS/DANKWOORD

Allereerst wil ik graag alle patiënten bedanken die aan de verschillende onderzoeken hebben meegedaan. Bedankt voor uw medewerking!

Hiernaast wil ik mijn promotieteam bedanken. Allereerst mijn promotor Prof.dr. Frank Huygen voor zijn steun en de mogelijkheid op de afdeling Pijngeneeskunde mijn proefschrift te verdedigen. Daarnaast wil ik Dr. B.S. Harhangi bedanken voor de begeleiding gedurende dit traject. Ten slotte wil ik de grote en kleine commissie bedanken voor de bereidheid mijn thesis te beoordelen: Prof.dr. D. Eygendaal, Prof. dr. C. Önur, Prof.dr. P. Willems, Prof.dr. H-A. Leroy, Prof.dr. M. A. Ikram, Prof.dr. K. M. Ikram en Prof.dr. C. Vleggeert-Lankamp.

Voorts wil ik alle mede-onderzoekers, sponsors, student-onderzoekers, research verpleegkundigen en firma's bedanken. Het zijn er te veel om op te noemen maar in het bijzonder wil ik het Park MC, Robert Boelen, Jaap Hoogland, Paul Depauw, Pieter Schutte, Michiel de Boer, Esther de Bekker-Grob, Nicholas Smeele, Kayoumars Azizpour, Mandy de Jong, Anita van Toor, Jacqueline van Putten, Yvette de Beer, Chantal Ritskes, Steffi van Beek en Esther Willemsen bedanken.

Dan mijn paranimfen; Judith de Rooij mijn *cervicale partner in crime*. Ook al zijn wij in alles totale tegenpolen van elkaar, toch staan onze neuzen altijd dezelfde kant op. Karan Gadjradj, dit proefschrift komt uit een totaal andere veld dan waar jij in zit, maar desalniettemin kon ik ook altijd op jouw steun rekenen.

और अंत में मैं पूरे ब्रह्मांड को धन्यवाद देना चाहता हूँ

LIST OF PUBLICATIONS

1. **Gadjradj PS**. Conducting reliable research: transparency, integrity and disclosing conflicts of interest. **J Spine Surg.** 2024 Jun 21;10(2):327-328.
2. **Gadjradj PS**, Fiani B, Sommer F, Ramirez RN, Harhangi BS. Expanding indications of full endoscopic spine surgery. **J Spine Surg.** 2023. doi: 10.21037/jss-23-65
3. **Gadjradj PS**, Cofano S, Sommer F, Bielecki M, Navarro-Ramirez R, de Rooij J. Letter to the Editor Concerning "Does Erector Spinae Plane Block Decrease Analgesia Requirements after Minimal-Invasive Posterior Transpedicular Stabilization in Patients with Vertebral Body Fracture?". **Global Spine J.** 2023 Mar 27:21925682231166903.
4. **Gadjradj PS**, Basilious M, Goldberg JL, Sommer F, Navarro-Ramirez R, Mykolajtchuk C, Ng AZ, Medary B, Hussain I, Härtl R. Decompression alone versus decompression with fusion in patients with lumbar spinal stenosis with degenerative spondylolisthesis: a systematic review and meta-analysis. **Eur Spine J**. 2023 Jan 6.
5. **Gadjradj PS**, Ullah K, Härtl R. Sciatica: predicting who would undergo surgery and who not. **J Spine Surg**. 2022 Dec;8(4):406-408.
6. **Gadjradj PS**, Sommer F, Navarro-Ramirez R, de Rooij J. Letter to the editor regarding, "Biportal Endoscopic versus Microscopic Discectomy for Lumbar Herniated Disc: A Randomized Controlled Trial" by Park et al. Concepts, analyses and interpretation of noninferiority randomized controlled trials. **Spine J.** 2022 Nov 15:S1529-9430(22)01009-9
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9. **Gadjradj PS**, Sommer F, Navarro-Ramirez R. Letter to the editor regarding "decompression alone versus decompression plus fusion for lumbar spinal stenosis with degenerative spondylolisthesis": when do we have enough evidence? **Ann Transl Med** 2022;10(19):1075
10. **Gadjradj PS,** Harhangi BS. Full-endoscopic Transforaminal Discectomy versus Open Microdiscectomy for Sciatica: Update of a Systematic Review and Meta-analysis. **Spine (Phila Pa 1976)**. 2022, July 15, spine-10.1097
11. **Gadjradj PS,** Sommer F. Letter to the Editor concerning "ProDisc-C versus anterior cervical discectomy and fusion for the surgical treatment of symptomatic cervical disc disease: two-year outcomes of Asian prospective randomized controlled multicentre study" by N. Kumar, et al. **Eur Spine J.** 2022 May 30.

12. **Gadjradj PS**, Depauw PR, Schutte PJ, Vreeling AW, Harhangi BS. Body Image and Cosmesis after Percutaneous Transforaminal Endoscopic Discectomy versus Conventional Open Microdiscectomy for Sciatica. **Global Spine J.** 2022 May 24:21925682221105271.
13. **Gadjradj PS.** Full-endoscopic lumbar disc surgery: the new gold standard? (PhD Academy Award). **Br J Sports Med.** 2022 May 19:bjsports-2022-105434.
14. **Gadjradj PS**; PTED-study group. Infographic. Endoscopic versus open discectomy for sciatica? Which is more cost-effective? **Br J Sports Med.** 2022 May 18:bjsports-2022-105766.
15. **Gadjradj PS**, Sommer F. Letter to the editor regarding a recent article "The MOTION Study" Putting a Mild Brake on the MOTION. **Pain Med**. 2022 May 14:pnac063.
16. **Gadjradj PS**, Rubinstein SM, Peul WC, Depauw PR, Vleggeert-Lankamp CL, Seiger A, van Susante JL, de Boer MR, van Tulder MW, Harhangi BS. Full endoscopic versus open discectomy for sciatica: randomised controlled non-inferiority trial. **BMJ**. 2022 Feb 21;376:e065846.
17. **Gadjradj PS,** Broulikova HM, van Dongen JM, Rubinstein SM, Depauw PR, Vleggeert C, Seiger A, Peul WC, van Susante JL, van Tulder MW, Harhangi BS. Cost-effectiveness of full endoscopic versus open discectomy for sciatica. **Br J Sports Med**. 2022 Feb 20:bjsports-2021-104808.
18. **Gadjradj PS**, Arjun Sharma JRJ, Harhangi BS. Quality of conscious sedation using dexmedetomidine during full-endoscopic transforaminal discectomy for sciatica: a prospective case series. **Acta Neurochir (Wien).** 2022 Jan 31.
19. **Gadjradj PS**, Chin-See-Chong TC, Donk D, Depauw PR, van Tulder MW, Harhangi BS. Cross-Cultural Adaptation and Psychometric Validation of the Dutch Version of the Core Outcome Measures Index for the Neck in Patients Undergoing Surgery for Degenerative Disease of the Cervical Spine. **Neurospine.** 2021 Dec;18(4):798-805.
20. **Gadjradj PS,** Smeele NVR, de Jong M, Depauw PRAM, van Tulder MW, de Bekker-Grob EW, Harhangi BS. Patient preferences for treatment of lumbar disc herniation: a discrete choice experiment. **J Neurosurg Spine.** 2021 Nov 26:1-9.
21. **Gadjradj PS,** Matawlie RH, Harhangi BS. Telemedicine use by neurosurgeons due to the COVID-19 related lockdown. **Brain and Spine.** Volume 1, 2021, 100851.
22. **Gadjradj PS,** Chalaki M, van Tulder MW, Harhangi BS. Cross-cultural adaptation and psychometric validation of the Dutch version of the Core Outcome Measures Index for the back (COMI -back) in patients undergoing surgery for degenerative disease of the lumbar spine. **Brain and Spine**. Volume 1, 2021, 100004.
23. **Gadjradj PS,** Harhangi BS. Percutaneous transforaminal endoscopic discectomy in a nine-year-old patient with sciatica: case report, technical note and overview of the literature. **Childs Nerv Syst.** 2021 Jul;37(7):2343-2346.

24. **Gadjradj PS**, Jalimsing M, Jalimsing S, Voigt I. Authorship in Oral and Maxillofacial Surgery. **J Maxillofac Oral Surg.** 2021 Jun;20(2):330-335.
25. **Gadjradj PS,** Harhangi BS, van Tulder MW, Peul WC, de Bekker-Grob EW. Surgeons preference for lumbar disk surgery: a discrete choice experiment. **Eur Spine J.** 2021 Apr 19
26. **Gadjradj PS**, Ghobrial JB, Booi SA, de Rooij JD, Harhangi BS. Mistreatment, discrimination and burn-out in Neurosurgery. **Clin Neurol Neurosurg.** 2021 Mar;202:106517.
27. **Gadjradj PS**, Harhangi BS, Amelink J, van Susante J, Kamper S, van Tulder MW, Peul WC, Vleggeert-Lankamp C, Rubinstein SM. Percutaneous Transforaminal Endoscopic Discectomy versus Open Microdiscectomy for Lumbar Disc Herniation: A Systematic Review and Meta-analysis. **Spine (Phila Pa 1976).** 2020.
28. **Gadjradj PS**, Ghobrial JB, Harhangi BS. Experiences of neurological surgeons with malpractice lawsuits. **Neurosurg Focus.** 2020;49(5):E3.
29. **Gadjradj PS**, Willemsz L, Spoor JK. Spontaneous externalization of a ventriculoperitoneal shunt tip through the navel. **Br J Neurosurg.** 2020:1-2.
30. **Gadjradj PS**, Matawlie RH, Harhangi BS. Letter to the Editor: The Use of Telemedicine by Neurosurgeons During the Covid Era: Preliminary Results of a Cross-Sectional Research. **World Neurosurg**. 2020;139:746-8.
31. **Gadjradj PS**, Matawlie RH, Harhangi BS. The neurosurgical curriculum: Which procedures are essential? **Interdisciplinary Neurosurgery** 21 (2020) 100723
32. **Gadjradj PS**, Matawlie RHS, Voigt I, Harhangi BS, Vleggeert-Lankamp C. Gender Differences Between Male and Female Neurosurgeons: Is There Equality for All? **World Neurosurg.** 2020;136:348-56.
33. **Gadjradj PS**, Ogenio K, Voigt I, Harhangi BS. Ergonomics and Related Physical Symptoms Among Neurosurgeons. **World Neurosurg**. 2020;134:e432-e41.
34. **Gadjradj PS**, Peul WC, Jalimsing M, Arjun Sharma JRJ, Verhemel A, Harhangi BS. Who should merit co-authorship? An analysis of honorary authorships in leading spine dedicated journals. **Spine J**. 2020;20(1):121-3.
35. **Gadjradj PS**, Spoor JKH, Eggink AJ, Wijnen R, Miller JL, Rosner M, Groves ML, DeKoninck PLJ, Harhangi BS, Baschat A, van Veelen ML, de Jong THR. Neurosurgeons' opinions on the prenatal management of myelomeningocele. **Neurosurg Focus.** 2019;47(4):E10.
36. **Gadjradj PS**, Harhangi BS. Safety Culture and Attitudes Among Spine Professionals: Results of an International Survey. **Global Spine J.** 2019;9(6):642-9.

37. **Gadjradj PS**, van Tulder MW, Vleggeert-Lankamp C, van Susante JL, Rubinstein SM, Peul WC, et al. Letter to the Editor Regarding "Percutaneous Endoscopic Lumbar Discectomy Versus Posterior Open Lumbar Microdiscectomy for the Treatment of Symptomatic Lumbar Disc Herniation: A Systemic Review and Meta-Analysis": A Critical Appraisal. **World Neurosurg.** 2019;122:715-7.
38. **Gadjradj PS**, Fezzazi RE, Meppelder CA, Rietdijk WJ, Matabadal NN, Verhemel A, Harhangi BS. Letter: Honorary Authorship in Neurosurgical Literature: A Cross-sectional Analysis. **Neurosurgery.** 2018;82(1):E25-E8.
39. **Gadjradj PS**. Lumbale herniaoperatie: endoscopisch of open? **Ned Tijdschr Geneeskd** 2018;162: D2640.
40. **Gadjradj PS**, Arts MP, van Tulder MW, Rietdijk WJR, Peul WC, Harhangi BS. Management of Symptomatic Lumbar Disk Herniation: An International Perspective. **Spine (Phila Pa 1976).** 2017;42(23):1826-34.
41. **Gadjradj PS**, Harhangi BS. Percutaneous Transforaminal Endoscopic Discectomy for Lumbar Disk Herniation. **Clin Spine Surg.** 2016;29(9):368-71.
42. **Gadjradj PS**, van Tulder MW, Dirven CM, Peul WC, Harhangi BS. Clinical outcomes after percutaneous transforaminal endoscopic discectomy for lumbar disc herniation: a prospective case series. **Neurosurg Focus.** 2016;40(2):E3.
43. de Rooij JD*, **Gadjradj PS*,** Huygen FJ, Luijsterburg PA, Harhangi BS. Management of Symptomatic Cervical Disk Herniation: A Survey Among Dutch Neurosurgeons. **Spine (Phila Pa 1976)**. 2017;42(5):311-7.
44. de Rooij JD*, **Gadjradj PS*,** Soria van Hoeve JS, Harhangi BS. Anterior cervical discectomy without fusion for a symptomatic cervical disk herniation. **Acta Neurochir (Wien).** 2017;159(7):1283-7.
45. Chin-See-Chong TC*, **Gadjradj PS*,** Boelen RJ, Harhangi BS. Current practice of cervical disc arthroplasty: a survey among 383 AOSpine International members. **Neurosurg Focus.** 2017;42(2):E8.
46. Sommer F, **Gadjradj PS**, Pippig T. Spinal injuries after ejection seat evacuation in fighter aircraft of the German Armed Forces between 1975 and 2021. **J Neurosurg Spine.** 2022 Oct 21:1-8.
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48. de Rooij JD, **Gadjradj PS,** Aukes H, Groeneweg G, Speksnijder CM, Huygen FJ. Long-Term Clinical Results of Percutaneous Cervical Nucleoplasty for Cervical Radicular Pain: A Retrospective Cohort Study. **J Pain Res.** 2022;15:1433-1441

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50. Arjun Sharma J, **Gadjradj PS**, Peul WC, van Tulder MW, Moojen WA, Harhangi BS, et al. SIZE study: study protocol of a multicentre, randomised controlled trial to compare the effectiveness of an interarcuair decompression versus extended decompression in patients with intermittent neurogenic claudication caused by lumbar spinal stenosis. **BMJ Open.** 2020;10(10):e036818.
51. Spoor JKH, **Gadjradj PS**, Eggink AJ, DeKoninck PLJ, Lutters B, Scheepe JR, van Meeteren J, de Laat PCJ, van Veelen ML, de Jong THR. Contemporary management and outcome of myelomeningocele: the Rotterdam experience. **Neurosurg Focus.** 2019;47(4):E3.
52. Chalaki M, **Gadjradj PS**, Harhangi BS. Minimally Invasive Surgery for Symptomatic Lumbar Disc Herniation, **Contemp Neurosurg** 2016 - Volume 38 - Issue 9
53. Depauw PR, **Gadjradj PS**, Soria van Hoeve JS, Harhangi BS. How I do it: percutaneous transforaminal endoscopic discectomy for lumbar disk herniation. **Acta Neurochir (Wien)**. 2018;160(12):2473-7.
54. de Rooij JD, **Gadjradj PS**, Soria van Hoeve JS, Huygen FJ, Aukes HA, Harhangi BS. Percutaneous Nucleoplasty for the Treatment of a Contained Cervical Disk Herniation. **Clin Spine Surg**. 2017;30(9):389-91.
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