Timing of surgery for sciatica

Peul, W.C.

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Wilco C. Peul

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Aan Erica, Olivier, Cylemarijne en Roderick

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INTRODUCTION
&
OUTLINE OF THE THESIS

"L'art de la médecine consiste à amusant alors que le patient cures de la nature."

-Voltaire-

"……Thou cold sciatica,
Cripple out senators, that their limbs may halt
As lamely as their manners….."

William Shakespeare 1564 Timon of Athens, Act IV. Scene I

Shakespeare permitted Timon of Athens to rage against false friends in high places and wish them to suffer from sciatica. Although the natural course of sciatica is said to be favorable, classical literature, myths and even the Bible refer to sciatica as a punishment or demon curse, which disables people by means of excruciating lower leg pain.

The literal translation of the Greek word 'sciatica' is hip pain[1], which leaves room for dispute about today's use of the word 'sciatica' in scientific communications. Undoubtedly "lumbosacral radicular syndrome" (LSRS) or sciatic neuralgia is a better description of the disease but it is not often used in peer reviewed manuscripts and thus in this thesis. Sciatica is defined as pain radiating from the low back or buttock into a lumbar or sacral dermatome. In addition to radiating leg pain patients may present with motor and sensory deficits and decreased tendon jerks or reflexes as a result of malfunction of the compressed spinal nerve, near its exit from the dural sac. Generally this area of the nerve is misnamed as the nerve root. Strictly speaking, the roots or radices have their origin proximal to the spinal cord or conus medullaris. Although literally incorrect, this thesis makes use of the term 'nerve root' to describe the former anatomical area of the nerve, to avoid inconsistencies with existing scientific publications. Compression of the spinal nerve root generates pain directly or indirectly by an inflammatory response. The most frequently cited cause of impingement of lumbar nerve roots is extruded or herniated disk material, which occupies the natural space under and beside the nerve root and displaces the nerve within the bony margins of the nerve root, which extends from the lateral recess to the intervertebral foramen. Through a weak spot in the annulus fibrosis, the fibrous outer ring of the intervertebral disk, the centrally located soft nucleus pulposis tissue leaks outward, which results in three successive degrees of disk herniation: local disk protrusion, disk extrusion and sequestrated nuclear fragments in the epidural space. A herniated disk most commonly occurs at one of the two lower disk levels of the lumbar spine. The intensity of pain and severity of neurological deficit vary and are not correlated with either site or size of the herniated disk. Sciatica results in loss of the ability to move freely and function normally at home and work or during leisure activities. In the vast majority of cases sciatica decreases in the course of two months[2,3].

Figure 1. "Just before crossing into the land, Jacob wrestles with an angel and defeats him. Jacob refuses to release the angel until the angel blesses him. The angel gives Jacob a new name—Yisrael—Israel, "the God fighter," "one who struggles with God." But in the struggle, Jacob is also hurt. Torah tells us that the angel wrenches Jacob's thigh. The Hebrew text says he tears Jacob's sciatic nerve, which we know runs all the way down the lower back (Genesis 32:25–29). Further, Torah says that Jacob was limping (Genesis 32:32)".

How to intervene in the natural course for the remaing minority of patients with persistent sciatica?

Before the advent of disk surgery in 1934[4;5], this problem was of great interest to physicians and scientists for many centuries.

It is generally believed that Hippocrates (460-370 BC) was the first to describe the treatment of sciatica[6]. He advocated traction as a beneficial method to relieve patients of their pain and loss of function (ref). However, when Egyptian, Etruscan, and Arabic manuscripts (1550 BC) were reviewed, earlier descriptions of the clinical phenomena of spinal disorders were encountered[7]. Furthermore the Bible describes Jacob as enduring sciatica after struggling with an angel in the desert (fig.1).

Whereas the emperor's physician Galen (129-200 A.D.)[8] is claimed to be the first pioneer of spinal research, Caelius Aurelianus, born in Algeria (400 A.D.), was the first author to describe sciatica[7]. He taught and practiced in Rome and described sciatica as a clinical syndrome with pain radiating to the buttocks and leg. "In advanced stages muscle wasting could occur". He associated the radiating complaints with lift-

Figure 2.

ing heavy objects and published his hypotheses in "De Morbis acutis et chronicis"[9] (figure 2).

Paulus of Aegina (625-690 A.D.) seems to be the first one to perform laminectomies when the posterior elements were fractured and pushed into the spinal cord or cauda equina[10]. The next known successful laminectomy was performed almost 12 centuries later! After the fall of Rome, during the Dark Ages, knowledge and many of the skills of this ancient era were lost or not described.

Just before the 16th century Sabuncuöglu (Turkish scientist and physician), who treated patients with medicine and heat cauterization, and described this therapy for non-refractory sciatica in "The Imperial Surgery"[11]; Turgut, 2007 2713 /id}. In the same century Andreas Vesalius (1514-1564) wrote and depicted his findings about human intervertebral disk spaces and the spinal column in "De humani Corporis Fabrica" (1543)[12] [13]. The second person, after Caelius Aurelianus, who discussed sciatica in depth as a clinical entity was Domenico Cotugno (1736-1822). His monograph "De ischiade nervosa commentarius"[14] described this radiating pain as a disease of the sciatic nerve. For at least a century sciatica was known as "Cotugno's disease"[15]. He (figure 3) did not relate the disease of the sciatic nerve to compression of the root in the spinal canal or to the plate drawings of disks by Vesalius. In the belief that the pain arose from the nerve itself, Cotugno probably was not aware of a possible relationship.

Figure 3.

"For it seems to be an acrid and irritating matter, which lying on the nerve, preys on the stamina, and gives rise to pain".

Domenico Cotugno 1764

Localization of neurological complaints or deficit and their anatomical correlation with the spinal cord and cauda equine was of no concern to scientists after Hippocrates. In the 18th century this problem was a primary concern for the first time when Giovanni Morgagni (1682-1771) described neural tissue compression caused by "tumors", which in fact were probably cases of Pott's disease[16]. Spinal surgery for this reason was not performed until 1829 when Alban G. Smith performed a laminectomy in the United States[17]. An anatomical relationship between sciatica and compression of nerve roots in the spinal canal was still not suspected by the scientific community, not even after the earliest report of posterior displacement of intervertebral disk material in 1806 by Kocher[18]. During post mortem investigations the latter scientist suspected the correlation between disk displacement at the spinal cord level and loss of function below this level.

Rudolf Virchow (1821-1902) described the traumatic rupture of an intervertebral disk in 1857[19] which was known thereafter as "Virchow's Tumor"[20]. A few year later in 1864 Ernest Lasègue (1816-1883) recognized the association between sciatica and low back pain and wrote about the physical signs of patients' neuritis[21-23]. However, while living in the same time period and scientifically interested in closely correlated pathology, the completely different scopes of the works of Ernest Lasègue and Rudolf Virchow prevented the recognition of one disease. It was at least a half a century later before this relationship was described.

In 1909 Fedor Krause described (figure 4) the surgical relief of sciatic pain[24]. Together with Oppenheim, he reported on the removal of an "enchondroma", which in retrospect can be regarded with certainty as a ruptured disk.

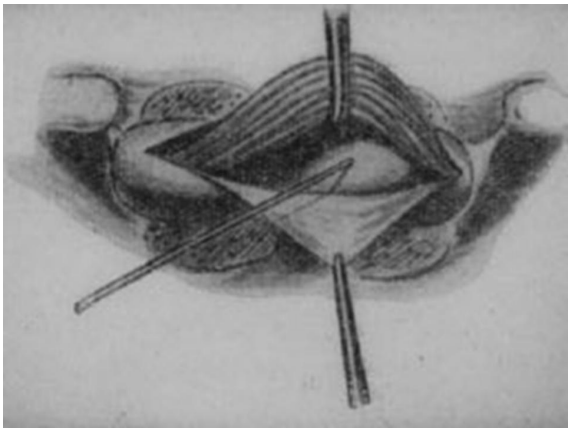

Figure 4. Surgical transdural approach of 'disk enchondroma' by Dr. Oppenheim as described by Fedor Krause, 1909. "He made a low lumbar midline incision and reflected the paravertebral muscles far laterally exposing the laminae with their spinous processes. The laminar arches were removed in one piece, after which the dura was opened longitudinally, nerve roots separated and again opening the dura but now the posterior dural sac covering the space-occupying lesion. This so-called enchondroma, a tumor of cartilaginous tissue had a close relationship with the lumbar disc and seemed to originate from it".

In the same year Taylor described an unilateral approach performed on a cadaver[25]. Joel Goldthwait (1911)[26] reported on a patient with recurrent sciatica who had been operated on by Harvey Cushing[27]. No lesion was found but they concluded that the pain originated from recurrent disk dislocation into the spinal canal, explaining the negative surgical exploration by assuming that the disk had slipped back into place. Goldthwait, who hypothesized that this condition could produce sciatica, was with far in advance of his time but failed to arouse much interest. Looking at his manuscript today, his honest description of the negative exploration by Cushing resembles the experience of many surgeons today, despite the help of sophisticated imagery. Four years later Charles Elsberg (1915) surgically removed a piece of ruptured ligament of "*subflavum*" which was compressing the fourth lumbar nerve root; the sciatica then disappeared[28;29].

Walter Dandy introduced air myelography in 1918 for the diagnosis of space- occupying brain lesions. It never worked well for spinal pathology but it was a big step forward in neuro-imaging after the discovery of the X-ray in 1895 by William Conrad Roentgen[30]. In 1920 an assistant of the French neurosurgeon Sicard injected Lipiodol into the subarachnoid spaces by mistake. After this "mistake" they observed the patient in the vertical position under the fluoroscope and to their surprise saw the first myelogram; they described lesions compressing lesions the dural sac[31].

In 1927 Putti suggested that sciatica was caused by an inflammation of the lumbar nerve roots in the spinal neuroforamina[32;33]. He thought that the pain was second-

Figure 5. Dr. William Jason Mixter, neurosurgeon

ary to irritation caused by arthritis of the posterior intervertebral articulations. In addition to the fact that his conclusions were far ahead of his time, he was the first to conclude that sciatica could be explained by degenerative low back disorders and not by a tumor.

In the same period Walter Dandy 1929 found cartilaginous fragments (extruded and sequestrated disk material) lying loose in the spinal canal. He discovered that these nodules were of disk origin and could produce sciatica[30]. He thought that the "lumbar disk syndrome" was related to trauma and that the disk was affected by a process he called osteochondritis desiccans with fragments acting as a sequester. His drawings are beautiful examples of a herniated disk. In his opinion the lumbar spine had a predisposition toward such pathology because of a deficiency of the posterior longitudinal ligament in this area. At that time neurosurgical and orthopedic societies were still convinced that nerve root compression was caused by a benign tumor, whereas neurological and rheumatological literature did focus on an inflammation of the sciatic nerve.

However Dandy stated that removal of these masses would cure the pain and improved function. Unfortunately he still called these masses "tumors", which in a strict sense they are, but this did not result in a scientific breakthrough. In the same year this observation was also reported in Paris by the neurologist, Alajouanine, who successfully guided a famous general surgeon, Petit Dutaillis, who used a transdural approach for a "disk tumor" at the level L3-L4[34-36].

Shortly thereafter the German pathologist Schmorl (1931) described his findings on the anatomy and pathology of disks investigated by radiological examination of post-mortem dissection of spines[37]. These descriptions established modern understanding of degenerative changes and disk herniations.

A neurosurgeon, William Jason Mixter (figure 5), and an orthopedic surgeon, Joseph Seaton Barr, working close together presented their surgical and pathology

findings and conclusions at the annual meeting of the New England Surgical Society in September 1933[4]. Barr was assigned to review Schmorl's German book[37] and had great interest in the histology of the disk. After treating a sciatic patient conservatively without success, he performed a Lipiodol myelogram and convinced Mixter to perform surgery. During surgery a "disk tumor" was removed. The patient did well and Barr asked the pathologist to review the slides together. He immediately recognized the microscopic pictures as being nucleus pulposis shown by Schmorl in his photographs. They reviewed cases which in recent years had been depicted as chondroma's and related diagnoses. Their publication the next year in 1934 [4]convinced the world that sciatica is not caused by a tumor, but that a simple herniation of the nucleus pulposis gives rise to compression of the nerve root. This publication changed the treatment of sciatica. The message was to relieve sciatica by surgery and that the results obtained were very satisfactory if compression had not lasted for too long a period. Most scientific societies adopted this view. Farfan even stated that the "Dynasty of the Disk" had started[5]. After this breakthrough publication, lumbar diskectomy became and remained the most frequently performed neurosurgical intervention worldwide. In the Netherlands the first disk surgeries were performed not earlier than after 1937[38;39] From that time until 1983[40] a major question did not arise.

What is the appropriate conservative treatment strategy and how long should this period of natural cure last before surgery is discussed with the patient?

In retrospect however Ernest Hunt questioned the publication directly in the same journal in 1934[4], asking whether the extensive transdural approach described by Mixter and Barr could be replaced by displacement of the dura and nerve root medially. Moreover he asked whether most patients really needed to undergo surgery.

> **"I should think there might be a question as to when we should consider that lesion important enough or large enough to justify the rather severe operation of laminectomy; that is to say, are there instances in which with the passing of time nature would take care of it without the necessity of operation with attendant risk, which was apparently five percent in this group?"**
>
> *Comment Ernest Hunt (N. Eng. Journal 1934)*

As expected his latter comment had little impact on society compared to the fact that surgery was a safe and effective option for sciatica. It was suddenly a curable disease in the hands of surgeons.

The direct comparison between surgery and conservative treatment has only

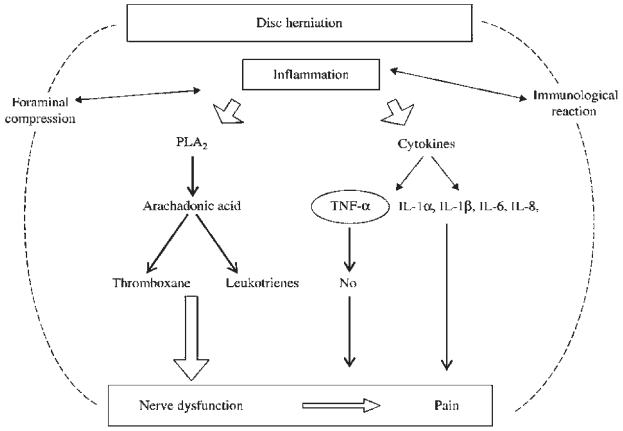

Figure 6. Adapted with permission from Stafford et al. 2007

been described properly once in a randomized trial performed by Henrik Weber[40]. Although the study received considerable methodological criticism, it is still only one of the few trials which tried to directly compare surgery versus conservative treatment. The well known favorable natural course of sciatica and innovative findings with regard to the pathogeneses[41] changed scientific ideas about the treatment of sciatica to a more conservative and medical approach again. In well designed experimental and clinical studies strong evidence was found of an inflammatory response by nuclear disk tissue on lumbar nerve roots, causing sciatic neuralgia by a local release of phospholipase A2 (PLA-2), leukotrienes or cytokines, such as various interleukins (IL) and tumor necrosis factor-α (TNF-α)[42] (figure 6).

Although apparently very attractive to direct treatment to the chemical or immunological pathogeneses of sciatic neuralgia, randomized controlled trials, investigating treatment by corticosteroids[42] and anti-TNF-α[43] failed to show beneficial short- and long-term effects of this potential hazardous medical treatment when compared with placebo.

Besides spontaneous cure surgery remains the only proven effective treatment option to directly resolve mechanical compression and hypothetically indirect chemical irritation of compressed nerve roots.

Still being the most frequent procedure carried out by neurosurgeons worldwide one would expect that lumbar disk surgery would be high on the agenda of scientific meetings as well as orthopedic and neurosurgical journals. This, however, is not the case, probably because lumbar disk surgery is considered to be highly effective, is not

very difficult to perform and most spine surgeons do not doubt the scientific basis of timing disk surgery after 6 weeks of persistent sciatica[44;45] .

Objective and outline of this thesis

After the first description of surgery for sciatica in 1934[4] and despite the warning about performing surgery too soon by Ernest Hunt, disk surgery increased in popularity with highly variable rates of surgery between countries in the last decade of the twentieth century[46]. The main explanation for this difference rates of surgery rates is the timing of disk surgery per country[47]. The United States and The Netherlands await the natural cure of sciatica for 6 weeks before surgery is considered, while for instance the United Kingdom and Sweden wait at least several months and offer surgery only after a prolonged period of conservative treatment without any result. Which timing strategy is the best is unknown and has not yet been investigated in a randomized trial; only a few observational cohort series have been described. Although the randomized Weber trial and recent SPORT trial[48;49]compared surgery with conservative treatment, they were not designed to evaluate the current timing of disk surgery for sciatica.

The main objective of this thesis is to compare at random the effectiveness over one year and at two years of the timing of disk surgery after 6 to 12 weeks of sciatica with a strategy of prolonged conservative care for some months.

When a physician meets a patient with sciatica, information is gathered to predict the absence or presence of a disk herniation and to decide what the appropriate treatment strategy should be within the framework of the natural course. In **chapter 2** the actual state of the art of the diagnosis and treatment of sciatica is described.

Data that define the optimal timing strategy for sciatica are not available. Despite ample available epidemiological methods to compare at random surgery after 6 weeks of severe sciatica with conservative care and delayed surgery, such a trial had not yet been designed yet. In **chapter 3** the design is described of the Sciatica Trial, a randomized cost-effectiveness study to answer the question whether the current international guideline which recommends surgical intervention after 6 to 8 weeks of conservatively treated sciatica is supported by high level evidence .
Chapter 4 presents the short-term one year results of this randomized controlled trial, comparing early surgery with prolonged conservative treatment for patients with a clear surgical indication after 6 to 12 weeks of sciatica.

Before implementation of a new treatment algorithm can be considered, the results of epidemiological outcome research should be weighed against the direct and

indirect costs of the different treatment strategies compared. The results of this cost-effectiveness analysis are reported in **chapter 5**.

The presence of a positive straight leg raising test, neurological deficit, MRI appearances of the disk herniation and patient preference guide clinicians in their decision to plan surgery. A subgroup analysis of predictive variables and their interaction with the randomized surgical timing strategy is the main subject of **chapter 6**.

According to the study protocol conservative treatment could be followed by surgery after a delayed period of time following randomization. Persistent complaints of sciatica, despite adequate guidance and analgesics, were of major importance for the decision to perform late surgery. **Chapter 7** might be of great interest to patients and physicians who want to know early in the disease which variables affect the risk of delayed surgery**.**

Most intervention studies focus on good outcome. The societal impact of unsatisfactory outcome of low back disorders is however high. What is the one year prognosis for patients with sciatica of at least 6 weeks duration, which variables influence the outcome and does gender play a role? To answer these questions in **chapter 8,** all randomized patients of the Sciatica Trial are described as an observational cohort with an unsatisfactory result at one year as outcome of interest.

The goal of this randomized trial was to evaluate the timing of surgery and it's effect on speed of recovery. The high costs of low back disorders are however due to persisting, recurrent or deteriorating sciatica, chronic low back pain and the inability to work or perform daily duties. In **chapter 9** the 2-year results of this trial are described and contemporary scientific study results are compared with other studies on surgical timing.

A synthesis of the results in **chapter 10** includes our future scientific "quest" to define further the optimal timing of disk surgery for sciatica. The dissertation is concluded with a summary in **chapter 11**.

2

REVIEW OF LITERATURE

Diagnosis and treatment of sciatica

Bart W. Koes
Maurits W. van Tulder
Wilco C. Peul

BMJ 2007; 334(7607):1313-1317

Introduction

Sciatica affects many patients who are commonly treated in primary health care settings, but a small proportion of patients are referred to secondary care and may eventually undergo surgery. Many synonyms for sciatica are being used in the literature such as lumbosacral radicular syndrome, ischias, nerve root pain and nerve root entrapment.

The most important symptoms are pain radiating in the leg and related disability. In approximately 90 % of the cases, sciatica is caused by a herniated disk with associated nerve root compression, but lumbar stenoses and (less frequently) tumors are also possible causes. The diagnostic and therapeutic management of patients with sciatica is characterized by a considerable variation within and between countries. There is, for example, a striking variation in the surgery rates for lumbar diskectomy between countries[46]. A more recent publication confirms the still large variation of disk surgery, even within one country[50]. This may in part be caused by a paucity of evidence regarding the value of diagnostic and therapeutic interventions and the lack of clear clinical guidelines, but may also reflect differences in health care and insurance systems. This review presents the current state-of-science regarding the diagnosis and treatment of sciatica.

Methods

We used the Cochrane library to identify relevant systematic reviews evaluating the effectiveness of conservative and surgical interventions for sciatica. Medline searches up to december 2006 were used to find other relevant systematic reviews on diagnosis and treatment of low back pain. Keywords were sciatica, hernia nuclei pulposi, ischias, nerve root entrapment, systematic review, meta-analysis, diagnosis, and treatment. In addition, our personal files were used for additional references, including a few publications of recently conducted randomized clinical trials. Finally we checked if clinical guidelines were available.

Who gets it?

Exact figures on the incidence and prevalence of sciatica are lacking. In general, an estimated 5-10 % of patients with low back pain suffer from sciatica, while reported lifetime prevalences of low back pain range from 49 % to 70 %(w2). Direct estimates of (disk-related) sciatica in the open population show an annual prevalence rate of 2.2 % (2). A few individual and occupational risk factors for the occurrence of sciatica have been reported (table 1). Factors that have been associated with the occurrence

Table 1. Risk factors for acute sciatica[62;70]

	Occurrence
Individual factors	Age (peak 45-64 years) Length (higher) Smoking Mental stress
Occupational factors	Strenuous physical activity: Frequent lifting especially while bending and twisting Occupational driving of motor vehicle, including whole-body vibration

of sciatica include age, length, mental stress, cigarette smoking and some occupational factors such as exposure to vehicular vibration (w2,2,3) For an association of sciatica with gender or physical fitness there is conflicting evidence (w2,2,3).

How is it diagnosed?

The diagnostic process is mainly based on history taking and physical examination. By definition the patients suffer from radiating pain in the leg. Patients may be asked to report the distribution of their pain and whether the pain radiates below the knee. Pain drawings may be used to evaluate the distribution of pain. Sciatica is characterised by radiating pain following a dermatomal pattern. Patients may also report sensory symptoms. Physical examination largely depends on neurological testing. The most applied test is the straight leg raising (SLR) test or Lasègue's sign. Patients with sciatica may also suffer from low back pain, but the back pain is usually less severe than the leg pain. The diagnostic value of history and physical examination has not been well studied[51]. There are no history items or physical examination tests with both high sensitivity and high specificity. The pooled sensitivity of the straight leg raising test is estimated to be 91 % with a corresponding pooled specificity of 26 %[52]. The only test with a high specificity is the crossed SLR test with a pooled specificity of 88 % but the sensitivity is only 29 %[52]. Overall, if a patient reports the typical radiating pain in one leg combined with a positive result on one or more neurological tests indicating nerve root tension or neurological deficit the diagnosis sciatica seems justified. Table 2 shows the signs and symptoms that are relevant for the distinction between sciatica and non-specific low back pain.

What is the value of imaging?

Diagnostic imaging is, in general, only useful if its results influence further management of the patient. In acute sciatica, the diagnosis will be based on history taking and physical examination and treatment will be conservative (non-surgical). Imag-

Table 2. Indicators for sciatica.
Unilateral leg pain > LBP
Radiates to foot or toes
Numbness & paresthesia in the same distribution
Straight leg raising (SLR) test induces more leg pain
Localized neurology (i.e. limited to one nerve root)

Source: Waddell (The Back pain revolution, 1998)[71]

ing may only be indicated at this stage if there are indications or 'red flags' that the sciatica may be caused by underlying pathologies (infections, malignancies) other than disk herniation.

Diagnostic imaging may also be indicated in patients with severe symptoms who fail to respond to a period of 6-8 weeks of conservative care. In these cases surgery might be considered and imaging is used to identify if a herniated disk and nerve root compression indeed is present, and what its exact localisation and size is. It is very important for the decision to operate or not that the clinical findings and symptoms of the patient correspond well with the imaging findings. This is especially relevant because disk herniations identified with CT and/or MRI are highly prevalent (varying from 20 %-36 %) in asymptomatic people not having sciatica at all[53;54]. It is also true that in many people with clinical symptoms of sciatica no lumbar disk herniations are present on imaging scans[55;56]. At present, there is no clear advantage of one type of diagnostic imaging method compared to others. Although some authors favor MRI above other imaging techniques because of the higher radiation dose of CT and/or the better performance of MRI with visualising soft tissues[57;58], there is evidence that CT and MRI both are equally accurate for diagnosing lumbar disk herniation[59]. The use of X-rays for diagnosing lumbar disk herniation is not recommended because X-rays are not able to visualise the disk[59].

What is the prognosis?

In general, the clinical course of an episode of acute sciatica is favourable and most pain and related disability will resolve within a couple of weeks. For example, in a randomized trial evaluating NSAIDs versus placebo in patients with acute sciatica in primary care 60 % of all patients recovered within a period of 3 months and 70 % within 12 months[3]. Improvement rates of patients with acute sciatica included in placebo groups in randomized trials evaluating non-surgical interventions indicate that about 50 % of the patients report 'improvement' within 10 days and about 75 % report improvement after a period of 4 weeks[2]. These figures show that in the majority of patients the

Table 3. Evidence of conservative treatments for sciatica	
Beneficial	
Trade off	Bed rest
Likely to be beneficial	Advice to stay active (in CR bedrest)
Unknown effectiveness	Analgesics/NSAIDs Acupuncture Epidural steroid injections Spinal manipulation Traction therapy Physical therapy Behavioral treatment Multidisciplinary treatment
Unlikely to be beneficial	
Ineffective or harmful	

prognosis is good, but at the same time a substantial proportion (up to 30 %) continues to suffer from their complaints after a period of one year and longer.[2;3]

What is the efficacy of conservative treatments for sciatica?

Conservative treatment is primarily aimed at pain reduction, either by pain medication or by reducing pressure on the nerve root. A recent systematic review found that the available conservative treatments do not clearly improve the natural course of sciatica in most of the patients nor do they reduce symptoms[60]. Adequately informing patients about the causes and expected prognosis of sciatica may be regarded as an important part of the management strategy. However, patient-education has not specifically been investigated in RCTs in patients with sciatica.

Table 3 summarizes the evidence of effectiveness of commonly available conservative treatments for sciatica, including injection therapy. For most of the available interventions strong evidence is lacking. The contrast of bedrest versus advice on staying active does not show large differences in effect regarding pain and functional status[61]. Because of this finding bedrest, which for a long period has been the mainstay of treatment of sciatica, is not widely recommended anymore[62;63]. Analgesics, NSAIDs and muscle relaxants do not clearly seem to be more effective in reducing symptoms than placebo. Evidence is lacking for opioids and various compound medications. A previous systematic review also reported that there was no evidence that traction, NSAIDs, intramuscular steroids, and tizanidine are superior to placebo[2]. This review suggested that epidural steroid injection might be effective in patients with acute sciatica. However, a more recent systematic review including a larger number of randomised trials reported that there was no evidence of positive short effects of corticosteroid injections and that the long term effects were un-

A patient's perspective (A)
After an episode of lumbago during a vacation, I continuously had low back pain and tingling feet for about 9 months. Then suddenly my right foot started to hurt badly and after a while the pain became so severe that I was unable to leave my house. The specialist ordered an MRI scan and it revealed a large lumbar disk herniation. Since it only got worse after that, I decided to have surgery.
After the operation, I recovered quickly and the back pain and leg pain were completely gone. I soon was able to go back to work and rebuild my social life. Unfortunately, after a couple of months the low back pain and the other symptoms returned, although not as severe as before surgery. A new MRI scan now revealed two small disk herniations and two bad intervertebral disks. The specialist told me that it was too early for a second operation.
Now it is unclear to me what the doctor can do about it and I don't even know which measures I can take myself. The constant back and leg pain are greatly interfering with my work and my social life. I sometimes feel like an elderly person because of my physical limitations. I try to stay positive, but it is hard to cope with the uncertainty.

Ms P., aged 32 years, Rotterdam

known[60]. The same systematic review reported that active physical therapy (exercises) appeared not to be better compared with inactive (bedrest) treatment and other conservative treatments such as traction, manipulation, hotpacks or a corset)[60].

What is the role of surgical procedures in patients with sciatica?
Surgical intervention is focused on removal of disk herniation and eventually part of the disk or be directed at foraminal stenosis with the purpose of eliminating the suspected cause of the sciatica. The treatment is directed at easing the leg pain and corresponding symptoms and not directly at reducing the accompanying back pain. There is consensus that a cauda equina syndrome is an absolute indication for immediate surgical intervention. For unilateral sciatica the decision for surgery is elective. Until recently there was only one relatively old randomised trial available comparing surgical intervention versus conservative treatment for patients with sciatica[40]. This study showed that surgical intervention had better results after one year, while after 4 and 10 years of follow up there were no significant differences[40].

The Cochrane review summarized the available randomised clinical trials evaluating disk surgery and chemonucleolyses[64]. Chemonucleolyses concerns injection with the enzyme chymopapain in the discus with the purpose of shrinking the nucleus pulposus. They reported better results of disk surgery compared to chemonucleolyses (in patients with severe sciatica of relatively long duration). Chemonucleolyses was more effective than placebo. So, indirectly they suggested disk surgery to be more effective than placebo also. Based on data from three trials the authors concluded that there is considerable evidence that surgical diskectomy provides ef-

fective clinical relief for carefully selected patients with sciatica due to lumbar disk prolapse that fails to resolve with conservative management. A recently published review came to the same conclusion[65]. The Cochrane review further concluded that the long term effects of surgical intervention are unclear and that there also is a lack of evidence on the optimal timing of surgery[64].

Recent RCTs not yet included in systematic reviews

Two additional RCTs have been published comparing disk surgery versus conservative treatment. One trial (n=56) compared miscrodiskectonomy with conservative treatment in patients with 6 to 12 weeks of sciatica[66]. Overall no significant differences were found regarding leg pain, back pain, subjective disability over a two-year follow-up period. However, patients in the diskectomy group initially seemed to improve more rapidly regarding leg pain. The large SPORT randomised trial and related observational cohort study was conducted in the USA[48;49]. Patients with at least 6 weeks of sciatica with confirmed disk herniation were invited for either participation in a randomized trial or in an observational cohort study. Patients in the trial were randomised to disk surgery or conservative care. Patients in the cohort study decided themselves to receive disk surgery or conservative care based on their preference. The randomised trial (n=501) showed that both treatment groups improved substantially over a two-year period for all primary and secondary outcome measures. There were small differences in favor of the surgery group, but these differences were not statistically significant for the primary outcome measures. Remarkably, only 50 % of the patients randomised to the surgery group actually received surgery within 3 months after inclusion. At the same time 30 % randomized to conservative care received surgery within this 3-month period[67]. After 2 years follow-up 45 % of the conservative group underwent surgery versus 60 % in the surgery group[49].

The observational cohort included 743 patients. Both groups improved substantially over time, but the surgery group showed significantly better results regarding pain and function in comparison with the patients receiving conservative treatment. The authors suggest that these findings should be interpreted with caution, because of potential confounding by indication and by the self-reported nature of the outcome measures[48].

The results indicate that both conservative treatment and disk surgery are relevant treatment options for patients with sciatica of at least 6 weeks duration. Surgical intervention may provide some quicker relieve of symptoms compared to conservative treatment, but there are no large differences in success rate after one to two years follow-up. Patients (and doctors) may thus weigh the benefits and harms of both options in order to make their individual choices. This is especially relevant since the preference of patients for a certain type of treatment may have a direct positive influence on the magnitude of the treatment effect.

Table 4. Summary of recommendations of the clinical guideline for diagnosis and treatment of sciatica of the Dutch College of General Practice[63].

Summary of recommendations for diagnosis of sciatica:
• Check 'red flags' for malignancies, osteoporotic fractures, radiculitis and cauda-equina syndrome • History taking for determining localization, severity , loss of strength, sensibility disorders, duration, course, influence of coughing, rest or movement, and consequences for daily acitivities. • Physical examination: neurological testing: straight leg raising test (SLR)/Laseque sign • In case of leg pain according to dermatomal pattern, positive SLR, loss of strength or sensibility disorders further investigate: reflexes (Achilles/knee tendon); sensibility of lateral and medial sides of feet and toes, strength of big toe during extension, walking on toes and heel (left-right differences), crossed Laseques sign. • Imaging or laboratory diagnostics are only indicated in red flag conditions but are not useful in cases of (suspected) disk herniation
Summary of recommendations for treatment of sciatica:
• Explain cause of the symptoms and reassure patients (symptoms usually diminish over time without specific measures) • Advise to stay active and continue daily activities; a few hours of bedrest may provide some symptomatic relief but does not improve a faster recovery • Prescribe medication if necessary (according to 4 steps) 1) paracetamol, 2) NSAIDs, 3) Tramadol; or paracetamol/NSAID in combination with codeine, 4) morfine • Refer to neurosurgeon immediately in case of cauda-equina syndrome or acute severe paresis or progressive paresis (within a few days) • Refer to neurologist, neurosurgeon or orthopedic surgeon to consider surgery in cases of intractable radicular pain (not responding to morfin) or if pain and suffering do not dimish after 6-8 weeks of conservative treatment . (note: in other countries referrals to rheumatologist or physiatrist are more common due to local circumstances)

What are the recommendations in clinical guidelines?

Although in many countries there are clinical guidelines available for the management of non-specific low back pain this is not the case for sciatica[68]. Table 4 shows the recommendations from the recently issued clinical guidelines for sciatica (lumbosacral radicular syndrome of the Dutch College of General Practice[63]. After excluding specific pathologies based on red flags the diagnosis is made on the basis of history taking and physical examination. Initial treatment is conservative, with a strong focus on patient-education, advice to staying active and continuing daily activities and adequate pain treatment. In this phase there is no role for imaging. Referral to a medical specialised, e.g. neurologist, rheumatologist, spine surgeon is indicated in patients who do not improve their symptoms after conservative treatment for a period of at least 6-8 weeks. In these referred cases surgery may be considered. Immediate referral is indicated in cases with a cauda equina syndrome. Acute severe paresis or progressive paresis are also reasons for referral (within a few days).

A patient's perspective (B)

My complaints started about 4 months ago with pain in the lower back. Soon hereafter the pain radiated into my legs for which I went to my general practitioner. His analysis was no herniated disk. A muscle relaxant in combination with referral to a physiotherapist would reduce the symptoms. Three weeks of physiotherapy followed by several treatments by a chiropractor did not provide any symptom relief. In fact, the symptoms became worse. Especially during walking and standing. Laying down and cycling were much better tolerated. Additional complaints were reduced strength in the left leg, not being able to stand on the heel or toes, a cold feeling in the lower leg at the end of the day, while in the morning it felt like standing in a bunch of needles.

About 1 month ago, a neurologist diagnosed a herniated disk on the right side based on an MRI-scan that was taken. However, this could not explain the symptoms in the left leg. The symptoms in the left leg could be due to spinal stenosis. The complaints were not severe enough to recommend surgery and the neurologist told me that a substantial improvement was to be expected within a period of 3-4 months. His advice was to continue normal daily activities as much as possible. At present (one month later) I feel some improvement of my symptoms.

Mr. J. V., aged 49 years, The Haque

Promising developments

More evidence based information has become available regarding the efficacy of surgical versus conservative care for patient with sciatica. Important knowledge is the initial finding that in the long run (after 1-2 years follow-up) there are no important differences in effect between these two distinct approaches. Although it must be stressed that there is only limited evidence available on long term effects of either conservative or surgical interventions. In addition, part of this finding may be explained because patients who initially receive conservative care undergo disk surgery at a later stadium. In all available studies it appears that fortunately a substantial part of the patients improve over time. This holds true for patients receiving surgery as well as patients receiving conservative treatment. Patients receiving disk surgery are more likely to get quicker relieve of their leg symptoms compared to patients receiving conservative care. After an initial period of 6-8 weeks without improvement of symptoms patients may thus opt for disk surgery to get quicker relieve of their leg pain. Patients who are hesitant regarding surgery and who can bear the severity of their symptoms may also opt for continued conservative care. Patient preference is therefore an important feature in this decision proces.

The last years have shown a switch in the management of sciatica from more passive treatments, including bed rest towards a more active approach and the advice to patients to continue their daily activities as much as possible.

Future research

Further knowledge is desirable regarding the importance of clinical signs and symptoms for the prognosis of sciatica and the response to treatment. This includes the value of size and location of the disk herniation, (visible) nerve root compression, sequestration and the results of history taking and physical /neurological examination. Subgroup analysis in the Finnish trial showed that diskectomy was superior to conservative treatment in cases with herniation at L4-L5[69]. For many of the available conservative treatments there is no strong evidence for or against their efficacy. Much progress can be achieved here. Questions exist regarding the efficacy of pain medication for sciatica, the value of physical therapy and of patient-education and counseling. No trials have yet evaluated the effectiveness of behavioral treatment and multidisciplinary treatment programs.

TNF-alfa has been identified in animal and human studies to be one of the chemical factors involved in the etiology of sciatica[67;69] The first randomized trial evaluating TNF-alfa antagonist in patient with sciatica did not find a positive result[43] but further studies are warranted.

Summary points:

- Most patients with acute sciatica have a favorable prognosis, but about 20-30 % has persisting complaints after 1-2 years
- The diagnosis is based on history taking and physical examination
- Only in patients with red flags conditions or if disk surgery is considered imaging is indicated.
- Passive (bedrest) treatments have recently been replaced with more active treatment approaches.
- There is consensus that initial treatment is conservative for about 6-8 weeks.
- Recent evidence suggest that disk surgery may provide quicker relief of leg pain compared to conservative care, but after one-two years initial evidence suggests that there are no clear differences.
- Apart from the cauda equina syndrome, patient preference for or against surgrey may play an important role in the treatment decision.
- Further studies are needed investigating the optimal timing of surgery and the efficacy of the majority of conservative interventions that are commonly used for sciatica.

3

DESIGN & PROTOCOL

Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disk herniation: rationale and design of a randomized trial

Wilco C. Peul
Hans C. van Houwelingen
Wilbert B. van den Hout
Ronald Brand
Just A.H. Eekhof
Joseph Th. J. Tans
Raph T.W.M. Thomeer
Bart W. Koes

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ABSTRACT

Background: The design of a randomized multicenter trial is presented on the effectiveness of a prolonged conservative treatment strategy compared with surgery in patients with persisting intense sciatica (lumbosacral radicular syndrome).
Methods/design: Patients presenting themselves to their general practitioner with disabling sciatica lasting less than twelve weeks are referred to the neurology outpatient department of one of the participating hospitals. After confirmation of the diagnosis and surgical indication MRI scanning is performed. If a distinct disk herniation is discerned which in addition covers the clinically expected site the patient is eligible for randomization. Depending on the outcome of the randomization scheme the patient will either be submitted to prolonged conservative care or surgery. Surgery will be carried out according to the guidelines and between six and twelve weeks after onset of complaints. The experimental therapy consists of a prolonged conservative treatment under supervision of the general practitioner, which may be followed by surgical intervention in case of persisting or progressive disability. The main primary outcome measure is the disease specific disability of daily functioning. Other primary outcome measures are perceived recovery and intensity of legpain. Secondary outcome measures encompass severity of complaints, quality of life, medical consumption, absenteeism, costs and preference. The main research question will be answered at 12 months after randomization. The total follow-up period covers two years.
Discussion: Evidence is lacking concerning the optimal treatment of lumbar disk induced sciatica. This pragmatic randomized trial, focusses on the 'timing' of intervention, and will contribute to the decision of the general practictioner and neurologist, regarding referral of patients for surgery.

BACKGROUND

One of the greatest advantages of publishing the design of a randomized controlled trial (RCT) before results are available is the accessibility to criticism of the methodological quality irrespective of the results. Firstly the scientific reader must be enabled to search for epidemiological shortcomings when the results differ from the expected outcome as compared to results in line with one's expectations. Secondly, it is possible to more extensively elaborate the background and rationale of the research question, the study population, the chosen treatments and outcome measures, as compared to publications describing the trial results. Thirdly, but not less important, publishing the design of a RCT is instrumented in preventing publication bias in subsequent meta-analyses. Studies with non-significant results are less likely to be published than those with significant results[72;73]. It is a considerable loss for data pooling that unpublished trial results are omitted. After pre-publishing the study design even unpublished data can be used in a systematic review, since these can be required from the study group. This article describes the rationale and parallel group design of a RCT in which the optimal timing of disk surgery for sciatica will be investigated.

The lumbosacral radicular syndrome (LSRS or LRS; also called sciatica) is typically characterized by radiating pain in the dermatome of a lumbar or sacral spinal nerve root. Occasionally more than one root is involved. Contained in the syndrome pain may be accompanied with lumbar fixation, reflex abnormalities motor and sensory disturbances. In diagnosis includes stenosis of the spinal and/or root canal, infection, multiple sclerosis, autoimmune or metabolic neuropathy, and tumour. This study will be restricted to herniations at the lowest three lumbar disk levels, since these represent the most common sites. In the vast majority of cases LSRS is the result of a herniated disk. In the Netherlands annually between 60,000 and 75,000 new cases of LSRS are diagnosed by the General Practitioner (GP)[74]. The presumed direct medical costs of treatment of LSRS are € 133 million each year[75]. Most of these costs are attributable to in-hospital treatment; only a small portion is incurred by GP's or physiotherapists (€ 3.2 million). In a study, performed in 1988, more than 11.000 patients were operated in the Netherlands and this frequency did not change in the past years[75;76]. The combined direct and indirect costs are estimated to be € 1,2 billion per year[77]. The indirect costs are considerable due to the high rate of production loss caused by sciatica.

The natural history of LSRS is in general favourable. In 60-80 percent of patients, the leg pain decreased or disappeared within 6-12 weeks after onset[40;78-80]. These patients no longer experienced problems at work or in their private lives after three

months. The minority with lasting complaints beyond three months further decreases with time. At one year only a small proportion of herniated disks continues to produce discomfort and disability. At present it is not possible to identify these latter groups of patients in an early stage of their disease by means of intensity of pain, neurological deficit, root irritation signs, or diagnostic imaging. For this reason it is not helpful to perform early diagnostic imaging (CT or MRI), unless a disease entity different from disk herniation is considered. After the indication for surgery has been set diagnostic imaging is helpful in defining the exact site of disk herniation and its anatomical relationship with the nerve root involved. Since the first publication on lumbar disk surgery by Mixter and Barr[4] many studies have demonstrated the success of surgery for the treatment of LSRS. Unfortunately only a few prospective studies investigated the difference in outcome between surgical and conservative care[40;78;81-85]. The published treatment results vary as much as the frequency of reported complications and the recurrence rate. The only study, which compared surgery with conservative care directly in a RCT, was performed by Weber more than 20 years ago[40;78]. He found better results for surgery at one-year follow-up. At four and ten years follow-up the results of surgical and conservative care no longer differed. Being the only published RCT comparing surgical and conservative care, this study regrettably carries some important methodological flaws in both design and outcome measures when compared to today's epidemiological standard rules[86]. One of the main shortcomings is the exclusion of patients, who do have an indication for surgery because of "intolerable" pain. Those are the current patients who ask for surgery and are not comparable to the randomized population of Weber. Therefore it is impossible to extrapolate and generalize these results to the treatment policy of today. Since 1983 a few cohort studies have been published on non-surgical treatment of patients with at least six weeks of leg pain with good short-term results at one-year follow-up[84;87]. These studies also suffer from methodological flaws. The only conclusion that can be drawn from these reports and the study of Weber is that the policy of prolonged conservative care can be effective, as a result of the favourable natural course of LSRS. Epidemiological and clinical studies have shown that most lumbar disk protrusions resolve spontaneously with the elapse of time[88;89]. Another finding is that prolonged conservative care appears safe and without complications if the patient remains active. Recent population based studies however state that the natural history is not favourable at all[90]. Whether particular demographic findings, symptoms, physical signs and/or MRI findings either separately or combined do have prognostic value has not been investigated scientifically yet. It would be of great value if one were able to identify early in the course of the disease those patients who will have an unfavourable outcome without surgery. In spite of the known favourable natural course the surgical rate in the Netherlands is quite high[46].

We perform six times as many lumbar diskectomies compared to Scotland, four times the number in England and two times the number in Sweden. In the latter study comparing 12 Western countries the United States is the only country where more operations are performed for the indication LSRS. There are no substantial differences in the incidence of this disease in the countries mentioned that can explain the difference in surgical rates. There is no indication[77] that the surgical rate has changed under influence of the consensus reports[44;91]. Actually change was not likely to occur because the published guidelines were representative for daily practice and normal care before 1996 in the Netherlands. With respect to the indications for and timing of surgery no evidence in the literature is available to either support or contradict these guidelines. These guidelines were produced after agreement between all medical (sub-) disciplines involved in the care for patients with LSRS. Our high surgical rate, as contradictory as it may seem, may reflect good clinical practice.

Because of the observation that most people recover from their complaints in the first 6-8 weeks[79;80] this period of persistent radicular leg pain is considered a good indication for surgery in the Netherlands. Although there is consensus that surgery is only offered in case of persistent pain, the timing of this treatment seems to depend on local production capacity and patient and doctor preferences rather than on evidence-based practice. This lack of evidence for the timing of surgery after the 6-8 week period explains the large variations in daily practice. Exact data on the problems associated with surgery, such as surgical failure, recurrent disk herniation and adverse effects are limited. This is one of the reasons that in some regions surgery will only be carried out after a period of 3- 6 months of LSRS[92].

It is not known whether the relative high rate of disk surgery in the Netherlands is cost-effective or not, compared to other countries[88;89].

In summary, consensus is missing on the preferred timing of disk surgery, due to insufficient evidence that a prolonged conservative care strategy is effective. More insight is needed into the potential short-term effects of a relative early surgery strategy, as compared to an extended wait-and-see period. In particular the effects on the return to work or resumption of previous daily activities as well as the complications of both strategies have not yet been investigated.

The main goal of this comparative study is to investigate whether the completion of a 6-12 weeks period of lasting radicular pain constitutes a solid indication for surgery and is superior to prolonged conservative care. A secondary goal is to identify possible subgroups of patients who will substantially benefit from one of the proposed treatment strategies. The cost-effectiveness results will be a trade-off between a quicker relief of leg pain in the surgery group versus the advantage of lower costs

and avoiding the negative effects of surgery in the conservatively treated group. The difference in disease related quality of life depends on the duration of persisting pain and disability after randomization in the prolonged conservative care group.

This study to investigate this scientific gap in our understanding of the effectiveness of surgery for LSRS is in line with a recommendation by the Dutch Health Council in 1999 to the Minister of Health [75] and the current Cochrane Review[88;89].

The results of this trial will lead to a more rational use of the existing guidelines if the hypothesis is rejected. If the latter is accepted and prolongation of the conservative treatment policy is more cost-effective than surgery after 6-12 weeks, the current guidelines for the timing of surgery need correction.

METHODS/DESIGN

To answer the main research question the investigators propose to conduct a multicentre comparative randomized clinical trial with parallel group design. The main research question will be answered after a follow-up of six months (Figure 1). The complete follow-up will last two years. The multi-centre design is necessary to collect enough patients in two years. The Medical Ethics Committee of all participating hospitals approved the study protocol.

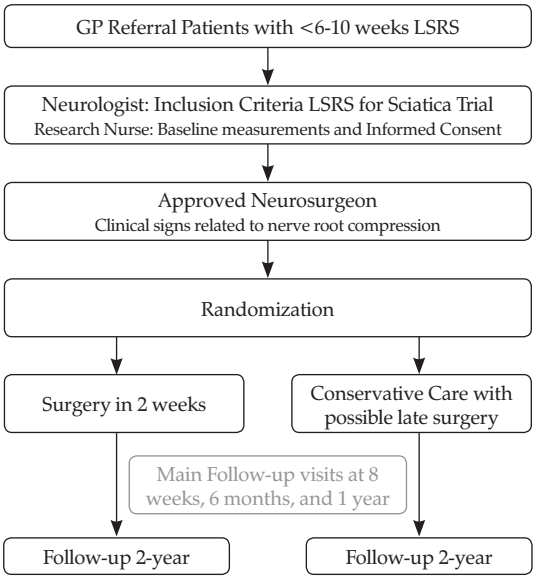

Figure 1. Flow chart of the Sciatica Trial

Table 1. Selection criteria for trial eligibility

Inclusion criteria:

- Age 18-65 yr.
- Persistent radicular pain in the L4, L5 or S1 dermatome with or without mild neurological deficit
- Severe disabling leg pain of 6-12 weeks duration
- Evidence of a unilateral disk herniation confirmed on MRI
- Sufficient knowledge of Dutch language
- Informed consent

Exclusion criteria:

- Cauda equina syndrome or severe paresis (MRC<3)
- Complaints of a lumbosacral radicular syndrome in the same dermatome within the past 12 months
- A history of unilateral disk surgery on the same level
- Spinal canal stenosis
- Degenerative or lytic spondylolisthesis
- Pregnancy
- "Severe life-threatening" or psychiatric illness
- Planned (e)migration to another country in the year after randomization

Patients

All patients between 18 and 65 years with sciatica of less than 12 weeks duration are eligible for this study. Because of the multi-centre (15 hospitals) design the patients in a large region in the western part of the Netherlands can be included in this trial if they meet the in- and exclusion criteria (Table 1). Because these are the only hospitals, which treat lumbar disk herniations in this area, included patients will reflect a representative population treated in primary and secondary care. Inclusion of patients will be started after a visit to the neurological outpatient clinics. Randomization will start after at least 6 weeks persistent disabling pain in the dermatome of the leg served by the L4, L5 or S1 root. All 1100 GP's involved will be informed about this study and receive information about developments and the results of the trial. They will refer patients within the first 6-12 weeks after onset sciatica. During the first visit to the neurological outpatient clinic the patient's history will be taken and a standardized neurological examination will be performed. During this visit the neurologist will inform the patient on the cause and course of a lumbosacral radicular syndrome and convey the doubt regarding the timing of surgery for this condition. The study will be explained to the patient and in case of a positive reaction an appointment is made to meet one of the research nurses as soon as possible.

Preferably the study MRI scans will be performed after informed consent during the first visit to the research nurse. Because the patient needs some time to consider participation a second visit will be planned at least two days after the first visit to the outpatient clinic. The research nurse will give all extra information needed to under-

stand the trial and will ask the patient if he/she agrees to be randomized. Informed by the radiologist and surgeon, the research nurse will only randomize the patient during the third visit if the MRI confirms the presence of unilateral disk herniation and the patient is eligible according to the inclusion and exclusion criteria. The patient will not be aware of detailed MRI data. The radiologist and neurosurgeon independently using a standardized Case Record Form (CRF) will register the MRI findings. The MRI will be performed according to a standardized protocol and including Gadolinium series for the intended subgroup analysis.

Treatment allocation

Patients will randomly be allocated to either surgery within 1-2 weeks or prolonged conservative treatment by their GP. Patients, their doctors and research nurses can obviously not be blinded for the allocated treatment. Blinding of the outcome measurements is not possible, due to the fact that mainly self-reported outcomes are used. A randomization list is prepared for every participating hospital. Permuted blocks of random number patients are formed to ensure near-equal distribution of patients over the two randomization arms in the hospitals. Using random number tables generates the random sequence of the permuted blocks. The data manager, who is not involved in the selection and allocation of patients will prepare coded, sealed envelopes containing the treatment allocation. During the second patient visit the research nurse will open the envelope together with the patient and appointments will be made for the allocated treatment, either surgery or referral back to the GP, to ensure that treatment is started as soon as possible after randomization. This will be done after checking all the criteria and especially the persistence of pain with disability in daily functioning. A letter about the allocated treatment arm informs all caregivers. Although the principal investigator will not include and operate upon trial patients he may be biased with a preference for surgery, which could theoretically influence analysis. Therefore the principal investigator is blinded for the allocated treatment. As he is not involved in treatment of the study population blinding during later analysis is only possible after blinding during the randomization and follow-up period.

Interventions

After randomization two groups of patients will exist.
Group A; the surgically treated patients and *group B;* the conservatively managed patients.

Surgical treatment (A) will be performed in the conventional manner with microscope or loupe magnification. The investigators prefer the standard surgical approach

because the other (minimally invasive) surgical approaches have limited indications, are not more cost-effective, and have a long learning curve. During the transflaval approach care is undertaken to minimize bony removal and on the other hand to prevent overstretching of the compromised nerve root. In addition to removal of herniated disk material as much as possible nuclear material will be removed with pituitary forceps, curettes and rongeurs in order to prevent recurrence. The participating treating doctors are 2 orthopaedic- and 12 neurosurgeons with large experience in the standard approach with loupe magnification or microscope. A standardized CRF will register the findings of the surgeon and the herniated disk material will be investigated histologically for granular infiltration.

Surgery will take place as soon as possible and within a maximum of two weeks after randomization. Hospital admission will be 2-7 days, including the day of surgery. During the immediate post-operative period the patients will be mobilised with the help of a physiotherapist. At home guidance is confirmed by their own physiotherapist. The frequency will be 2 times a week for 8 weeks.

Conservative management (B) will be conducted by the general practitioner (GP) or neurologist when necessary. The GP will provide ample information about the favourable prognosis of LSRS. The treatment of LSRS is aimed primarily at pain relief and maintenance/restoration of normal day-to-day activities. Unfortunately, the effect of giving information and counselling has not been studied specifically among LSRS patients. However, various studies have evaluated the effect of such support for people suffering from other pain syndromes[93]. Inferences can reasonably be made from the findings of these studies. Hence, it may be assumed that adequate and unambiguous information about what is wrong (the nature of the condition) and what the patient can expect (the prognosis), together with trustworthy counselling can reduce the anxiety and uncertainty felt by the patients and thus ease the pain[44]. The GP's will encourage the patients to continue with normal day-to-day activities in so far as possible. When necessary analgesic medication can be prescribed according to the guidelines. The GP will advise the patients to stay active and if possible return to work and/or their leisure activities.

After the first consultation the GP will make a follow-up schedule. During the next visit the patient and doctor will look at the changes since the first visit to determine whether there is any improvement in the ability to perform normal activities. The doctor will check the efficacy of the prescribed pain medication and may adjust the dose or sort of analgesics according to the NHG guidelines. In these guidelines paracetamol is the first choice. If not effective, NSAID's (ibuprofen, diclofenac or naproxen) are to be prescribed. Only in the event of severe disabling pain morphine may be given for a restricted period of time. By preference all analgesics should be

taken at fixed times of the day rather than on a 'if necessary' basis. If the GP and the patient conclude that there is considerable kinesiophobia because of the fear that the radicular or low back pain will increase, the help of a physiotherapist can be recommended. Guided by the GP (and physiotherapist) the patient will upgrade his or her activities according to the agreed time schedule[87;94]. The guide will be time, not the intensity of the pain. The GP will be free in her/his choice of prescription of medication and referral to physiotherapists. The research nurse will register the conservative management strategy after communication with the responsible GP. In case of progressive neurological deficit or worsening intolerable pain the GP can refer the patient back to the research nurse or neurosurgeon. If, six months after randomization, the patient has still not improved or suffers from intermittent LSRS, surgical treatment will be offered. Some patients will ask for surgery earlier because of worsening drug resistant leg pain. In these cases and in the case of a progressive neurological deficit, surgery will be performed in consultation with the patient. If after maximum conservative treatment and counselling the patient is still not able to cope with the functional disability surgery can be requested. If surgery in these cases is not offered by the study-group the patient does have the right to have a second opinion with an undependable neurosurgeon of another university hospital.

Outcome assessment

In the LSRS the most common complaints are pain and disability to perform normal daily activities. We will use below described validated outcome parameters, which will be assessed by means of questionnaires. Patients are not informed about their earlier scores. Follow-up examinations by the research nurse will take place 8, 26 and 52 weeks after randomization and the patients will keep a diary (Table 2). In between at 2, 4, 12, 38, and 78 and after 104 weeks the main questionnaire (primary outcome measures) will be filled in at home and send to the data centre.

Primary outcome measures:

1) Roland Disability Questionnaire for Sciatica. This illness-specific 23-item functional assessment questionnaire is frequently used for low back pain and sciatica[95;96]. Scores range from 0 to 23, reflecting a simple unweighted sums of items endorsed by the respondent. Patients with high scores at baseline do have a severe disabling LSRS. To define recovery a difference of at least 11 points from baseline has to be seen[4;95]. The Roland Questionnaire for Sciatica has a documented high level of internal consistency; construct validity, and responsiveness[95;96]. It is the main primary outcome measure in this trial.

2) Perceived recovery. This is a seven-point Likert scale measuring the perceived recovery, varying from 'completely recovered' to 'worse than ever'. This outcome

Table 2. Data collection and outcome measures

Time in weeks	?	0	2,4	8	12	26	38	52	78	104
Likert	X	X	X	X	X	X	X	X	X	X
Neurological examination		X		X		X		X		
Severity of complaints (VAS)	X	X	X	X	X	X	X	X	X	X
McGill	X									
Health Status (SF 36)	X			X		X		X		X
Functional Status (RDQ)	X	X	X	X	X	X	X	X	X	X
EuroQol/VAS Q-of-life	X	X	X	X	X	X	X	X	X	X
MRI		X							X	
Costs	X	X	X	X	X	X	X	X	X	X
Prolo	X			X		X		X		
Complications		X		X		X		X		
Surgery				X		X		X	X	X
SFBI	X	X		X		X		X		X

scale has been used in previous studies and appears to be valid and responsive to change[97]. Next to this global self-assessment a job and hobby specific Likert will be scored. During the intake of the study the patient will be asked to rank their five most important functional disabilities in daily live (work, hobby), which they can use in their own evaluation overall and in separate items.

3) VAS pain in the leg. This parameter will measure the experienced intensity of pain in the leg during the week before visiting the research nurse. Pain will be assessed on a horizontal 100 mm scale varying from 0 mm, 'no pain in the leg', to 100 mm, 'the worst pain ever'. Patients do not see the results of earlier assessments and will score the pain experienced at the visit[98-102].

Secondary outcome measures:

1) EuroQol classification system and VAS rating personal health. A cost-utility analysis will be performed using QALY's based on the EuroQol questionnaire, which has been validated in many studies and is easy to fill out[79;103;104]. The EuroQol will be measured twice a week during the first four weeks and at all follow-up moments. Patients describe their general health status using the EuroQol classification system, consisting of 5 questions on mobility, self care, usual activities, pain/discomfort, and anxiety/depression[105]. From the EQ-5D classification system, the EQ-5D utility index will be calculated[106]. This utility measure reflects how the general public values the health status described by the patient, which is preferred for economic evaluations

from a societal perspective. Patients also rated their personal health using a visual analog scale (VAS) ranging from worst imaginable health to best imaginable health.

2) Short-Form 36 (SF-36). Quality of life was also assessed using the RAND-36 questionnaire. This is a generic health status questionnaire, which can easily be filled out at home. The questionnaire consists of 36 items on physical and social functioning has 8 domains; 1) physical functioning, 2) physical restrictions, 3) emotional restrictions, 4) social functioning, 5) somatic pain, 6) general mental health, 7) vitality, 8) general health perception. This questionnaire has been used frequently and was validated in studies on low back pathology and surgery[107;108]. From the RAND-36, the SF-6D utility index was calculated. Like the EQ-5D, this SF-6D reflects the general public's valuation of the health described by the patient. The SF-6D is a recent instrument that has not been used much yet, but it richer classification system could make it a more sensitive utility measure than the EuroQol measure.

3) Sciatica Frequency and Bothersome Index (SFBI). This is a scale from 0 to 6, which can assess the frequency (0=not at all to 6=always) and bothersomeness (0=not bothersome to 6=extreme bothersome) of back and leg symptoms. The sum of the results of four symptom questions yields both indexes, ranging from 0 to 24: leg pain; numbness and/or tingling in the leg; weakness in the leg or foot; pain in the back or leg while sitting[81].

5) PROLO-scale. This scale measures the evaluation of the research nurse of the functional-economic status of the patients. This parameter has been used in studies on the difference in functional outcome between different techniques of lumbar spine fusion[104].

6) VAS pain in the back. This parameter measures the intensity of the pain in the back experienced during the week before visiting the research nurse. Assessment will be based on a horizontal 100 mm scale varying from 0 mm, 'no pain in the back', to 100 mm, 'the worst pain ever'. Patients do not see the results of earlier assessments and will score their pain during the visit. This parameter is included because a lot of patients with LSRS also have back pain in varying intensities, which can change after surgery or conservative treatment[109;110].

Other Outcome Measures

1) Costs. The societal costs during the first year will be estimated in accordance with the recent pharmacoeconomic guideline[111;112]. The costs of hospital admission and surgery will be based on an integral top-down cost analysis in three large regional participating hospitals (aggregated according to the total number of patients per department). From this institutional analysis, the constant costs per admission and the variable costs per admission day will be estimated. From these constant and variable costs, the individual costs of hospital admission and surgery for all patients

can be estimated, using the duration of the hospitalization. In the study an MRI is performed in all cases. The costs of this MRI will only be calculated for patients undergoing surgery, because in the normal situation MRI would only be performed when a surgical indication exists.

Patients will register other health care needs in a diary (including physiotherapy, visits to GP's and specialists, nursing care and medication). Each diary covers a period of 3 months and will be discussed with the patient during the follow-up visits to the research nurse. The volume of health care will be assessed using standard prices[112].

In the diary the patient will also register direct non-medical costs (including time costs, travel expenses and domestic help). To estimate productivity costs the patients will also report absenteeism in the diary. At the follow-up visits, the research nurse will register the work situation, work efficiency and gross wages. Absenteeism will be valued according to the friction-cost method.

2) Incidence of (re-) surgery. One of the goals of the policy for group B is to avoid surgery while achieving at least the same effects. The surgical rate is therefore an indication of the success or failure of this policy. The incidence of re-operation at the same disk level in group A will be an indication of the failure rate for surgery.

3) Side-effects or complications that are ascribed to the treatment are recorded by the patients, their treating physicians and the research nurses.

4) MRI findings. The results of the differences between the baseline MRI and the MRI made 52 weeks after randomization are important secondary outcome measures. The difference in size of the disk herniation (in mm), nerve root compression, and amount of scar tissue will be registered. Failures of surgery can be recognized by inadequate disk removal or decompression of the nerve. The data will be gathered, using a standardized CRF, which will be filled out by the local radiologist, orthopaedic- or neurosurgeon and (neuro-) radiologist

Sample size

The result of this study is based on the short-term success of surgical intervention and will be a trade-off between a quicker relief of leg pain versus an advantage in cost-effectiveness for conservatively managed patients. The sample size is calculated on the basis of the Roland Disability Questionnaire for Sciatica averaged during the 12 months follow-up period. The numbers used for this sample-size are drawn from the Maine Lumbar Spine Study 1 year and recently published 5-year results[81;113]. The difference in the Roland score between the surgical- and non-surgical group in this study did not change between 3 and 12 months follow-up as shown in their study[81] and can be averaged over the first year. The main aim of this study is to measure the short-term functional difference at 12 months follow-up. Surgical treatment is

considered better when the post treatment change is at least 4 points more when compared to the conservative treatment arm[95;114] and constant over time. Considering this constant difference and a mean standard deviation=10 over the first year[113] 140 patients per treatment arm are needed to reach a power (1-β) of 0,90 with $\alpha=0.05$ (two-sided). To answer the main research question 280 patients are needed for analysis with at least 12 months follow-up. The aim is to enrol 300 (150 per arm) patients in the study, including 8 % loss to follow-up after 1 year. The total number of operated patients each year in all participating hospitals exceeds 1400. With this number of patients also a clinically important difference in median time to recovery of two months can be detected by survival analysis. Although the time to recovery is the main issue, the problem of recurrent complaints is still not solved in the different approaches of survival and proportional hazard analysis.

Statistical and cost analysis

Baseline comparability will be investigated by descriptive statistics to examine if randomisation was successful. Differences in success rates between both groups are calculated, together with 95 per cent confidence intervals. In addition to an analysis of the difference in recovery between the two groups (as explained under the paragraph Sample Size Calculation) analyses of the difference in time to recovery will be carried out. Due to lack of data in the literature we could not base our sample size calculations on these differences. Survival-analysis is used to calculate differences in median time to recovery. Continuous outcomes are evaluated as change scores (differences between baseline measurement and each follow-up measurement). Multivariable analyses are performed to adjust for the eventual differences between the groups at baseline in prognostic indicators. All the analyses are performed according to the intent-to-treat principle. An additional per protocol analysis is performed comparing patients in the wait-and-see group who received surgery with patients in the same group who had not and with patients in the surgery group. To compare the actual treatment sec instead of strategies an explorative analysis will be performed in subgroups off all patients who actually received surgery and who did not receive surgery in both groups. All patients who withdraw from the study are included in the analysis until the time of withdrawal.

The result of this study will be a trade off between the disadvantages of surgery (hospitalisation, reduced quality of life and costs) versus the possible advantages (earlier relief of pain and return to work). For that reason recovery, measured as an 11 point difference in score when compared to baseline (Roland Disability Questionnaire for Sciatica), is the clinically most relevant patient outcome. Quality of Life (SF-36) and perceived recovery are important to compare the reduced quality of life from surgery to the possibly prolonged pain from conservative therapy and also

Table 3: Selected prognostic variables for subgroup analysis

Demographic Variables
- Age < 39 years versus > 39 years,
- Intellectual versus physical demanding job,

Anamnestic and Neurological Variables
- Acute start LSRS versus slow start,
- History of backpain versus no history,
- Influence of coughing, sneezing on complaints versus no influence,
- Difficulty to put on shoes and/or socks versus no difficulty,
- Straight leg raising ≤ 30 degrees versus > 30 degrees,
- Positive crossed straight leg raising sign versus negative sign,
- VAS-pain > 70 versus < 69 mm,
- Tingling/numbness in pain area versus no tingling (9),
- Pain leg worse by sitting versus no worsening (9),
- McGill affective high score versus low score,

Radiological Variables
- MRI disk sequester versus contained disk herniation,
- MRI circumferential gadolinium enhancement versus no enhancement of disk herniation,
- Mediolateral versus median and lateral disk herniation,
- High versus low height of disk level (height 9 mm),

Miscellaneous Variables
- Preference for surgery versus no preference for surgery.
- Disk Herniation at L5S1 vs. L4L5

to be able to compare cost-effectiveness with that of other spine interventions. The EuroQol is important to obtain cost-utility ratio's that can be compared with those of a wide range of other interventions. Utilities are obtained from the descriptive classification system of the EuroQol, using the model described by Dolan[106;115]. Conservative treatment may decrease costs compared to surgery but possibly at the expense of delayed effectiveness. In an incremental cost-effectiveness analysis, societal costs during the first year will be compared to the primary outcome measure (Roland Disability Questionnaire for Sciatica, averaged over the first year), Quality of Life (SF-36, during the first year) and perceived recovery (7-points Likert scale). Cost-effectiveness analyses with these effectiveness measures have been conducted before, allowing comparison with other spine interventions.

Finally, to answer the second research question explorative analyses are conducted to investigate whether the treatment effect after two, six and twelve months varies in specific subgroups of patients (Table 3).

Using logistic regression for success rate and linear regression for severity of the disability, each prognostic indicator is checked for interaction with treatment. If the interaction term is significant, a stratified analysis will be performed.

DISCUSSION

In this article the rationale and design of a pragmatic RCT on the cost-effectiveness of timing of disk surgery for LSRS is described. The only randomized trial[40] so far on this subject only included patients where the caregiver was in doubt about the surgical indication. Patients with severe disabling pain were not randomized[78]. The Sciatica Trial is directed to those patients with a clear surgical indication according to current usual care. The study is pragmatic because it acknowledges that sometimes it may not be possible to postpone surgery for every conservative care patient until 6 months after allocation and that some patients will recover before surgery is performed in the surgical group. In these cases we consider it unethical to hold on to the randomized treatment. Because of the Intent-to-Treat analysis these cases will be analysed in their own allocated randomization arm and will not cause methodological problems because it is two healthcare strategies that are compared, as opposed to two treatments. The objective of this trial is to provide evidence on the preferred timing of disk surgery for sciatica. A prolonged conservative treatment strategy is compared to the international guideline advise of surgery after 6-8 weeks LSRS. The intended size of the study population is sufficiently large to detect short and long term differences between both strategies.

4

ONE-YEAR RESULTS RANDOMIZED TRIAL

Surgery versus prolonged conservative treatment for Sciatica

Wilco C. Peul
Hans C. van Houwelingen
Wilbert B. Van Den Hout
Ronald Brand
Just A.H. Eekhof
Joseph Th. J. Tans
Raph T.W.M. Thomeer
Bart W. Koes

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ABSTRACT

Background: Lumbar disk surgery is often performed in patients who have sciatica that does not resolve within 6 weeks, but the optimal timing of surgery is not known.

Methods: We randomized 283 patients with 6-12 weeks of severe sciatica to early surgery or continued conservative treatment, with delayed surgery if needed. Primary outcome measurements were the Roland Disability Questionnaire, visual analogue scale for leg pain and patient's report of perceived recovery during the first year after randomization. Repeated measurement analysis by intention-to-treat was used to estimate the outcome curves for both groups.

Results: Of 141 patients assigned to undergo early surgery, 125 (89 percent) underwent microdiskectomy after a mean of 2.2 weeks; of 142 patients designated for conservative treatment, 55 (39 percent) were treated surgically after 18.7 weeks. There was no significant overall difference in disability scores during the first year ($p=0.13$) Improvement in the intensity of leg pain was faster for patients randomized to early surgery ($p<.001$). Early surgery also achieved a faster rate of perceived recovery hazard ratio (CI) of 1.97 (1.72-2.22), $p<.001$). In both groups, however, the probability of perceived recovery after one year of follow-up was 95 percent.

Conclusions: The strategies of early surgery and of conservative treatment with delayed surgery if needed resulted in similar outcomes at one year, but early surgery achieved more rapid recovery and pain relief.

Sciatica is characterized by radiating pain in an area of the leg typically served by one lumbar or sacral spinal nerve root; sciatica is sometimes associated with sensory and motor deficit. The most common cause of sciatica is a herniated disk. The estimated annual incidence of sciatica is 5 per 1000 adults[46]. The economic impact of lumbar spine disorders is high, ranking the fifth most expensive disease category for hospital care. It is the most expensive category as far as work absenteeism and disablement are concerned[77]. The natural history of sciatica is favorable, with resolution of leg pain within 8 weeks from onset in the majority of patients[57;79;116]. Starting from the first successful surgical treatment in 1934[4] international consensus has been that surgery should be offered only if symptoms persist after a period of conservative treatment[117]. There is however no consensus on how long conservative therapy should be tried before surgery is considered. Sociocultural preferences account for a wide variation[46] in the rates of surgery. For example in the US and the Netherlands surgery rates are relatively high. Dutch guidelines[44] recommend offering the patient the option of surgery if symptoms do not improve after 6 weeks of conservative treatment. However, the optimal timing of disk surgery has not been established. This report describes the efficacy of early surgical intervention compared to a strategy of prolonged conservative care and delayed surgery, if needed, for patients with disabling sciatica.

Methods

We conducted a multicenter prospective randomized trial among patients with 6-12 weeks of severe sciatica to determine whether a strategy of early surgery leads to better outcomes during the first year than a strategy of conservative treatment for an additional 6 months and performing delayed surgery for patients who had not improved. The medical ethics committee at each of 9 participating hospitals approved the protocol. Written informed consent was obtained from all patients. Details of the design and study protocol have been published previously[118] (Figure 1).

Eligibility and Randomization

Eligible patients were between 18-65 years of age, had a radiological confirmed disk herniation, and had been diagnosed by an attending neurologist with an incapacitating lumbosacral radicular syndrome lasting between 6 and 12 weeks. Correlation of MRI to complaints was registered by the neurosurgeon. At the time of enrolment an independent research nurse verified persistence of complaints. Patients presenting with a cauda equina syndrome, muscle paralysis or insufficient strength to move against gravity were excluded. Patients were also excluded if they had identical com-

Table 1. Base-line and Follow-up Characteristics of Patients with Sciatica*

	Early Surgery (N=141)	Conservative (N=142)
Age (yr)	41.7 ± 9,9	43.4 ± 9,6
Male sex –no (%)	89 (63)	97 (68)
Quetelet-index†	25.9 ± 4.1	25.8 ± 4.0
Duration of sciatica in weeks	9.43 ± 2.37	9.48 ± 2.11
Took sick leave from work, no (%)	107 (76)	116 (82)
Duration sick leave in weeks	5.32 ± 2.78	5.28 ± 2.62
Radiating pain left leg-no (%)	67 (48)	73 (51)
Positive straight leg-raising test % ‡	100 (71)	104 (73)
Positive crossed straight leg-raising test % ‡	71 (50)	70 (49)
Sensory loss, no (%)	123 (87)	128 (90)
Dermatome anaesthesia, no (%)	31 (22)	33 (23)
Muscle weakness, no (%)	93 (66)	99 (70)
Knee tendon reflex difference, no (%)	54 (38)	51 (36)
Ankle tendon reflex difference, no (%)	75 (53)	107 (75)
Clinical suspected level herniated disk		
Clinical suspected disk level L3-L4 no (%)	6 (4)	5 (4)
Clinical suspected disk level L4-L5 no (%)	69 (49)	57 (40)
Clinical suspected disk level L5-S1 no (%)	66 (47)	83 (58)
Roland Disabilty Questionnaire Score §	16.5 ± 4.4	16.3 ± 3.9
Score on visual analogue scale ¶		
VAS leg pain	67.2 ± 27.7	64.4 ± 21.2
VAS back pain	33.8 ± 29.6	30.8 ±27.7
VAS leg and back pain	61.0 ± 22.3	58.2 ± 20.0
VAS general health #	47.8 ± 24.5	46.0 ± 24.5
Short Form-36 Scores **		
SF-36 bodily pain	21.9 ± 16.6	23.9± 18.1
SF-36 physical functioning	33.9 ± 19.6	34.6 ± 19.0
SF-36 social functioning	44.6 ± 30.1	43.3 ± 27.1
SF-36 role-physical functioning	8.2 ± 20.7	8.3 ± 21.0
SF-36 role-emotional functioning	51.0 ± 46.0	52.4 ± 46.0
SF-36 mental health index	67.8 ± 19.7	67.7 ± 19.5
SF-36 vitality	47.5 ± 21.3	47.9 ± 21.3
SF-36 general health perception	64.6 ± 20.3	64.1 ± 20.3
Sciatica Frequency/ Bothersome Index ††		
Frequency index	16.0 ± 4.6	16,2 ± 4.2
Bothersome index	14.6 ± 5.1	14.5 ± 4.1
Preference conservative treatment-no (%)	42 (30)	43 (30)

Table 1. Continued

	Early Surgery (N=141)	Conservative (N=142)
Surgical Treatment during follow-up	**Early Surgery**	**Conservative**
Surgery actually performed (%)	125 (89)	55 (39)
Mean time to surgery in weeks (CI)	2.2 (1.9-2.5)	18.7 (14.3-23.0)
Median time in weeks (Interquartile Range)	1.9 (1.1-2.4)	14.6 (6.4-26.0)
Recurrent disk surgery (%)	4 (3.8)	1 (2)

* Plus-minus value are means ± SD. There were no significant differences among the two groups on any of the baseline characteristics.

† Quetelet-Index or Body-Mass Index is calculated by dividing the weight in kilograms by the squared length in meters. Higher scores define overweight.

‡ Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

§ The Roland Disability Questionnaire for Sciatica is a disease specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.

¶ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

\# General Health perception was indicated on a visual analogue scale, on a 100 millimeter line with 0 representing the worst and 100 the best health perception a patient can imagine.

** SF-36 is the abbreviation of Medical Outcomes Study 36-Item Short Form Health Survey (Range 0-100) and is a generic health status questionnaire consisting of 36 items on physical and social functioning delineating 8 domains of quality . Higher score indicates less severe symptoms.

†† The Sciatica Frequency and Bothersome Index (SFBI) is a scale from 0 to 6, which assesses the frequency (0=not at all to 6=always) and bothersomeness (0=not bothersome to 6=extreme bothersome) of back and leg symptoms. The sum of the results of four symptom questions yields both indexes, ranging from 0 to 24: leg pain; numbness and/or tingling in the leg; weakness in the leg or foot; pain in the back or leg while sitting.

plaints in the past twelve months, a history of spine surgery, bony stenosis, spondylolisthesis, pregnancy or severe comorbidity.

A computer-generated permuted-block scheme was used for randomization, stratified according to center (n=9). One hour before randomization patients were again evaluated. If at that moment, eligibility criteria were no longer met due to recovery, patients were excluded. Otherwise they were included and the next numbered opaque envelope containing the assigned strategy was opened. Patients could not be blinded to treatment arm.

Treatment

Early surgery was scheduled within 2 weeks of assignment and only cancelled if spontaneous recovery occurred before the date of surgery. Under either general or spinal anesthesia the symptomatic disk herniation was removed by a minimal unilateral transflaval approach with magnification. The goal of surgery was to decompress the nerve root and reduce the risk of recurrent disk herniation by an annular fen-

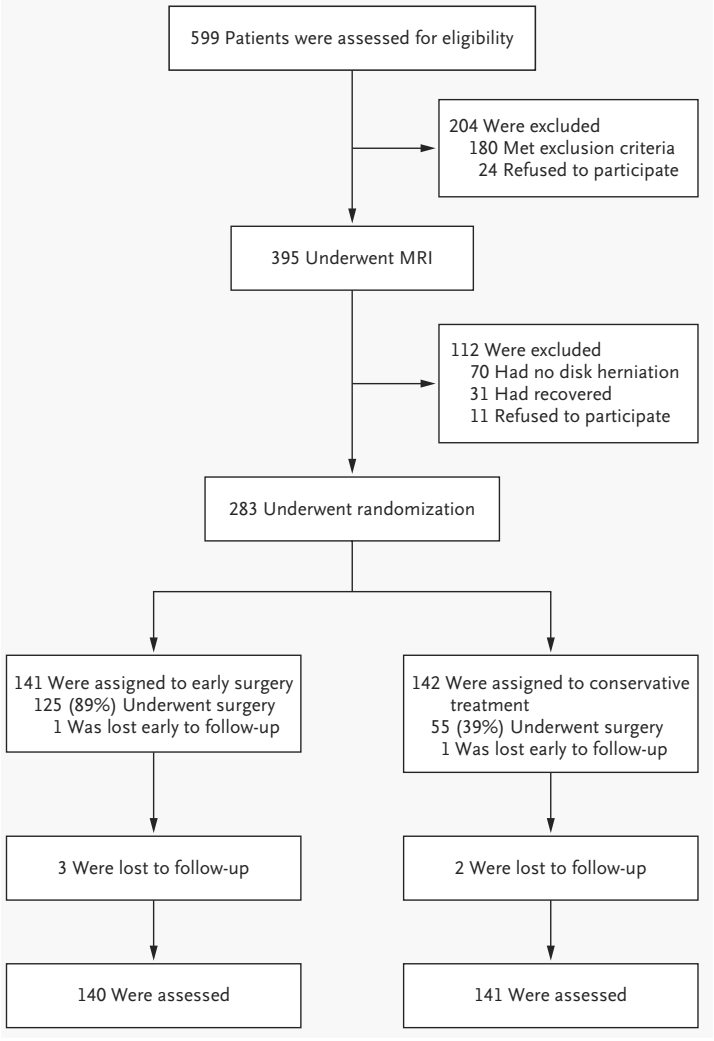


Figure 1. Flow-diagram

estration, curettage and removal of loose degenerated disk material out of the disk space using a rongeur, without any attempt to perform a subtotal diskectomy. The duration of the hospital stay depended on the patient's functional ability to mobilize. Usual care was provided according to the protocols of the participating surgical departments. At home the rehabilitation process was supervised by the physiotherapist who used a standardized exercise protocol. Patients were advised to resume their regular jobs when able, depending on the nature of the work.

Prolonged conservative management was provided by the general practitioner. Ample information was provided about the favorable prognosis. Study participants were offered to visit our trial website, exclusively designed to inform patients about their successfully natural course irrespective of the initial pain intensity. Treatment was mainly aimed at resuming daily activities. If necessary the prescription of pain medication was adjusted according to existing clinical guidelines[118]. Patients who had considerable fear of movement were referred to a physiotherapist. If sciatica persisted 6 months after randomization microdiskectomy was offered. Increasing leg pain not responsive to medications or progressive neurological deficit were reasons for performing surgery earlier than 6 months.

Outcomes

Patients were assessed by means of the Roland Disability Questionnaire for Sciatica (RDQ)[114], 100 mm visual analogue scale for leg pain (VAS-leg)[109] and a 7-point Likert self-rating scale of global perceived recovery. Functional disability, intensity of leg pain and global perceived recovery questionnaires were the primary outcomes and were assessed at 2, 4, 8, 12, 26, 38 and 52 weeks.

Secondary outcomes, such as a repeated neurological examination, functional-economic observational assessments (PROLO)[104] by the independent research nurse, as well as the Short Form-36 scale[107], Sciatica-Frequency-and-Bothersomeness Index[165] and a 100 mm visual analogue scale for health perception[118] were filled out at monitoring visits scheduled at 8, 26 and 52 weeks. Research nurses observed their own patients at the planned follow-up moments and were not blinded to the patients' treatment assignment.

Statistical analysis

The aim of this study was to estimate the difference between the two treatment groups in disease-specific disability of daily functioning measured with the RDQ, the VAS-leg pain intensity and to estimate the difference in median time to recovery, measured with dichotomized self-assessment on the Likert scale as a function of time since randomization. Assuming a mean standard deviation of 10 points[81] over the first year 140 patients were calculated to be required per treatment arm to provide a statistical power of 0.90 with a two-tailed significance level of 0.05 to detect at least three points difference on the RDQ.

Recovery was defined as complete or near complete disappearance of complaints measured with a 7-point Likert scale. Although this trial was primarily meant to study average differences in functional outcome, it was also initially estimated that this sample size would also have a statistical power of 90 percent to detect a difference of 2 months in median time to recovery using estimates from survival models.

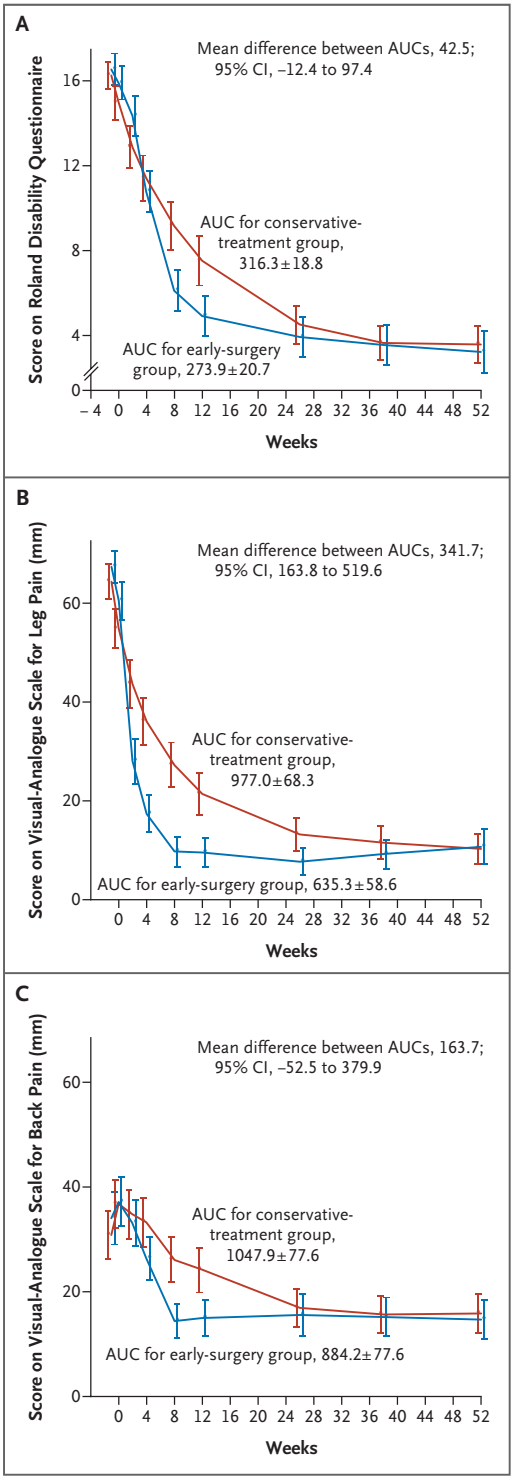


Figure 2. Repeated Measurement Analysis Curves of Mean scores for Roland Disabilty Questionnaire (Panel A), Leg Pain (Panel B) and Back Pain (Panel C) on a Visual-Analogue Scale.

All three panels show the 52-week curves with 95 percent confidence intervals represented by vertical bars at consecutive moments of measurement. Red lines represent the conservative treatment group, while the blue lines represent early surgery.

Panel A** represents the mean disability scores at consecutive moments of measurement. Although the curves differ, and the short term mean results at 8 and 12 weeks show significantly non-overlapping confidence intervals the overall difference between the areas under the curves (AUC) over 12 months is not significant **(p=0.13).

***Panel B** represents mean visual analogue scores for intensity of leg pain in mm, showing an early effect for leg pain in favor of the surgical group from 2 to 26 weeks, but with near equal scores at one year. The difference between the mean AUC's is significantly different **(p<0.001)**.*

Panel C** represents mean visual analogue scores for intensity low back pain in mm. Starting with a lower intensity score when compared to leg pain, the mean AUC's exhibit a less strong and not significant difference **(p=0.14)

** Area's under the curve are expressed by their means ± SE, while the mean difference is expressed by the corresponding 95 percent confidence interval*

Data collection and quality checking were performed with the ProMISe data management system of the Department of Medical Statistics & BioInformatics[119] of the Leiden University Medical Center . For all statistical analyses SPSS 12.0[120] was used. Differences between groups at baseline were assessed by comparing means, medians or percentages, depending on the type of variable. Baseline values of variables were used as covariates in the main analyses whenever appropriate to adjust for possible differences between the randomized groups and to increase the power of the analyses. Outcomes of function and pain were analyzed using a repeated measurements analysis of variance using a first order autoregressive covariance matrix. Estimated consecutive scores were expressed as means and 95 % confidence intervals. Pointwise estimates were obtained using models with time as a categorical covariate to allow assessment of systematic patterns. Differences between randomization groups were assessed by either estimating the main effect of the treatment or the interaction between treatment and time. As a second approach to quantify the differences between the two groups over total follow-up time, "area under the curve" quantities (AUC) were calculated between randomization and week 52 and subsequently compared using Student t-tests. Finally a Kaplan-Meier survival analysis was used to estimate the "time elapsed from randomization until recovery" and curves were compared using a logrank test. A Cox model was used to compare speeds of recovery by calculation of a Hazard Ratio. Whether "speed of recovery" can be demonstrated to differ among subgroups[118] was assessed by testing the interaction between each subgroup variable and the randomization variable with a cutoff value of 0.10 for significance in view of the lower power of the interaction test. All analyses were performed by intention-to-treat.

RESULTS

Between November 2002 and February 2005, 599 patients meeting the criteria for a surgical indication according to their GP were contacted (Figure 1). After initial consultation with the neurologist, 395 patients who met the inclusion criteria were referred for MRI. At the second visit 283 patients continued to suffer from sciatica, the causal disk herniation had been visualized as well and subsequently were allocated to one of two treatment strategies. No significant differences were noted in baseline characteristics between patients in the two study groups (Table 1). Of 141 patients assigned to receive early surgical treatment, 16 patients recovered before surgery was actually performed. Median time to early surgery for the remaining 125 patients was 1.9 weeks (Table 1) after randomization. Of the 142 patients assigned to the conservative treatment group 55 underwent surgery during the first year (Table 1) after

Table 2. Primary and Secondary Outcomes based on Intent-to-Treat Repeated Measurements Analysis and Treatment effects*

	2 weeks			8 weeks		
Primary Outcomes	**Surgery**	**Conservative**	**Treatment effect (95% CI)**	**Surgery**	**Conservative**	**Treatment effect (95% CI)**
Roland Disabilty †	14.4 (0.5)	13.0 (0.5)	**-1.6 (-2.8 to -0.3)**	6.1 (0.5)	9.2 (0.5)	**3.1 (1.7 to 4.3)**
VAS-Legpain ‡	28.5 (1.9)	44.2 (1.9)	**15.7 (11.7 to 19.7)**	10.2 (1.9)	27.9 (1.9)	**17.7 (12.3 to 23.1)**
VAS-Backpain §	33.3 (2.1)	34.9 (2.1)	**1.5 (-4.5 to 7.4)**	14.4 (2.1)	25.7 (2.1)	**11.3 (5.6 to 17.4)**
Likert-Global ‡ ¶	3.1 (0.1)	3.5 (0.1)	**0.4 (0.1 to 0.6)**	2.2 (0.1)	3.1 (0.1)	**0.9 (0.6 to 1.2)**
Secondary Outcomes						
PROLO Functional ‖ **	1.1 (0.08)	1.1 (0.08)	**0.04 (-0.2 to 0.3)**	2.8 (0.09)	2.0 (0.09)	**-0.8 (-1.1 to 0.6)**
PROLO Economic ‖ **	1.2 (0.1)	1.3 (0.1)	**0.2 (-0.2 to 0.6)**	1.8 (0.1)	2.3 (0.1)	**0.5 (0.09 to 0.8)**
SF-36 bodily pain	-	-	**-**	62.8 (2.1)	54.4 (2.0)	**-8.4 (-13.5 to -3.2)**
SF-36 physical functioning	-	-	**-**	71.2 (1.7)	61.9 (1.9)	**-9.3 (-14.2 to -4.4)**
SF-36 social functioning	-	-	**-**	69.9 (2.3)	67.6 (2.3)	**-2.3 (-8.3 to 3.7)**
SF-36 role physical functioning	-	-	**-**	29.5 (3.1)	29.3 (3.2)	**-0.2 (-5.9 to 5.5)**
SF-36 role emotional functioning	-	-	**-**	69.3 (3.5)	66.2 (3.7)	**-3.1 (-9.3 to 3.0)**
SF-36 mental health index	-	-	**-**	82.1 (1.3)	73.0 (1.7)	**-9.1 (-13.4 to -4.8)**
SF-36 vitality	-	-	**-**	67.5 (1.7)	57.1 (1.7)	**-10.4 (-15.1 to -5.7)**
SF-36 general health perception	-	-	**-**	75.7 (1.5)	65.2 (1.6)	**-10.5 (-15.2 to -5.8)**
SFBI Frequency	-	-	**-**	5.3 (0.4)	9.3 (0.5)	**4.0 (2.7 to 5.3)**
SFBI Bothersomeness				4.0 (0.4)	7.6 (0.5)	**3.6 (2.3 to 4.9)**
VAS Health	59.8 (1.9)	55.2 (2.2)	**4.6 (-1.2 to 10.4)**	74.7 (2.3)	62.7 (2.4)	**12.0 (5.3 to 18.8)**
Cumulative Surgeries performed (%) ††	87 (62)	2 (1)	**Δ 85 (61)**	123 (87)	16 (11)	**Δ 107 (76)**

* Results are described by their mean (SE)
† Overall difference between scores not significant (p=0.12)
‡ Fixed effects significantly different in favor of early surgery ($p < 0.001$)
§ Significantly different in favor of early surgery (p =0.045)
¶ Likert global perceived recovery is defined by a 7-point scale "Worse" to "Complete" recovery. Lower scores represent recovery.
‖ PROLO is a 4-point qualitative functional-economic scale filled in by the observer; it is divided into a functional and an economic scale. A lower value represents poor functioning and decreased possibility to work
** Functional observation scores show a difference in favor of surgery ($p<0.001$) while the overall Economic scores were not significantly different (p=0.154) with an outcome at 8 weeks in favor of conservative treatment

Table 2. Continued

	26 weeks			52 weeks		
Primary Outcomes	**Surgery**	**Conservative**	**Treatment effect (95% CI)**	**Surgery**	**Conservative**	**Treatment effect (95% CI)**
Roland Disabilty †	4.0 (0.5)	4.8 (0.5)	**0.8 (-0.5 to 2.1)**	3.3 (0.5)	3.7 (0.5)	**0.4 (-0.9 to 1.7)**
VAS-Legpain ‡	8.4 (1.9)	14.5 (1.9)	**6.1 (2.2 to 10.0)**	11.0 (1.9)	11.0 (1.9)	**0 (-4.0 to 4.0)**
VAS-Backpain §	15.5 (2.2)	17.8 (2.1)	**2.3 (-3.6 to 8.2)**	14.2 (2.2)	16.5 (2.1)	**2.3 (-3.6 to 8.2)**
Likert-Global ‡ ¶	2.1 (0.1)	2.3 (0.1)	**0.2 (-0.07 to 0.5)**	1.9 (0.1)	2.1 (0.1)	**0.2 (-0.1 to 0.4)**
Secondary Outcomes						
PROLO Functional ‖**	3.4 (0.08)	2.9 (0.08)	**-0.5 (-0.7 to -0.2)**	3.3 (0.08)	3.3 (0.08)	**0. 04 (-0.19 to 0.28)**
PROLO Economic ‖**	3.0 (0.1)	2.9 (0.1)	**-0.1 (-0.5 to 0.3)**	3.2 (0.1)	3.4 (0.1)	**0.2 (-0.2 to 0.6)**
SF-36 bodily pain	76.1 (1.1)	72.8 (1.9)	**-3.3 (-8.4 to 1.8)**	81.2 (2.0)	78.5 (1.9)	**-2.7 (-7.9 to 2.6)**
SF-36 physical functioning	79.1 (1.9)	77.6 (1.7)	**-1.5 (-6.4 to 3.4)**	84.2 (1.8)	82.0 (1.9)	**-2.2 (-7.2 to 2.8)**
SF-36 social functioning	86.9 (1.8)	82.4 (1.9)	**-4.5 (-10.6 to 1.4)**	89.4 (1.6)	88.1 (1.7)	**-1.3 (-7.3 to 4.7)**
SF-36 role physical functioning	69.1 (3.5)	61.9 (3.6)	**-7.2 (-13.0 to -1.4)**	78.4 (3.2)	74.5 (3.3)	**-3.9 (-9.7 to 1.9)**
SF-36 role emotional functioning	84.9 (2.7)	81.0 (3.0)	**-3.9 (-10.1 to 2.3)**	87.2 (2.6)	88.6 (2.5)	**1.4 (-4.8 to 7.6)**
SF-36 mental health index	83.2 (1.3)	80.5 (1.5)	**-2.7 (-7.0 to 1.6)**	83.0 (1.3)	81.1 (1.4)	**-1.9 (-6.2 to 2.4)**
SF-36 vitality	71.7 (1.5)	68.5 (1.6)	**-3.2 (-7.9 to 1.3)**	72.2 (1.7)	69.9 (1.5)	**-2.3 (-7.1 to 2.5)**
SF-36 general health perception	74.1 (1.7)	71.6 (1.6)	**-2.5 (-7.2 to 2.2)**	74.2 (1.8)	74.3 (1.7)	**-0.1 (-4.8 to 4.7)**
SFBI Frequency	4.8 (0.4)	6.6 (0.4)	**1.8 (0.7 to 1.9)**	4.8 (0.5)	5.3 (0.4)	**0.5 (-0.8 to 1.8)**
SFBI Bothersomeness	3.2 (0.4)	4.4 (0.4)	**1.2 (0.1 to 1.3)**	3.1 (0.4)	3.5 (0.4)	**0.4 (-0.7 to 1.5)**
VAS Health	76.2 (2.2)	71.7 (2.4)	**4.5 (-2 to 11.0)**	79.3 (2.2)	77.9 (2.2)	1.4 (-2.0 to 11.0)
Cumulative Surgeries performed (%) ††	125 (89)	42 (30)	**Δ 83 (59)**	125 (89)	55 (39)	**Δ 70 (50)**

†† Just before crossing over to surgery, patients (n=55) assigned for conservative treatment had a mean VAS leg pain score (CI) of 54.0 mm (46.2-61.8) and RDQ score (CI) of 15.0 (13.3-16.8).

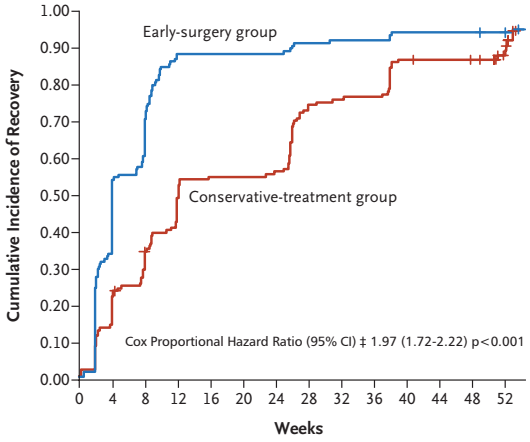


*Figure 3. Inverse Kaplan Meier Curves representing Cumulative Incidence of Recovery * † .*

Not recovered	*8w*	*26w*	*38w*	*52w*
Early Surgery	*54*	*13*	*10*	*6*
Conservative	*97*	*48*	*28*	*8*
Δ %	*36*	*22*	*9*	*6*
CI of Δ % §	*25-47*	*12-32*	*0.7-17*	*0.1-12*

Median time to recovery (CI 95 %) was 4.0 (3.7-4.3) weeks for early surgery and 12.1 (9.5-14.8) weeks for conservative treatment. The number of patients who had not yet recovered patients at each measurement are listed, with the proportion difference Δ (%) of recovered patients and 95 percent confidence interval.

** Recovery is defined as complete or near complete recovery using the Likert 7-point scale.*

† Log Rank (p< 0.001)

‡ The hazard ratio (with 95 percent confidence interval and p value) , obtained with the unadjusted Cox model, estimates the average ratio of recovery rate between patients assigned to receive a strategy of early surgery, versus the rate among those assigned to conservative treatment.

§ 95 percent Confidence Interval of Difference

a median period of 14.6 weeks, because of intractable pain expressed by a mean VAS-leg score of 54 mm and RDQ of 15.0, measured shortly before choosing surgery. In the early surgery group 3.2 percent suffered recurrent sciatica leading to a second surgical intervention, compared to 2 percent after delayed surgery. Complications occurred in 1.6 percent of all surgical patients, involving 2 dural tears and 1 wound hematoma. All complications recovered spontaneously. None of the patients developed neurological signs after surgery.

After randomization, RDQ curves (Figure 2) initially separate in favor of conservative treatment. The slopes cross at 4 weeks, indicating the moment when a better outcome was noted in the early surgery arm. The major difference in function was noted between 8 and 12 weeks. Analysis of the area under the curves (AUC) of the mean RDQ revealed no significant difference (p=0.13) over the 52-

week follow-up period. The difference between the AUC's of the mean VAS-leg pain however was significantly ($p<0.001$) in favor of early surgery. After surgery, leg and concomitant back pain diminished quickly whereas a slower and linear recovery of pain was noted in the prolonged conservative treatment group. One year after randomization the RDQ, Likert and VAS-leg pain scores however show nearly equal recovery rates for the two arms (Table 2). The subgroup of 55 patients with persistent sciatica and delayed surgery experienced identical improvement of these scores at one year, when compared those patients allocated to early surgery. The survival analysis (Figure 3; logrank $p<0.001$) highlights the influence of early surgery on the speed of recovery during the first 9 months, but the difference in cumulative incidence of recovery decreased over time with similar recovery rates of about 95 % for both groups after one year. Median time (CI) to recovery was 4.0 (3.7-4.4) weeks for early surgery and 12.1 (9.5-14.9) weeks for prolonged conservative treatment.

The Hazard Ratio as estimated in a univariable Cox model with recovery as an endpoint, was 1.97 (1.72-2.22), favoring early surgery. Analyses of treatment groups according to predefined baseline characteristics showed that surgery was beneficial in all subgroups assessed, with the possible exception of patients without sciatica provocation by sitting (Figure 4).

Discussion

Although relief of complaints was twice as fast for sciatica patients treated with early surgery, this multicenter randomized trial demonstrated that this strategy did not result in a better overall 1-year functional recovery rate when compared with a policy of prolonged conservative treatment with eventually offering delayed surgery. During one year 89 percent of patients in the early surgery group and 39 percent of the conservative treatment group were treated by microdiskectomy. At one-year follow-up no significant differences were detected in mean scores for any outcome measurement, including leg pain. Thus, the major advantage of early surgical treatment remained the faster relief of sciatica.

Slow recovery of daily functioning two weeks after early surgery may have been caused by standard microdiskectomy techniques when compared to modern micro-endoscopic or sequestrectomy methods[121-123]. This period was however followed by faster recovery during the following weeks, but without an overall significant difference over the first year. RDQ scores did not reach the minimal clinical important difference (MCID) of 4 points, required to conclude clinical relevance in favor of early surgery[114;118]. Leg pain exhibited a significantly faster recovery in the early surgery

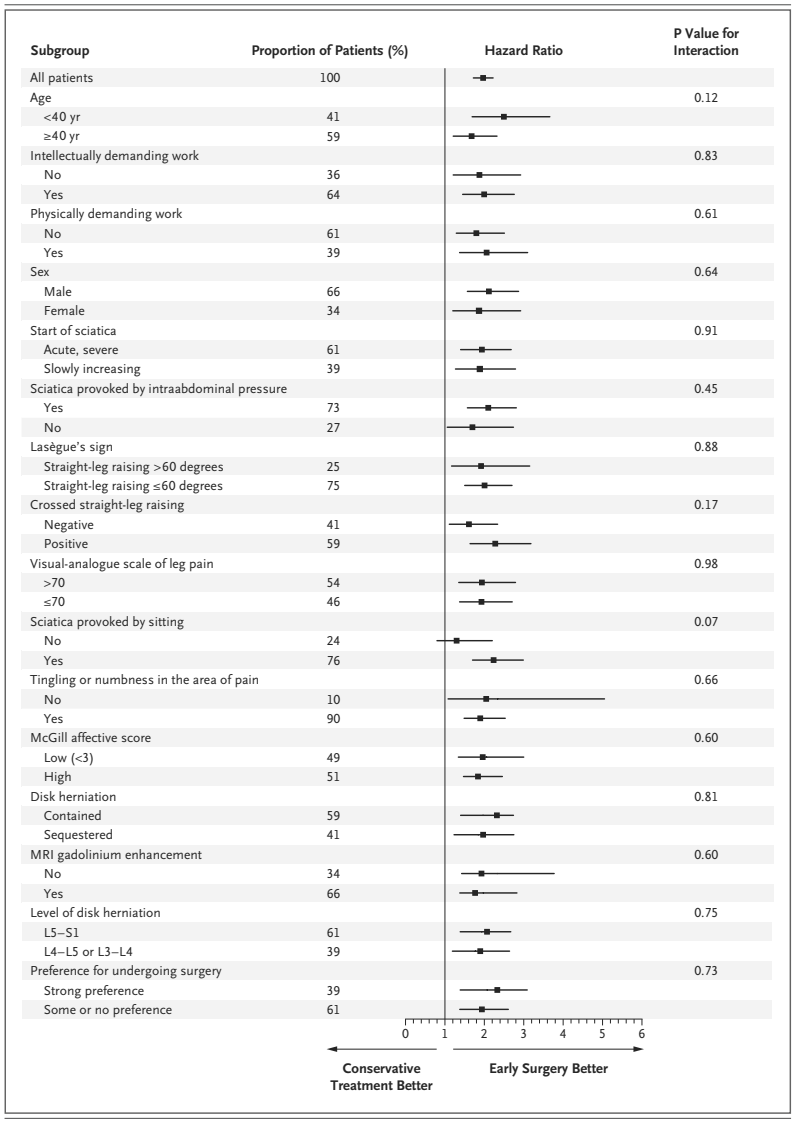


Figure 4: Time to complete recovery according to baseline patient characteristics. Hazard ratios (black squares), 95 % CI's (horizontal lines) show the effect within each subgroup. P values for the interaction between treatment effect and the predefined subgroup variables for prolonged conservative treatment versus early surgery are shown.

** These variables were dichotomized before entered in the Cox proportional hazard model. Results were comparable when analyses of continuous variables were performed.*

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The McGill affective score measure the qualitative perception of pain by the patient. High affective dimensional scores correlate to a more depressed and anxious individual mood when compared to patients who report low affective scores.

§ Sequestrated disk herniations are defined by a defect in the annulus fibrosis and loose disk fragments in the epidural space, visualized by MRI scanning.

group but maximum differences between mean scores were less then 20 mm, on a 100 mm scale, and at one year scores approached equivalence.

The benefits of surgery on speed of recovery and pain relief were consistent among all predefined subgroups except for patients who did not have provocation of sciatica by sitting. The interaction level is however marginally significant and the majority of patients (76 %) did experience provocation of sciatica by sitting. It is however reasonable to assume that daily functioning is highly influenced by the impossibility to sit. Remarkably and unexpected were the absent interactions of Lasègue's sign, pain intensity, MRI disk sequestrations and patient preferences with treatment strategies.

Since 1934 many studies have demonstrated the success of surgical treatment of sciatica. Weber's landmark study comparing surgery with conservative care in a randomized clinical trial, excluding patients with "intolerable" pain, demonstrated surgery to be superior at one-year follow-up while after four years the results no longer differed[40;124;125]. Surgery did show some early benefit in a randomized study[126] comparing surgery to corticosteroids. Weinstein et al. recently reported the results of their carefully designed SPORT trial trying to answer the same research question but failed to show any benefit of surgery on primary outcomes in their intention-to-treat analyses[49]. Substantial cross-over, however, occurred in both treatment arms leading to only 14 % proportional difference in surgery rates at six weeks. Furthermore only 59 % actually underwent this intervention after being allotted to surgery, apparently planned at highly variable moments in time during the first year instead of an early execution. Also in contrast to our study which enrolled patients with 6-12 weeks of sciatica, in the Weinstein et al study at least 20 % of patients at baseline had complaints for at least 6 months[122]. Notwithstanding the fact that primary outcomes of our study were also strongly influenced by a substantial crossover during conservative treatment, timing of surgery was executed early in the intervention arm. While 61 % of patients recovered quickly without surgery, the remaining 39 % continued to register relatively high pain and disability scores concordant with physical suffering for a prolonged period of time until surgery was performed. Recently Österman reported results of a comparable designed trial, showing the same trend with earlier recovery of those assigned to surgery and nearly 40 % undergoing seemingly "inevitable" surgery during conservative management, but did not accrue enough patients to gain adequate statistical power[66].

Sciatica results in high direct and indirect costs[77]. Most of these costs are not generated by medical treatment but are attributed to production loss. Annually more than 1.5 million disk surgeries are performed[127] worldwide, using different time windows for treatment. Prior studies did not succeed to evaluate how timing of surgery affects outcomes. Patients need a thorough understanding of the course of symptoms to in-

form their decisions about surgery. The results of this study will help in the decision making process.

This study had several limitations, which may limit the generalizability of its findings. Patients randomized to conservative therapy were guided by research nurses who participated in pain management. Although this additional support did not prevent surgeries in 39 % of patients with severe sciatica, it does not reflect usual care. This must be kept in mind when implementing a strategy of prolonged conservative treatment for general populations. It is clearly impossible to blind patients and independent research nurses. A methodological point of attention is the fact that "time until recovery" was calculated only at predefined moments in follow-up, leading to interval censoring. The exact date of recovery was not registered, but sampled at planned follow-up moments. This leads to an underestimated speed of recovery in the interval between the sampling time points, but affects both treatment groups in the same way.

The present study provides individual patients with sciatica, who are considering disk surgery, information about how early surgery and conservative treatment affect the three separate outcome parameters, i.e. disease specific disability, intensity of leg pain and time to recovery. Patients who are not able to cope with leg pain, experience an unacceptable slow natural course of sciatica and who want to minimize time to recovery of pain are likely to choose early surgery. Patients who are achieving control of pain that is acceptable to them may decide to postpone surgery with the hope that it will not be needed, without reducing the chance on complete recovery at twelve months. Although both policies result in equilibrium after one year, early surgery remains a valid treatment option for well informed patients.

5

ONE-YEAR COST UTILITY RESULTS

Cost-utility analysis of prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disk herniation

Wilbert B. van den Hout
Wilco C. Peul
Bart W. Koes
Ronald Brand
Job Kievit
Raph T.W.M. Thomeer

Submitted for publication

ABSTRACT

Background: Controversy exists on how long sciatica patients should receive conservative therapy before surgery is offered.
Methods: In a randomized controlled trial, patients with 6-12 weeks of sciatica caused by lumbar disk herniation received either six months of prolonged conservative care (n=142) or early surgery (n=141). One-year quality-adjusted life years (QALYs) and societal costs were estimated from patient-reported utilities (British and US EuroQol, Short Form 6D and Visual Analogue Scale) and cost diaries (health care, patient and productivity costs).
Results: Compared to prolonged conservative care, early surgery provided faster recovery, with a QALY gain of 0.044 according to the British EuroQol (95 %CI 0.005 to 0.083), 0.032 according to the US EuroQol (95 %CI 0.005 to 0.059), 0.024 according to the Short Form 6D (95 %CI 0.003 to 0.046) and 0.032 according to the visual analogue scale (95 %CI -0.003 to 0.066). From the health care perspective, early surgery provided higher costs ($2,020 difference; 95 %CI $935 to $3,099), with a cost-utility ratio of $46,000 (95 %CI $15,000 to $478,000) per QALY. From the societal perspective, savings on productivity costs led to a negligible cost difference ($-13; 95 %CI $-4,475 to $4,449).
Conclusions: Faster recovery from sciatica makes early surgery more likely to be cost-effective than prolonged conservative care. The estimated difference in health care costs was acceptable and was compensated by the difference in absenteeism. For a willingness to pay of $50.000 or more per QALY, early surgery need not be withheld for economic reasons.

Introduction

Since the natural history of sciatica is favorable, international consensus has been that surgery should be offered only if symptoms persist after a period of conservative treatment.[117] However, the optimal timing of disk surgery has not been scientifically established.[45;46;128] In a randomized controlled trial, we compared early surgery to six months of prolonged conservative care.[118;129] The trial showed faster recovery after early surgery, but without any difference after a year.

Several economic evaluations have compared surgical procedures[130-133] or non-surgical types of care.[134-137] The two economic evaluations that compared surgery to conservative care suggested favorable cost-effectiveness for surgery, but used either extensive modeling[93] or a case-control design.[138] As a result, the cost-effectiveness of early surgery for sciatica is yet unestablished.[139] We therefore conducted a cost-utility analysis for our randomized controlled trial, comparing observed one-year quality-adjusted life years (QALYs) to observed one-year societal costs, to determine whether the faster recovery after early surgery is attained at reasonable costs.

Methods

Patients participated in a multi-centre randomized controlled trial (ISRCT 26872154), comparing six months of prolonged conservative care to early surgery.[118] The Medical Ethics Committees of the nine participating hospitals approved the study and all participating patients gave written informed consent.

A total sample size of 280 patients was chosen, sufficient to detect a three-point difference on the Roland Disability Questionnaire for Sciatica.[114] Between November 2002 and February 2005, 283 patients were enrolled, without clinically or statistically significant baseline differences between both randomization groups (Table 1).[129]

Patients and treatment

Eligible patients were 18 to 65 years of age, with a radiologically confirmed disk herniation, and lumbosacral radicular syndrome that had lasted for 6 to 12 weeks. Patients presenting with cauda equina syndrome, muscle paralysis, or insufficient strength to move against gravity were excluded. Other exclusion criteria were the occurrence of another episode of symptoms similar to those of the current episode during the previous 12 months, previous spine surgery, bony stenosis, spondylolisthesis, pregnancy, or severe coexisting disease.

Early surgery was scheduled within 2 weeks after randomization and only cancelled if spontaneous recovery occurred before the date of surgery. Prolonged con-

Table 1. Baseline characteristics*

	Prolonged conservative (n=142)	Early surgery (n=141)
Age (yr)	43 (10)	42 (10)
Male sex	68%	63%
Quetelet index	26 (4)	26 (4)
Duration of Sciatica in weeks	9.5 (2.1)	9.4 (2.4)
Sick Leave	82%	76%
Positive straight leg-raising test†	73%	71%
Positive crossed straight leg-raising test†	49%	50%
Sensory loss	90%	87%
Dermatome anaesthesia	23%	22%
Muscle weakness	70%	66%
Knee tendon reflex difference	36%	38%
Ankle tendon reflex difference	75%	53%
Finger-ground distance (cm)	35 (17)	33 (16)
Patient-reported visual analogue scales		
VAS leg pain‡	64 (21)	67 (28)
VAS back pain‡	31 (28)	34 (30)
VAS leg and back pain‡	58 (20)	61 (22)
VAS general health§	46 (25)	47 (25)
Roland Disability score¶	16 (4)	17 (4)

* Averages (SD) or percentage of patients. There were no statistically significant differences between both randomization groups on any of the baseline characteristics.

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance below a unilateral 60 degrees angle provocative straight leg raising, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The intensity of pain was indicated on a 100 millimeter visual analogue scale (VAS), with 0 representing no pain and 100 the worst pain ever experienced.

§ General health was indicated on a 100 millimeter visual analogue scale (VAS), with 0 representing the worst imaginable health and 100 the best imaginable health.

¶ The Roland Disability Questionnaire for Sciatica is a disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.

servative care was provided by the general practitioner. If sciatica persisted 6 months after randomization, microdiskectomy was offered. Increasing leg pain not responsive to medication and progressive neurological deficit were reasons for performing surgery earlier than 6 months. All patients were advised to resume their regular jobs when they were able, depending on the nature of their work.

Utilities and QALYs

Utilities represent the valuation of the quality of life of the patients, on a scale from zero (as bad as death) to one (perfect health). Patients described their quality of life using the EuroQol classification system (EQ5D),[105] from which British (EQ5D-UK) and US (EQ5D-US) utilities were calculated.[106;140] Similarly, patients reported their quality of life using the Short Form 36 (SF36), from which Short Form 6D (SF6D)

utilities were calculated.[141] Both EQ5D and SF6D provide societal valuations, which is preferred for economic evaluations from a societal perspective. In addition, we obtained valuations by the patients themselves, using a visual analogue scale (VAS) ranging from 0 (worst imaginable health) to 100 (perfect health). VAS values were transformed to a utility scale,[142] using the power transformation $1-(1-VAS/100)^{1.61}$. EQ5D and VAS measurements were obtained at -2, 0, 2, 4, 8, 12, 26, 38, and 52 weeks after randomization. SF36 measurements were obtained less frequently, at -2, 8, 26, and 52 weeks after randomization. For the EQ5D, SF36 and VAS measurements, 4 %, 5 % and 5 % of the items were missing, respectively, and were imputed using the rounded average within the same randomization group at the same time. Average utility during each separate quarter and during the entire year (QALYs) were calculated from the area under the utility curves.

Costs

Costs during the one-year follow-up period were estimated from the societal perspective. Because of the limited time horizon, costs were not discounted. Costs were converted to US dollars, at price level 2006 (€ 1 = $1.153).[143]

Using cost diaries, patients reported hospitalizations, visits (specialists, general practitioner, physical therapy, paramedical professionals, and alternative health care), homecare, paid domestic help, informal care, medication and aids (like crutches), out-of-pocket expenses because of the hernia (like swimming) and hours of absenteeism. Diaries were scheduled to be handed in at 2, 4, 8, 12, 26, 38, and 52 weeks after randomization. The 26 (9 %) patients that did not return any cost diary were equally distributed over both randomization groups ($P = 0.98$), but were less likely to have been operated ($P < 0.001$). Selective non-response was corrected for by multiply imputing cost data from patients that did return cost diaries (from the same randomization group and with the same surgical status).[144] For patients that did return cost diaries, the diaries covered 97 %, 91 %, 83 % and 84 % of the first to fourth quarter, respectively. Periods of time that were not covered by a cost questionnaire were imputed with the closest available diary from the same patient.

In the Dutch funding system, individual hospitals set diagnosis-treatment prices for disk surgery, to facilitate competition and price containment. From the prices available from 75 different centers, we excluded the 5 % highest and lowest prices. The remaining prices ranged from $3,799 to $5,481, with an average of $4,445. To introduce a cost structure dependent on the duration of hospital stay, the average price was converted to $2,618 per hospitalization plus $433 per hospitalization day.[145;146] With an average hospital stay of 3.7 days, and adding the costs of related specialist visits, this renders average costs per hospitalization equal to the average diagnosis-treatment price.

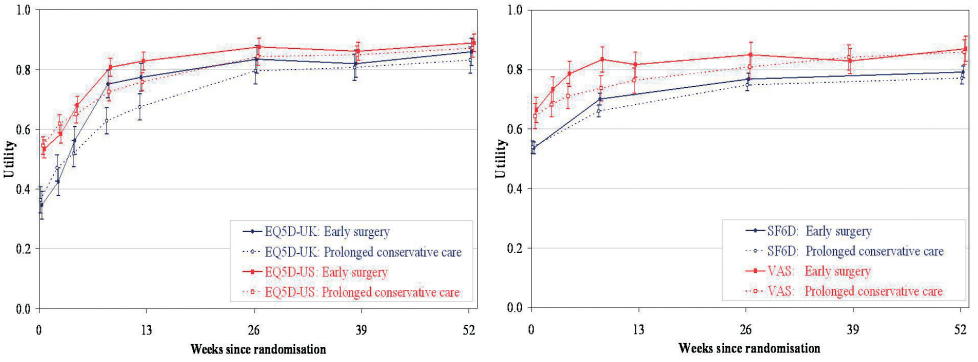


Figure 1. Utility, according to the EQ5D (British and US), SF6D and VAS

Table 2. Average utility and QALYs, according to the EQ5D (British and US), SF6D and VAS

	Prolonged conservative (n=142)	**Early surgery (n=141)**		
	Average (SD)	Average (SD)	Difference	P Value*
EQ5D-UK				
1st quarter	0.57 (0.22)	0.63 (0.18)	0.062	0.01
2nd quarter	0.74 (0.20)	0.81 (0.21)	0.067	0.006
3rd quarter	0.80 (0.18)	0.83 (0.21)	0.025	0.28
4th quarter	0.82 (0.19)	0.84 (0.18)	0.021	0.35
QALYs	0.73 (0.16)	0.78 (0.17)	0.044	0.03
EQ5D-US				
1st quarter	0.69 (0.15)	0.73 (0.13)	0.042	0.01
2nd quarter	0.80 (0.14)	0.85 (0.14)	0.049	0.003
3rd quarter	0.85 (0.13)	0.87 (0.15)	0.021	0.20
4th quarter	0.86 (0.14)	0.88 (0.13)	0.015	0.34
QALYs	0.80 (0.11)	0.83 (0.12)	0.032	0.02
SF6D				
1st quarter	0.63 (0.10)	0.66 (0.10)	0.030	0.01
2nd quarter	0.72 (0.11)	0.75 (0.11)	0.026	0.04
3rd quarter	0.75 (0.13)	0.77 (0.12)	0.020	0.19
4th quarter	0.77 (0.12)	0.79 (0.13)	0.020	0.18
QALYs	0.72 (0.09)	0.74 (0.09)	0.024	0.03
VAS				
1st quarter	0.72 (0.19)	0.79 (0.16)	0.069	0.001
2nd quarter	0.79 (0.20)	0.84 (0.20)	0.046	0.05
3rd quarter	0.83 (0.20)	0.84 (0.20)	0.012	0.62
4th quarter	0.85 (0.19)	0.85 (0.18)	0.000	0.99
QALYs	0.80 (0.15)	0.83 (0.14)	0.032	0.07

* Unequal-variance t-tests

For other health care, Dutch standard prices were used, designed to represent societal costs and to standardize economic evaluations.[145-148] Costs from the health care perspective are reported including the patients' time[148] and travel costs,[146] which on average accounted for 17 % of the total health care costs. Reported hours of absenteeism during the one-year follow-up period were valued according to the human capital method, at standard costs ranging from $19 per hour for younger women to $46 per hour for older men.[146]

Analysis

According to protocol, the base case analysis compared societal costs to QALYs based on the British EQ5D-UK. Sensitivity analyses were performed on the use of different utility measures (EQ5D-US, SF6D or VAS) and on the included cost categories (health care perspective or only the hospitalization for disk surgery). All analyses followed the intention-to-treat principle.

Depending on the willingness to pay (WTP) for obtained effectiveness, a strategy is cost-effective compared to an alternative strategy if it has a better average net benefit (WTP × QALYs - Costs). Given the statistical uncertainty of cost and QALY differences, cost-effectiveness acceptability curves graph the probability that a strategy is cost-effective, as a function of WTP. Confidence intervals for cost-utility ratios were calculated as those WTP values for which the difference in net benefit was not statistically significantly different.[149] To facilitate multiple imputation techniques, group differences were statistically analyzed using standard unequal-variance t-tests.

Result

Utilities and QALYs

According to the EQ5D, the valuation of quality of life two weeks after randomization was somewhat worse for early surgery than for prolonged conservative care (Figure 1). Other than that, the utility measures were almost consistently better after early surgery than after prolonged conservative care. The largest utility difference was 0.123 (95 %CI 0.061 to 0.185), according to the EQ5D-UK, 8 weeks after randomization.

QALYs during all four quarters and according to all four utility measures were consistently more favorable after early surgery (Table 2). Both the first and the second quarter showed statistically significant differences on all four utility measures. Likewise, over the entire first year, early surgery provided significantly (EQ5D-UK, EQ5D-US and SF6D) or marginally significantly (VAS) better QALYs. The QALY difference amounted to 0.044 according to the EQ5D-UK (95 %CI 0.005 to 0.083),

Table 3. Average health care costs and societal costs per patient (in US $)

	Prolonged conservative (n=129)		Early surgery (n=128)		Difference	
	Volume*	Costs	Volume*	Costs	Costs	P Value†
Hospitalization for disk surgery						
1st quarter	20%	743	88%	3,639	2,896	<0.001
2nd quarter	13%	689	2%	351	-338	0.05
3rd quarter	6%	396	0%	145	-251	0.11
4th quarter	3%	155	1%	210	55	0.67
Total (SD)	40%	1,983 (3,735)	89%	4,345 (3,509)	2,362	<0.001
Physical therapy						
1st quarter	82%	533	90%	630	97	0.15
2nd quarter	63%	359	60%	261	-98	0.10
3rd quarter	52%	289	46%	159	-131	0.01
4th quarter	35%	177	33%	120	-57	0.24
Total (SD)	89%	1,358 (1,577)	92%	1,170 (1,068)	-188	0.26
Other hospitalizations	4%	70	1%	12	-58	0.17
Neurologist	0.7	99	0.7	104	5	0.84
Neurosurgeon	1.1	158	1.5	235	76	0.007
Other specialists	0.2	26	0.5	48	23	0.17
General practitioner	4.3	179	2.6	111	-69	0.006
Other paramed. professionals	0.3	20	0.2	15	-5	0.59
Alternative care	0.4	28	0.2	21	-7	0.79
Home care	4.8 h	149	2.6 h	77	-72	0.53
Pain medication	86%	88	87%	36	-52	0.001
Other medication	22%	12	32%	14	2	0.82
Aids	16%	57	21%	60	3	0.95
Total health care costs						
1st quarter		1,800		4,728	2,929	<0.001
2nd quarter		1,205		732	-472	0.02
3rd quarter		803		399	-404	0.03
4th quarter		421		388	-32	0.80
Total (SD)		4,228 (4,706)		6,248 (4,303)	2,020	<0.001
Paid domestic help	1.5 h	17	3.1 h	36	18	0.26
Informal care	25.2 h	306	71.2 h	867	561	0.04
Out-of-pocket	12%	24	13%	126	102	0.18
Productivity costs						
1st quarter	193 h	7,383	224 h	8,098	714	0.42
2nd quarter	117 h	4,533	76 h	2,519	-2,013	0.004
3rd quarter	67 h	2,582	46 h	1,505	-1,077	0.05
4th quarter	39 h	1,478	31 h	1,140	-339	0.50
Total (SD)	416 h	15,976 (17,810)	377 h	13,261 (14,303)	-2,715	0.18
Total non-health care costs (SD)		16,324 (17,891)		14,290 (14,943)	-2,034	0.33
Total societal costs						
1st quarter		9,357		13,305	3,948	<0.001
2nd quarter		5,816		3,543	-2,273	0.005
3rd quarter		3,453		2,108	-1,345	0.04
4th quarter		1,925		1,582	-343	0.55
Total (SD)		20,552 (20,104)		20,538 (16,157)	-13	1.00

* Percentage of patients, number of visits, or number of hours
† Unequal-variance t-tests, correcting for selective non-response using multiple imputation

0.032 according to the EQ5D-US (95 %CI 0.005 to 0.059), 0.024 according to the SF6D (95 %CI 0.003 to 0.046) and 0.032 according to the VAS (95 %CI -0.003 to 0.066).

Health care costs

Of the patients randomized to receive early surgery, 89 % indeed received disk surgery during the first year, compared to 40 % for the patients randomized to receive prolonged conservative care (Table 3). Four and one percent, respectively, had recurrent sciatica leading to a second surgical intervention during the first year. The difference in disk surgery resulted in a $2,362 cost difference (95 %CI $1,494 to $3,229).

The higher surgery costs after early surgery were partly compensated for by statistically significant savings on general practitioner visits, physical therapy in the third quarter, and pain medication. Still, over the entire first year, total health care costs after early surgery remained significantly higher in comparison to prolonged conservative care, with a cost difference of $2,020 (95 %CI $935 to $3,099) per patient.

Societal costs

Of the non-health care costs, the use of informal care after early surgery was statistically significantly higher than after prolonged conservative care. Also, productivity costs were somewhat higher in the first quarter, but were lower in later quarters (statistically significant in the second and third quarter). The total difference in absenteeism was 39 hours per patient (95 %CI -67 to 144), in favor of early surgery, with an associated difference in productivity costs of $2,715 (95 %CI $-1,257 to $6,685). After one year, 6 % of the early surgery patients reported being disabled, compared to 4 % after prolonged conservative care (difference 2 %; 95 %CI -4 % to 7 %). The total non-health care costs after early surgery were lower than after prolonged conservative care, with a total statistically non-significant difference of $2,034 (95 %CI $-2,025 to $6,086). This difference was similar in size to the opposite difference in health care costs, resulting in a negligible difference in total societal costs of $-13 (95 %CI $-4,475 to $4,449), slightly in favor of early surgery.

Cost-utility analysis

In the base case analysis, comparing societal costs to QALYs based on the British EQ5D-UK, both costs and QALYs were in favor of early surgery. As a result, early surgery was preferred to prolonged conservative care, regardless the willingness to pay per QALY. The same holds true for the other utility measures (EQ5D-US, SF6D and VAS), but with somewhat smaller QALY differences.

From the health care perspective or taking only the costs for disk surgery hospitalizations into account, the higher health care costs were no longer compensated by

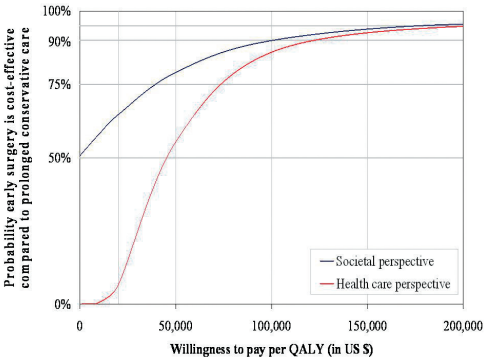


Figure 2. Cost-effectiveness acceptability curves (according to the British EQ5D-UK)

productivity costs. The estimated cost-utility ratios were $46,000 (95 %CI $15,000 to $478,000) and $54,000 (95 %CI $24,000 to $516,000) per QALY, respectively. A commonly used rule-of-thumb classifies costs as *definitely acceptable* up to $20,000 per QALY, as *acceptable* up to $50,000 per QALY, and as *possibly acceptable* up to $100,000 per QALY.[150] According to this rule, the higher health care costs for early surgery are classified as acceptable.

Uncertainty about cost-effectiveness was considerable, primarily because the difference in QALYs was only just statistically significant. Given the statistical uncertainty of the cost and QALY differences, the *probability* that early surgery is cost-effective, compared to prolonged conservative care, varies with the willingness to pay per QALY (Figure 2). From the health care perspective, this probability was 55 % at $50,000 per QALY and was 86 % at $100,000 per QALY. From the societal perspective, these probabilities increased to 79 % and 90 %, respectively.

DISCUSSION

Our randomized controlled trial compared early surgery to six months of prolonged conservative care, in patients with a lumbosacral radicular syndrome that had lasted for 6 to 12 weeks.[118] The trial showed faster pain relief and perceived recovery after early surgery, but without any difference after a year.[129] In both randomization groups, about 95 % of patients reported complete or near complete disappearance of symptoms. Likewise, the utility measures reported here, showed a faster recovery after early surgery, with a largest utility difference of 0.123 at 8 weeks. The total QALY difference was estimated at 0.044, which is the equivalent of a life prolongation of 16 days in perfect health.

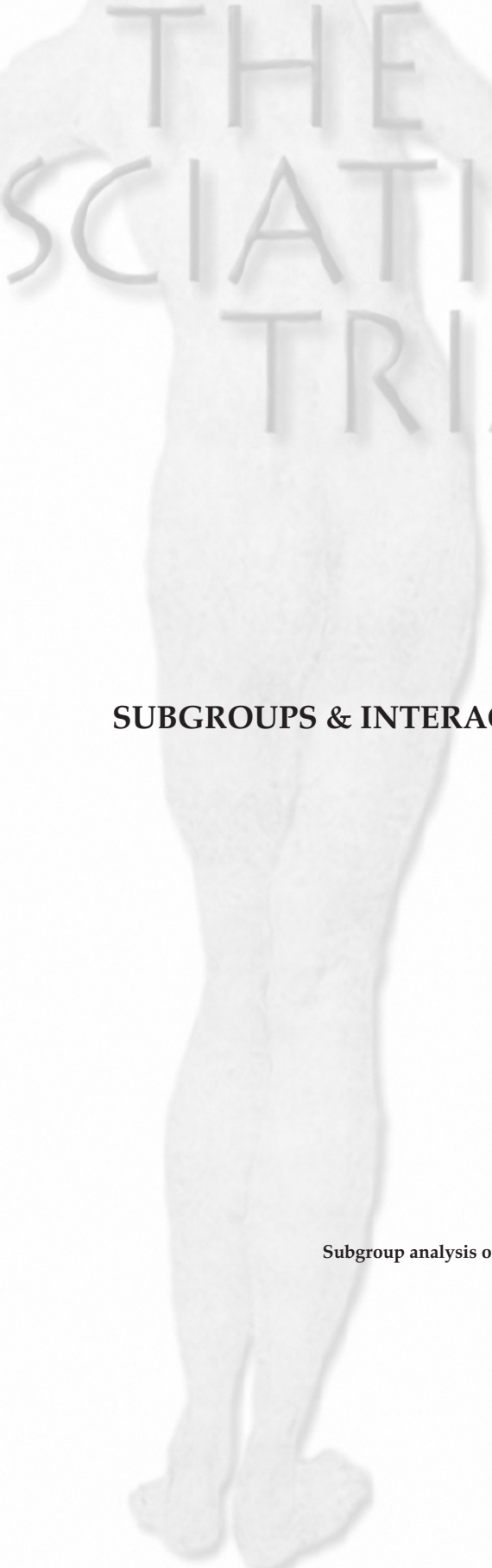
In the economic evaluation, we studied whether the faster recovery after early surgery was attained at reasonable costs. The difference in health care costs was estimated at $2,020 and mostly consisted of the difference in surgery costs. This difference is relatively small, because with prolonged conservative care, 40 % of the patients still underwent surgery because complaints increased or persisted after six months. Partly due to increased absenteeism directly after surgery, the observed total difference in absenteeism in favor of early surgery was only 37 hours. Still, this limited difference in productivity costs was sufficient to compensate for the difference in health care costs. As a result, from the societal perspective, early surgery was preferred on both QALYs and costs. From the health care perspective, the cost-utility ratio was estimated at $46,000 per QALY. From both perspectives, albeit with considerable uncertainty, early surgery was more likely to be cost-effective than prolonged conservative care, according to the current economic threshold of $50.000 or more per QALY.[150] Nevertheless, if a well-informed patient prefers conservative care, there is no health-economic reason to opt for early surgery, since surgery does not reduce costs and the QALY difference was relatively small.

Although the two earlier economic evaluations by Malter[93] and by Hansson[138] reported favorable cost-utility for disk surgery too, our results differ from theirs in a number of ways. Firstly, our observed QALY difference of 0.044 is considerably smaller. Based on the trial by Weber,[125] Malter's modeled a tenfold larger difference of 0.43 QALY, of which 0.10 QALY in the first year. Weber's control patients took longer to improve than our control patients, which is probably due to the more frequent disk surgery in our trial. Hansson estimated a 0.327 QALY difference, but this estimate was based on two measurements only, after 28 days and 2 years, which makes it impossible to estimate the course over time. Secondly, Malter's assumed average charge for disk surgery was considerably higher than our price ($11,930 versus $4,445). Yet, our price is similar to the cost estimate used by Hansson ($4,685) and to Malter's alternative HMO costs ($5,170), which Malter considers a better estimate of the true surgery costs. Thirdly, in our trial, the initial absenteeism due to surgery was compensated by lower absenteeism during the rest of the year, whereas in Hansson's study it was compensated by less frequent permanent disability. We did not find a difference in permanent disability, which may be due to the more frequent surgery in our control group or due to Hansson's non-randomized case-control design.

Our study has a number of limitations. Firstly, our Dutch setting may differ from other settings, both with respect to health care and labour. Like in the United States, surgery rates in the Netherlands are relatively high.[46] In settings with lower surgery rates, patients in the control group would be less likely to receive surgery, which might lead to larger QALY and cost differences, with an as yet unknown influence on the cost-utility ratio. Secondly, the duration of follow-up was only one year. How-

ever, the similarity of our randomization groups after one year makes group differences beyond the first year improbable in our trial. Thirdly, as patients were inevitably aware of which randomization group they were in, their reported utilities and costs may have been influenced by their treatment preference. Finally, some may consider the number of cross-overs in our study a limitation: 40 % of the patients randomized to receive prolonged conservative underwent disk surgery at any time during the first year. Compared to other recent randomized trials, our number of cross-overs was similar to the trial by Österman[66] and considerably less than the trial by Weinstein.[48;49] More importantly, we do not think that cross-overs are a limitation: our analysis does not evaluate surgery itself, but compares a strategy of early surgery to a strategy of prolonged conservative care. That persistent or increasing complaints cause some patients to cross-over, is part of clinical reality and should therefore also be part of the economic evaluation.

In conclusion, faster recovery from sciatica makes early surgery more likely to be cost-effective than prolonged conservative care, in patients with 6 to 12 weeks of sciatica caused by lumbar disk herniation. The estimated difference in health care costs was acceptable and was compensated by the difference in absenteeism. For a willingness to pay of $50.000 or more per QALY, early surgery need not be withheld for economic reasons.



6

SUBGROUPS & INTERACTION TREATMENT STRATEGY

Subgroup analysis of a randomized trial to evaluate timing of surgery for sciatica

Wilco C. Peul
Ronald Brand
Raph T.W.M. Thomeer
Bart W. Koes

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ABSTRACT

Context: After 6 to 12 weeks sciatica caused by a lumbar disk herniation, surgery speeds up recovery. Conservative care yields similar results at one year.
Objective: To determine whether baseline variables modify the difference in outcome between these treatment strategies.
Design, Setting and Patients: Baseline data of 283 patients enrolled in a multicenter randomized trial, comparing early surgery with prolonged conservative care, were used to analyze effect modification of the allotted treatment strategy by predefined variables.
Main Outcome measures: Recovery was registered by patients on a 7-point Likert scale, which for this study was dichotomized into "complete recovery" or "no recovery". For predictors shown to modify the effect of the treatment strategy (inferred from a significant interaction effect in a Cox model), repeated measurement analyses with the Roland Disability Questionnaire and VAS pain as continuous outcomes were performed for every level of that predictor (stratification).
Results: Presumed predictive variables did not have any interaction with treatment as far as speed of recovery is concerned, while "sciatica provoked by sitting" could be shown to be a significant effect modifier ($p=0.07$). In a Cox model we estimated a Hazard Ratio (surgery versus conservative) of 2.2 (95 % CI; 1.7 to 3.0) in favor of surgery when sciatica was provoked by sitting, while the HR was 1.3 (95 % CI; 0.8 to 2.2) when this sign was absent. The interaction effect is marginally significant (although interactions are usually tested at the 10 % level) but on the other hand the patterns generated by the repeated measurement analyses of all primary outcomes are completely consistent with the induced pattern in survival analysis.
Conclusions: Classical signs do not help to decide when to operate for sciatica, whereas treatment effects of early surgery are emphasized when sciatica is provoked by sitting and negligible when this symptom is absent.

Sciatica is characterized by radiating pain in an area of the leg typically served by one lumbar or sacral spinal nerve root and is sometimes associated with sensory and motor deficit. Apart from infrequent causes, sciatica is due to a herniated lumbar disk. Because of the high prevalence in general practice and the major impact of low back disorders on society[77], surgery is frequently performed to speed up recovery of sciatica. Probably as a result of socio-cultural circumstances, different timing of surgical removal of the herniated portion of the disk appears to vary greatly in the western countries[46]. Recently the option of surgery was offered to patients after only 6 weeks of unremitting sciatica. The major reason to offer early surgery was the unattractive alternative: the slow natural course of sciatica, occasionally extending over 4 years[40;117]. Globally two options were available: (1) early surgery and (2) prolonged conservative care, possibly with surgery at a later date. Since surgery is economically affordable and relatively safe, most patients in western countries prefer early surgery rather than to wait for months or even years, risking long term work-disability and presence of chronic pain. Recently a randomized trial provided evidence that the prolonged conservative care strategy resulted in complete recovery at one year but it took twice as long compared to early surgery[129]. The one-year effects of the two assigned treatment strategies were similar as far as function and pain were concerned in the randomized cohorts. The contribution to the clinical standard by this study is that patients, opting for surgery, now are able to base their decision on realistic data about the alternative natural course, with similar outcomes at one year compared to early surgery. If fast recovery is warranted individual decisions are still difficult. because both populations were heterogeneous regarding prognostic factors. Moreover surgery could not be avoided for 39 % of patients during prolonged conservative care. Although the complementary 61 % of patients recovered without intervention, they suffered sciatica for a prolonged period. Since treatment effects can differ between subgroups of patients, this might influence the indication for early disk surgery.

Therefore, it would be of great interest to patients and physicians to define determinants which occur early in the course of sciatica and predict the speed of recovery and therefore help in the decision about when to perform surgery. We carried out a subgroup analysis of data from the aforementioned randomized trial to evaluate anamnestic, neurological, and radiological variables which might in theory influence the difference in rate of recovery between the two treatment strategies.

Methods

A multicenter prospective randomized trial was designed to determine for patients with a short duration of severe sciatica, whether early surgery resulted in a more

effective outcome during the first year, compared to a strategy of prolonged conservative treatment possibly with delayed surgery if indicated. The medical ethics committee at each of the 9 participating hospitals approved the protocol. Written informed consent was obtained from all patients. Details of the design, study protocol and prognostic variables were published previously together with the primary outcomes[118].

Patients

Eligible patients were 18-65 years of age, with radiological confirmation of a clinically expected disk herniation causing an incapacitating lumbosacral radicular syndrome lasting between 6 and 12 weeks as documented by the attending neurologist. At the time of enrolment and randomization an independent research nurse verified persistence of complaints and surgical indication. Patients were excluded if they presented with a cauda equina syndrome or severe paresis (MRC<3). Identical complaints in the past twelve months, a history of spinal surgery, bony stenosis, spondylolisthesis, pregnancy or severe comorbidity also led to exclusion. A computer generated permuted-block scheme was used for randomization, stratified according to center (n=9). The patients were randomized by opening an opaque envelope containing the patient's assigned strategy. Obviously it was not possible to blind patients or their physicians.

Treatment

Early surgery was scheduled within 2 weeks of assignment and only cancelled if spontaneous recovery occurred before the date of surgery. Under either general or spinal anaesthesia the herniated part disk was removed together with as much as possible degenerated nuclear material. Bony removal to gain access to the disk space was minimized and likewise subtotal disk excision was never pursued. The duration of the hospitalization depended on the patient's functional abilities. Since the protocol of the participating surgical departments was not changed, usual care was provided. At home the rehabilitation process was supervised by the physiotherapist on the base of a standardized exercise protocol. Patients were advised to resume their regular jobs from 6 weeks on, depending on the nature of the work. Postoperative care included out-patient control at 8 weeks or earlier if the patient worried about the course and suffered aggravation of symptoms.

Prolonged conservative management was provided by the general practitioner. Ample information was provided about the favorable prognosis. If necessary the prescription of pain medication was adjusted according to existing clinical guidelines. If there was considerable fear of movement, the help of a physiotherapist was recommended. Further on treatment was aimed mainly at resumption of daily activi-

Table 1. Predefined prognostic variables. *

Demographic Variables
• Age < 40 years versus ≥ 40 years,
• Intellectual versus physically demanding job,
• Gender
Anamnestic and Neurological Variables
• Acute start LSRS versus slow start,
• History of back pain versus no history,
• Influence of coughing, sneezing on complaints versus no influence,
• Difficulty to put on shoes and/or socks versus no difficulty,
• Straight leg raising ≤ 30 degrees versus > 30 degrees, †
• Positive crossed straight leg raising sign versus negative sign, †
• VAS-pain > 70 versus < 69 mm, ‡
• Tingling/numbness in pain area versus no tingling,
• Pain leg worse by sitting versus no worsening,
• McGill affective high score versus low score, §
Radiological Variables
• MRI disk sequester versus contained disk herniation, ¶
• MRI circumferential gadolinium enhancement versus no enhancement of disk herniation, ‖
Miscellaneous Variables
• Preference for surgery versus no preference for surgery,
• Disk herniation at L5S1 vs. L4L5.

* During the design of the trial, variables were selected on the physiological assumption to be correlated to speed of recovery

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

§ The McGill affective score measure the qualitative perception of pain by the patient. High affective dimensional scores correlate to a more depressed and anxious individual mood when compared to patients who report low affective scores.

¶ Sequestrated disk herniations are defined by a defect in the annulus fibrosis and loose disk fragments in the epidural space, visualized by MRI scanning.

‖ Enhancement of the rim of disk herniation might correspond to removal of the herniated portion by an inflammatory reaction

ties. However if sciatica was still present at 6 months after randomization, microdiskectomy was offered after a repeat MRI showed the disk herniation again. Increasing drug-resistant leg pain or progressive neurological deficit were reasons for performing surgery even before 6 months.

Outcomes

Functional outcome assessed by means of the Roland Disability Questionnaire for Sciatica (RDQ), intensity of leg or back pain by a 100 mm visual analogue scale for leg pain (VAS-leg and VAS-back) and a questionnaire of patient's global impression

Table 2. Cox model recovery rates of early surgery compared to prolonged conservative care *

Subgroup	Proportion (%)	Lower	Mean	Upper	p-value interaction
Overall	100	1.72	**1.97**	2.22	
Age					**0.12**
< 40 years	41	1.69	**2.50**	3.66	
≥ 40 years	49	1.21	**1.68**	2.32	
Intellectual job					**0.83**
non-intellectual	36	1.21	**1.88**	2.92	
Intellectual	64	1.45	**2.00**	2.76	
Physical demanding work					**0.61**
non-physical	61	1.29	**1.80**	2.51	
physical demanding	39	1.37	**2.06**	3.1	
Sex					**0.64**
Male	66	1.57	**2.12**	2.87	
Female	34	1.20	**1.87**	2.92	
Start Sciatica					**0.91**
acute severe	61	1.40	**1.94**	2.68	
slowly increasing	39	1.27	**1.89**	2.79	
Influence intra-abdominal pressure					**0.45**
Provocation sciatica	73	1.57	**2.10**	2.81	
no provocation	27	1.06	**1.70**	2.74	
Lasègue's sign †					**0.88**
straight leg raising > 60 °	25	1.17	**1.92**	3.15	
straight leg raising ≤ 60 °	75	1.50	**2.01**	2.70	
Crossed straight leg raising †					**0.17**
Negative	41	1.11	**1.61**	2.34	
Positive	59	1.64	**2.28**	3.18	
VAS legpain intensity ‡					**0.98**
> 70	54	1.35	**1.94**	2.79	
≤ 70	46	1.37	**1.93**	2.71	
Sciatica provocation by sitting					**0.07**
no provocation	24	0.80	**1.30**	2.2	
Provocation	76	1.70	**2.24**	2.99	
McGill affective scores §					**0.60**
low score < 3	49	1.34	**2.05**	3.00	
high score	51	1.47	**1.90**	2.46	
MRI Sequester ¶					**0.81**
contained disk herniation	59	1.40	**1.96**	2.74	
Sequester	41	1.23	**1.84**	2.75	
MRI Gadolinium ‖					**0.60**
no enhancement	34	1.425	**2.32**	3.77	
enhancement	66	1.38	**1.97**	2.83	

Table 2. Continued

Subgroup	Proportion (%)	Lower	Mean	Upper	p-value interaction
MRI level disk herniation					**0.75**
L5S1	61	1.39	**1.93**	2.67	
L4L5 or L3L4	39	1.19	**1.77**	2.64	
Preference for surgery					**0.73**
strong preference for surgery	39	1.39	**2.07**	3.09	
some or no preference	61	1.38	**1.90**	2.61	
Tingling/numbness pain area					**0.66**
no sensation	10	1.1	**2.3**	5.1	
Sensation	90	1.5	**1.9**	2.5	

* Time to complete recovery according to baseline patient characteristics. Mean hazard ratios show the effect within each subgroup, with their corresponding 95 % confidence interval by lower and upper scores. Values for the interaction between treatment effect and the predefined subgroup variables for prolonged conservative treatment versus early surgery are shown.

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

§ The McGill affective score measure the qualitative perception of pain by the patient. High affective dimensional scores correlate to a more depressed and anxious individual mood when compared to patients who report low affective scores.

¶ Sequestrated disk herniations are defined by a defect in the annulus fibrosis and loose disk fragments in the epidural space, visualized by MRI scanning.

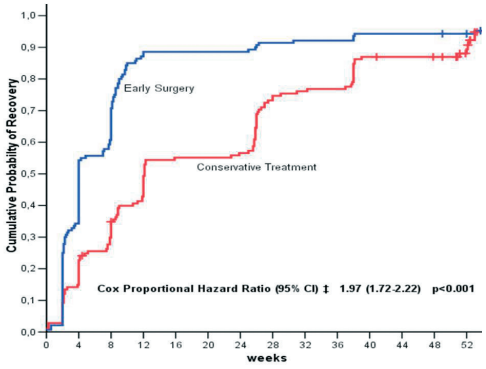
‖ Enhancement of the rim of disk herniation might correspond to removal of the herniated portion by an inflammatory reaction

of change questionnaires on a 7-points Likert self-rating scale of recovery were filled out at 2, 4, 8, 12, 26, 38 and 52 weeks[109;114].

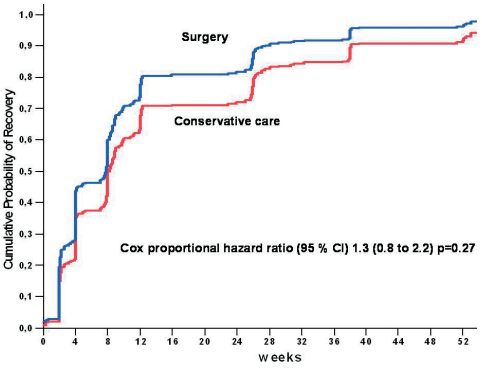
For the current subgroup analyses, the patient's global impression of change (PGIC) was used as dependant variable in dichotomized form. Next to obvious methodological advantages this dichotomized outcome form is easily applicable in general practice. "Very much improved" and "much improved" were coded as recovered, while "minimally improved", "no change", "minimally worse", "much worse" and "very much worse" were coded as not recovered.

Prognostic variables

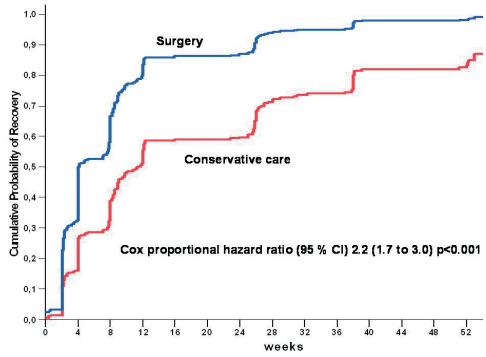
Possibly prognostic determinants were selected on the basis of classical physiological hypotheses or resulted from earlier studies. These socio-demographic, symptom, neurological, and radiological variables (Table 1) were collected before randomization was performed.



Panel A Unadjusted Survival Curves (5)



Panel B Sciatica not provoked by sitting



Panel C Sciatica provoked by sitting

Figure 1 Inverse Kaplan Meier curves.
Panel A presents the original unadjusted curves (5), while panel B and C represent stratified analyses, for sciatica not provoked by sitting and sciatica provoked by sitting, respectively.

Statistical Analysis

Data collection and quality checks were performed using the ProMISe data management system of the Department of Medical Statistics & BioInformatics of the LUMC. All statistical analyses were carried out using SPSS version 14.0.

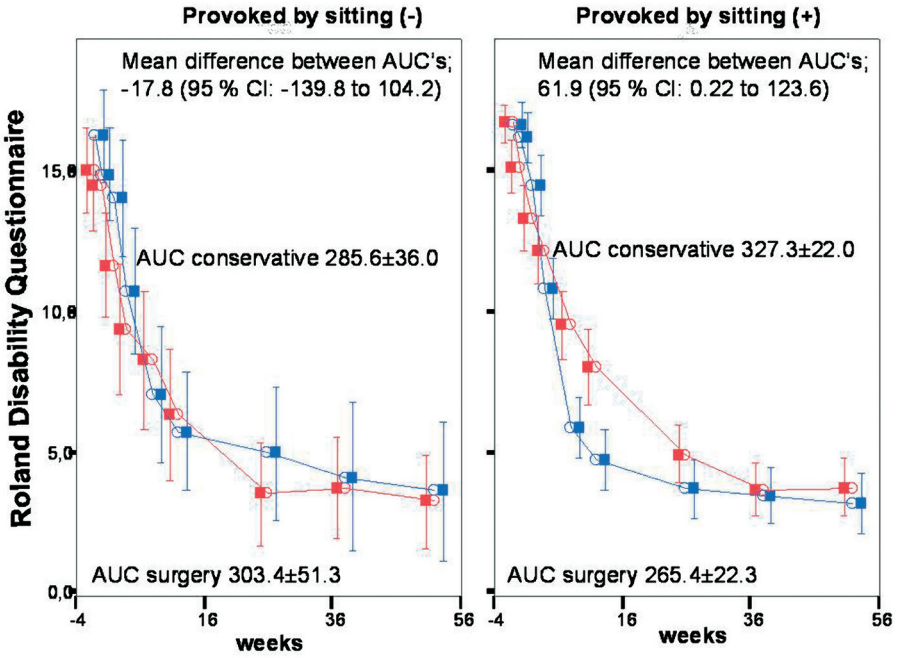
Effect modification of each predictor was first bivariately tested in a model containing the treatment allocation, the predictor and the interaction between them. If the p-value of the interaction term was smaller than 0.10, the predictor and its interaction term was retained for a multivariate model. In the multivariate Cox model, first all these interaction terms were removed by a backward stepwise procedure, also with a threshold of 0.10. The remaining interaction terms determined which predictors were subsequently used in a repeated measurements analysis of variance for continuous

outcomes (RDQ and VAS) where the predictor was used to define the strata in which the repeated effect was estimated. Following the analysis of the interaction effects, explorative Cox regression analyses of other basal demographic, neurological and radiological variables with some plausible relationship to outcome data were carried out.

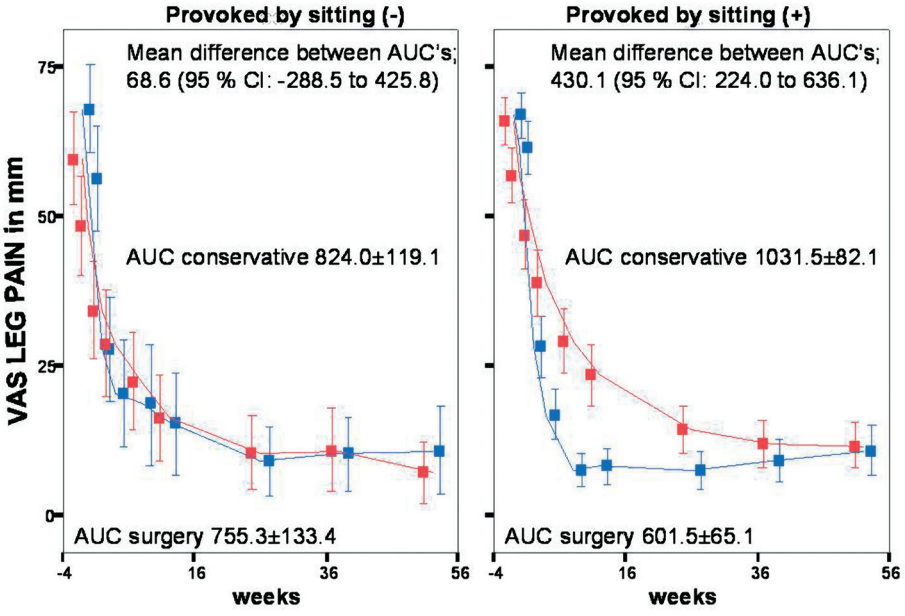
Results

Baseline demographic and neurological variables did not differ between groups[129]. The unadjusted hazard ratio as estimated in a univariable Cox model with recovery as endpoint was 2.0 (95 % CI 1.7 to 2.2), favouring early surgery (Figure 1 panel A). Univariate testing of the predefined prognostic variables showed a significant interaction effect of "sciatica provoked by sitting" with the "treatment strategy" ($p=0.07$), but no significant interaction effect of any of the other predefined variables was found (Table 2). Interestingly the presumed influence of classical neurological tests on speed of recovery could not be confirmed and, in contrast to former medical beliefs interactions were even absent, showing equal recovery rates for different levels of these variables. Treatment preference of patients did not show any interaction with early surgery either.

A survival model with "treatment-by-randomization", "sciatica provoked by sitting" as well as their interaction, revealed a differential effect on rate of recovery (Figure 1, panel B and C). Survival models lacking the treatment variable as an independent variable showed that presence or absence of sciatica provoked by sitting in itself did not provide any prognostic value for the speed of recovery rates. Patients with sciatica provoked by sitting did experience a slower rate of recovery when randomized to prolonged conservative treatment while surgery accelerated the rate of recovery with an estimated hazard ratio of 2.2 (95 % CI; 1.7 to 3.0). When patients did not experience leg pain provoked by sitting the survival curves come close together, corresponding with similar average speed of recovery rates: HR 1.3 (95 % CI; 0.8 to 2.2). Repeated measurement analysis, stratified by "sciatica provoked by sitting", gave similar findings with RDQ and VAS pain outcomes showing diverging curves when sitting provoked sciatica. Areas under the RDQ and VAS back pain curves over the first year of early surgery compared to conservative treatment were even statistically different ($p=0.05$ respectively $p=0.03$) in contrast to the original analysis without stratifying variables [129]. These outcomes over the first year between early surgery and conservative treatment did not show relevant differences when sciatica was not provoked by sitting and early surgery even gave less favorable results during the first months compared to conservative treatment in this group (Figure 2).



Panel A †



Panel B ‡

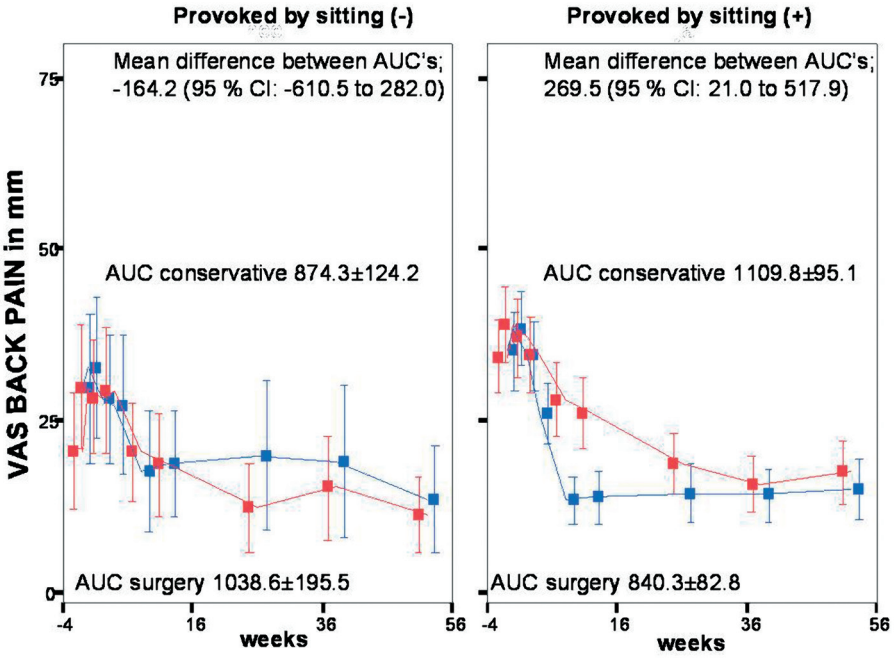


*Figure 2 . Repeated Measurement Analysis stratified for "sciatica provoked by sitting.**
Curves of Mean scores for Roland Disability Questionnaire (Panel A) † , Leg Pain (Panel B) ‡ and Back Pain (Panel C) ‡ . All three panels show the 52-week curves with 95 percent confidence intervals represented by vertical bars at consecutive moments of measurement. Red lines represent the conservative treatment group, while the blue lines represent early surgery. Areas under the curve (AUC) are described by their means ± SE.
***Panel A** represents the mean disability scores at consecutive moments of measurement stratified for sciatica provoked by sitting. The overall difference between the areas under the curves over 12 months is not significant for sciatica not provoked by sitting ($p=0.77$) and significant for provoked by sitting ($p=0.05$) in favor of early surgery.*
***Panel B** represents mean visual analogue scores for intensity of leg pain in mm. The difference between the mean AUC's is not significant for sciatica not provoked by sitting ($p=0.70$) and significant for sciatica provoked by sitting ($p<0.001$) in favor of early surgery.*
***Panel C** represents mean visual analogue scores for intensity low back pain in mm. Starting with a lower intensity score when compared to leg pain, the mean AUC's exhibit no significant difference for sciatica not provoked by sitting ($p=0.47$) and significant for sciatica provoked by sitting ($p=0.03$)*

** The mean difference between areas under the curves are expressed by the corresponding 95 percent confidence interval. To enhance visualization of the curves the error bars (95 % confidence intervals) are offset.*
† The Roland Disability Questionnaire for Sciatica is a disease specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23
‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced, with higher scores indicating worse functional status.

DISCUSSION

This randomized trial showed that early surgery led to significantly faster recovery compared to prolonged conservative care but failed to show any interaction with classical neurological signs and magnetic resonance imaging findings. Only "sciatica provoked by sitting" showed interaction with timing of surgery, and thus rate of recovery. These results were markedly consistent in stratified analyses of all primary outcomes over the first year.

The finding that classic physical signs and high preference for surgery did not affect the results of treatment strategies was surprising and not expected. Currently most physicians and physiotherapists refer patients for surgery under the near mandatory condition that the straight leg raise test provokes sciatica[45]. The design of this trial made it possible to include enough patients with a negative straight leg raising test. These, however, form a minority which may be due to selection bias. Therefore these results must have to be interpreted very carefully, which also holds true for the findings regarding patient preferences. Earlier prognostic studies suggested a realistic relationship between patient's and doctor's preferences and expectations on the one hand and outcome on the other[151]. These expectations are still likely to play a major role since the patients in this randomized trial were very willing undergo surgery; in fact this was their main motive to visit the outpatient clinic of the participating hospitals. Only a minority of patients did not have a clear preference for surgery and no patient had a preference for the conservative treatment strategy. Therefore the lack of influence of patient preferences on treatment strategies is not unrestrained applicable to general practice.

Sequestrated disk herniations also failed to follow a significantly different course when allotted to early surgery compared to prolonged conservative care. Earlier radiological studies showed strong associations between the type of disk herniation and the natural course or surgical outcome of sciatica[152;153]. According to some authors sequestrated disk fragments were likely to resolve in the spinal epidural space, making surgery an pointless intervention[152;154;155]. Similar conclusions were drawn in the past in favor of MRI gadolinium rim enhancement of the disk herniation, representing neo-vascularization corresponding to macrophage resorption of the disk fragment[156;157]. The current study did not show any relationship between this variable and timing of surgery. Other important effectiveness studies suggested a relationship between spinal level of disk herniation and the surgical timing strategy. This was not confirmed by this analysis, which contains more solid data on duration of sciatica complaints and timing of surgery[49] and sample size[66].

While the scientific value of "sciatica provoked by sitting" as a prognostic variable might be debated, a similar result for this anamnestic variable was found in

the randomized bed rest trial to predict the risk for patients undergoing surgery[153]. Although only a marginally significant different interaction effect was found by univariate Cox proportional hazard analysis, these results appeared consistent when repeated measurement analysis of primary outcomes was performed. Furthermore it is a simple question to ask and physiologically completely understandable that a patient, persistently unable to sit, will gain important relief of pain, quality of life and function with early surgery. On the other hand if patients do not suffer sciatica provoked by sitting, their chances of a beneficial result of early surgery, if any, are reduced. Most of the latter patients might be better off with prolonged conservative care. Since this subgroup, however, was relatively small, one must interpret these results carefully; further investigation in future studies on this subject is needed.

The lack of a prognostic value of physical signs and symptoms for the outcome of sciatica has been reported before, but these studies focussed on the long-term results and not on the short-term rate of recovery[158-160]. It still is important to define neurological deficits[116] when examining a patient but their predictive value, to alter a decision to operate or to advise patients to stay conservative for a prolonged time, is minimal or absent. Nowadays, spine-oriented clinics request magnetic resonance imaging quite early in the course of sciatica to comfort their patients and discuss treatment and prognosis. This study shows evidence of absent predictive and no prognostic value for this diagnostic strategy. Magnetic resonance imaging or a CT-scan is necessary for surgery but is less informative for the patient who must decide whether to undergo surgery or not.

Conclusion

Except for absent "sciatica provoked by sitting" early surgery compared to prolonged conservative care yielded significantly faster rates of recovery for all investigated variables, irrespective of their value. Neurological signs, patient preferences and magnetic resonance imaging findings fail to affect the outcome of early surgery versus prolonged conservative care. But a simple question regarding leg pain provoked by sitting, asked by the family practitioner, might help patients to opt for surgery to speed up recovery rates from sciatica as well as those who prefer to reduce the risk of on back surgery.

7

CAN WE PREDICT SURGERY FOR SCIATICA?

Improving prediction of "inevitable" surgery during non-surgical treatment of sciatica.

Wilco C. Peul
Ronald Brand
Raph T.W.M. Thomeer
Bart W. Koes

Submitted for publication

ABSTRACT

Background: After 6 weeks of sciatica surgery speeds up recovery. A randomized trial showed that conservative care yields results similar to early surgery at one year. However 39 % of this prolonged conservative care group ultimately underwent surgery during one-year follow-up. We evaluated variables to improve prediction of surgery in the conservatively treated cohort.

Methods: Baseline data on 142 patients enrolled in the conservative treatment arm of a randomized trial were analyzed to select those that could contribute to the prediction of surgery. The actual occurrence of surgery was used as the dependent outcome of interest. Variables measured at baseline included neurological examination results, the Visual Analogue score for pain (VAS) and the Roland Disability Questionnaire (RDQ).

Results: Of 142 patients receiving conservative care, 39 % underwent surgery after a mean period of 18.7 weeks. Higher pain intensity and higher functional limitations at baseline were associated with an increased likelihood of surgery during follow-up. Mutually adjusted Odds Ratios of 1.7 (95 % CI; 1.1 to 2.7) per 20 mm incremental intensification of pain on the VAS score and 1.8 (95 % CI; 1.2 to 2.9) per 3 points of deterioration of the RDQ score quantify the increasing chance of undergoing delayed surgery.

Conclusions: Despite maximal efforts to the contrary, surgery could not be prevented for a considerable proportion of patients in a conservatively treated cohort. Compared to those with lower pain and disability scores initially , patients with more intense leg pain or higher disability scores were at higher risk to undergo delayed surgery.

In general lumbar disk surgery for sciatica is performed to speed up recovery of leg pain and disability[161]. It ranks high among the most frequently performed surgical procedures for neuropathy and musculoskeletal disorders.[46;77]. The timing of surgery appears to vary greatly between different countries[46]. A recently published study revealed evidence that for the majority of patients both prolonged conservative care and early surgery resulted in complete recovery at one year but the conservative arm took twice as long to reach recovery[129]. Delayed surgery, however, had been necessary after all for 39 % of the patients assigned to the prolonged conservative treatment group, during the first year after randomization. Although the intention of prolonged conservative care reduced the number of surgical interventions substantially, those patients who underwent surgery at a later date suffered from pain and disability for quite a prolonged period, up to 6 months. It would be of great value to patients opting for a strategy of prolonged conservative care, if determinants available early in the course of sciatica could be found that would improve the prediction of surgery during follow-up. Therefore we evaluated the predictive value of clinical, demographic, and radiological variables for surgery actually performed in the conservative treatment cohort of a recently conducted randomized trial.

METHODS

A multicenter prospective randomized trial of patients with short-term severe sciatica was conducted to determine whether early surgery resulted in a more effective outcome during the first year compared to a strategy of prolonged conservative treatment (including, if indicated, delayed surgery). The medical ethics committee at each of the 9 participating hospitals approved the protocol. Written informed consent was obtained from all patients. Details of the design and study protocol were published previously[118;129].

Patients

Eligible patients were 18-65 years of age, with radiological confirmation of a clinically expected disk herniation causing an incapacitating lumbosacral radicular syndrome lasting between 6 and 12 weeks as documented by the attending neurologist. At the time of enrollment and randomization an independent research nurse verified persistence of complaints and the surgical indication. Cauda equina syndrome or severe paresis (MRC<3) were excluded as were identical complaints in the past twelve months, a history of spinal surgery, bony stenosis, spondylolisthesis, pregnancy or severe comorbidity.

For the purpose of the present analysis, the patients who originally were allocated at random to conservative care were selected as the study cohort.

Treatment

Prolonged conservative management was provided by the general practitioner. Ample information was provided about the favorable prognosis. If necessary the prescription of pain medication was adjusted according to existing clinical guidelines[44]. If there was considerable fear of movement, the help of a physiotherapist was recommended. Treatment was aimed mainly at resumption of daily activities. However if sciatica was still present at 6 months after randomization, microdiskectomy was considered if a repeat MRI still showed the disk herniation. Increasing drug-resistant leg pain or progressive neurological deficit were reasons for performing surgery even before 6 months. When patients requested surgery, they were again evaluated by their treating physician and the assigned research nurse, who had to confirm that recovery had not occurred and that the repeated MRI showed an unresolved disk herniation. Subsequently the neurosurgeon was consulted by the patient who requested surgery under the premise that further recovery was not to be expected in the next few months. If surgery was performed, the herniated part of the disk was removed together with as much degenerated nuclear material as possible [162]. Removal of bone to gain access to the disk space was minimized while total disk excision was never performed.

Variables

Prognostic determinants were selected on the basis of classical physiological hypotheses or inferred from earlier studies[2;163;164]. These socio-demographic, anamnestic, neurological, and radiological variables were collected before randomization was performed.

Outcomes

The occurrence of surgery performed during the course of prolonged conservative care was the event of interest. Functional outcome as indicated by means of the Roland Disability Questionnaire for Sciatica (RDQ)[114;165] and intensity of leg or back pain on a 100 mm visual analogue scale for leg pain (VAS-leg and VAS-back)[109] was assessed at 0, 2, 4, 8, 12, 26, 38 and 52 weeks, respectively. For the present analysis only data from the baseline measurements were used. Furthermore a 7-point Likert scale evaluated recovery. In a dichotomized form "satisfactory" outcome is similar to "complete" or "near-complete" recovery.

Statistical Analysis

Data collection and quality checks were performed using the ProMISe data management system of the Department of Medical Statistics & BioInformatics of the LUMC.

Table 1. Baseline scores and outcomes per treatment group at 12 months in patients initially started with a conservative treatment regimen *

	Conservative (n=87)	Late Surgery (n=55)	p-value
Roland baseline †	15.8±3.8	17.1±3.9	>0.05
12 months	3.9 ± 5.2	4.0 ± 6.2	>0.05
VAS leg pain base line (mm) ‡	64.0 ± 21.3	65.4 ± 21.3	>0.05
12 months	11.4 ± 17.5	13.4 ± 25.3	>0.05
VAS back pain baseline (mm) ‡	30.2 ±25.0	32.2 ± 32.3	>0.05
12 months	17.4 ± 21.3	14.6 ±24.8	
Satisfactory Recovery % §	79	85	>0.05 (Fisher's exact Test)

* Means and standard deviations
† The Roland Disability Questionnaire for Sciatica is a disease specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.
‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.
§ Likert global perceived recovery is defined by a 7-point scale "Worse" to "Complete" recovery. Satisfactory recovery is defined as complete or nearly complete recovery using the Likert 7-point scale.

All statistical analyses were carried out using SPSS, version 14.0[120]. All variables were recoded before being used in a logistic regression analysis as described previously in the protocol[118]. Since the VAS leg pain and RDQ are both continuous variables and the Odds Ratios of these variables correspond by definition to the effect of an increase in 1 unit of the underlying scale, these were rescaled (without any effect on their significance) for reporting purposes to let the Odds Ratios reflect the effect of an increment of 20 mm and 3 points respectively, both corresponding to the estimated Minimal Clinical Important Difference[166;167].

The predictive effect of variables was analyzed by constructing a multivariable logistic regression model with "the occurrence of surgery during the first twelve months" as the outcome of interest. The model was obtained using a stepwise backward elimination process with threshold values of 0.10 and 0.05 for removal and inclusion of predictors. Since follow-up observation was complete, there was no censoring and a survival modelling approach was not necessary, the outcome of interest simply being the probability of having undergone surgery by month 12 after being randomized to conservative care.

Finally, after having constructed the model that retained all significant predictors, the estimated probabilities were tabulated using some typical values of the predictors and the estimated odds ratios were tabulated with their respective confidence

Table 2. Uni- and multivariate analysis of baseline variables to determine predictive value on delayed surgery.

Variable	Comparison (%)	Univariate analysis			Multivariate analysis		
		OR	95 % CI	p value	OR	95% CI	p value
Gender	Female (32) vs Male (68)	0.80	0.37-1.70	0.56	-	-	-
Age (years)	≥ 40 (63) vs <40 (37)	1.04	0.51-2.13	0.92	-	-	
Job *	Mentally (69) vs Physical (31)	*0.56*	*0.29-1.09*	*0.09*			*0.89*
Housewife	Yes (10) vs No (90)	2.87	0.93-8.81	**0.066**	-	-	0.27
Spouse/partner	Yes (78) vs No (22)	1.38	0.58-3.28	0.47			
Children	Yes (68) vs No (32)	1.70	0.78-3.69	0.18			
Smoking	Yes (39) vs no (61)	1.00	0.49-2.04	0.99			
Quetelet index	Per 1 point increments	1.10	0.98-1.23	**0.093**	-	-	0.17
Start sciatica	Slowly (67) vs Acute (33)	1.66	0.80-3.43	0.17			-
Sciatica provoked by							
Sitting	Yes (75) vs No (25)	1.27	0.56-2.86	0.56			-
Coughing, sneeze	Yes (72) vs No (28)	1.13	0.52-2.46	0.75			-
Straight leg raising †	Pos. <60°(74) vs Neg. ≥ 60° (26)	1.52	0.66-3.49	0.32			
Crossed leg raising	Positive (57) vs Negative (43)	0.61	0.30-1.21	0.16			-
Kemp's sign	Positive (56) vs Negative (44)	2.75	1.31-5.79	**0.008**	2.18	0.85-5.36	0.09
Finger-ground in cm	>30 (59) vs ≤30 (41)	1.55	0.75-3.23	0.24			-
Bragard's test	Positive (28) vs Negative (72)	1.52	0.68-3.40	0.30			-
Sensory disturbance	Yes (91) vs No (9)	2.80	0.59-13.4	0.20			-
MRI-level herniation	L5S1 (66) vs L4L5 and L3L4 (34)	0.95	0.49-1.83	0.88			-
MRI-sequester	Yes (42) vs no (58)	0.84	0.43-1.63	0.61			-
Preference surgery	Mild (66) vs Strong (34)	0.48	0.23-0.98	**0.044**			0.72
Roland Disability (0-23)	Per 3 points increments	2.08	1.24-3.49	**0.006**	1.8	1.21-2.90	**0.007**
VAS leg pain (0-100mm) ‡	Per 20 mm increments	1.65	1.05-2.6	**0.030**	1.72	1.11-2.67	**0.015**
Roland difference (T2w-T0) §	Worse or equal (37) vs improved(63)	1.51	0.60-3.81	0.38			-
	Better	1.00	-		-	-	
	No difference or worse				-	-	
VAS difference (T2W-T0) ‡	Worse or equal (35) vs improved(65)	1.37	0.56-3.36	0.49			-

* Intellectual or physical jobs were defined by the patient.

† Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

‡ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

§ The Roland Disability Questionnaire for Sciatica is a disease specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.

Bold text defines statistical significance of variables in analysis.

Table 3. Classification table based on regression formula.

	Per protocol treatment	Predicted group membership (%)	
		Predicted non- surgical	Predicted surgery
Original †			
	Conservative	84.6	15.4
	Surgery	57.1	42.9
Cross-validated* ‡			
	Conservative	83.5	16.5
	Surgery	63.3	36.7

* Cross validation was done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.
† 70 % of original grouped cases are correctly classified.

‡ 67 % of cross-validated grouped cases are correctly classified.

intervals. Whether prediction is actually possible in a reliable way for an individual patient can be seen in a classification table under the assumption of allocating the patient to "surgery" if the probability of surgery is more than 50 % (as is common in, for example, diagnostic tests). In view of the restricted size of the study population we focused solely on identifying significant risk factors for surgery. No attempts were made to perform a more refined analysis with an ROC curve or a training/validation subset approach. However we did a linear discriminant analysis (almost identical to a logistic regression model in this case) to obtain a classification table which is usually shown with a diagnostic test context with cross-validated percentages of correctly classified cases.

Results

Of 142 patients assigned to receive prolonged conservative care, 55 (39 %) underwent surgery after a mean period of 18.7 (95 % CI 14.3 to 23.0) and median 14.6 (Interquartile range; 6.4 to 26.0) weeks. Before randomization the mean period of sciatic complaints was 9.5 (SD; 2.11) weeks for all patients treated conservatively initially. The mean Roland disability score for the 55 surgical patients was 15.0 (95 % CI; 13.3 to 16.8) shortly before surgery, while the mean visual analogue score at that time was 54 (95 % CI; 46.2 to 61.8) mm. Repeated surgery within the first year was performed in a single case. Mean baseline and one-year outcome scores for those eventually undergoing surgery in the conservative arm were not significantly different from the

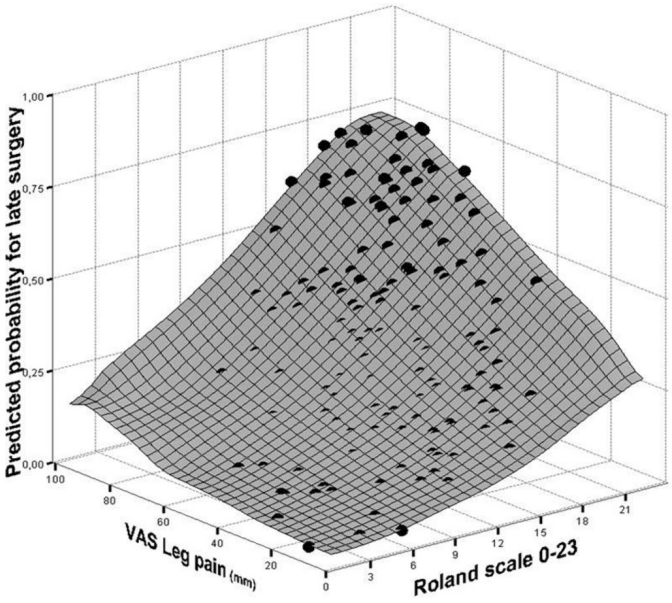


Figure 1: 3-D Scatter plot illustrating predicted probabilities of surgery as a function of VAS leg pain and RDQ at randomisation.*

** A patient with a Roland score of 20 and VAS leg pain of 79 mm has a predicted probability to undergo delayed surgery of 0,60, while for a patient with a Roland score of 8 and VAS leg pain of 61 presents a risk of 0.16.*

• Individual study patients.

scores for those treated without surgical intervention; the same holds for the proportion of recovered patients (Table 1).

Univariate logistic regression models with surgery as the event of interest did not reveal a significant association with the classical anamnestic, neurological and radiological variables (Table 2). Univariately significant odds ratios were obtained for "initially recorded leg pain intensity" (VAS; p=0.03), disability (RDQ; p=0.006) and the "Kemp neuroforamen compression test" (p=0.008), as well as for "magnitude of preference for surgery" (p=0.04). After entering these variables into one multivariable logistic regression model and performing a backward stepwise analysis, VAS leg pain intensity and severity of sciatica-specific disability RDQ were retained as significant factors. The adjusted Odds ratios were 1.7 (95 % CI; 1.1 to 2.7) per VAS 20 mm incremental increase in pain and 1.8 (95 % CI; 1.2 to 2.9) per 3 points deterioration on the RDQ score (Table 2).

Predictability of the risk to undergo delayed surgery seems high by the estimated odds ratios of leg pain intensity and disability, but the absolute risk never exceeds

levels higher than 80 % (table 3). Hence the sensitivity of the combined information of the two scores at intake and randomization is only around 43 % and the specificity is around 85 % with a total probability of correctly classifying surgery being estimated at 70 % (67 % cross-validated).

Since odds ratios describe relative effect sizes only, the estimated absolute risks of surgery as a function of combinations of pain and disability scores of the study patients is presented (Figure 1) to illustrate the estimated magnitude of the problem.

DISCUSSION

Delayed surgery did not lead to any differences in patient outcome at one year when compared to those treated strictly conservatively in a cohort of patients who had suffered from 6 to 12 weeks of sciatica. Baseline intensity of VAS leg-pain and RDQ disability scores were strong and independent determinants to predict delayed surgery, whereas traditional signs such as the straight leg raise test and the size or configuration of the disk herniation had similar distributions in the two groups.

High initial pain and disability scores were found to be predictive of a higher chance on delayed surgery in this study. However, these indicators are not yet used for the regular care of sciatica patients [114] but may be valuable in the decision process to opt for early surgery or for prolonged conservative care. Indeed, if initial scores after 6 to 12 weeks of persistent sciatica correspond to severe disability plus high pain intensity and do not regress after a few more weeks of 'wait-and-see', one may infer that the risk of surgery at a later stage is high. These patients might consider surgery without further delay to reduce the period of suffering and absence from work.

Previously we described the lack of interaction between initial pain intensities and the allocated timing of surgery on speed of recovery[129]. These analyses, however, were bound to an Intent-To-Treat methodology and the current 55 surgical patients were, thus, part of the prolonged conservative treatment arm as it was a pragmatic randomized controlled trial comparing two different timing-of-surgery strategies. The current analysis describes the predictive value of pain intensity for surgery performed at a later stage, instead of the possible interaction effects on speed of recovery or outcome per se.

The current results are clear but some restrictions in study design must be considered. Patients were recruited from neurological outpatient clinics after the usual referral by primary care physicians who stated that their patient had persistent sciatica and requested for surgery. One may concur that disability and pain are measured by subjective questionnaires which, except for study purposes, are not yet used for the

daily care of spine patients[167]. However, due to a lack of diagnostic, prognostic and outcome properties of neurological and radiological signs, these validated low back disease-specific questionnaires might be the best tools we have today to fulfil the request of society to measure quality of care.

So far, this is the first study that thoroughly analyzed variables which possibly affect the risk to undergo surgery in a conservative treatment regime for patients with 6 to 12 weeks of severe sciatica[47]. Although our findings may not be surprising for most physicians, we do not use these instruments for the regular care of sciatica patients. Obviously it is important to quantify the influence of pain and disability on the timing of surgery. Since timing of surgery did not influence outcome at 1 year the main indication for early surgery is to shorten the period of suffering. High pain intensities and disability scores complemented by personal preferences are valid arguments in support of the choice of surgery[168].

Despite maximal efforts of patients and physicians, surgery seems inevitable for a considerable proportion of a conservatively treated cohort. Compared to those with "tolerable" pain and disability, patients, who experience more intense leg pain and worse disability scores, run a higher risk of prolonged suffering and undergo delayed surgery and therefore might urge the spine surgeon to opt for earlier surgery to shorten their period of illness. Obviously we still can not reliably estimate exactly which patient will receive surgery during the follow-up period although the prediction is significantly improved when using these scales.

8

GENDER & SCIATICA

Influence of gender and other prognostic factors on outcome of sciatica; a post-hoc analysis of a randomized trial

Wilco C. Peul
Ronald Brand
Raph T.W.M. Thomeer
Bart W. Koes

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ABSTRACT

Background: Sciatica caused by a lumbar disk herniation is a frequently diagnosed disorder with a favourable natural course. While most prognostic studies focus on good outcome, patients might experience unsatisfactory results. Female gender has been found to be associated with chronic pain in other musculoskeletal disorders. Our aim is to quantify the relationship between gender and (1) rate of recovery and (2) outcome at one year.

Methods: Recovery was registered on a 7-point Likert scale for 283 patients with 6 to 12 weeks of persistent sciatica who participated in a randomized trial to investigate timing of surgery. Complete and near complete recovery were considered good outcomes. Function and pain were registered by the Roland Disability Questionnaire (RDQ) and a visual analogue scale (VAS). An univariate Cox model was used to study the influence of variables on rate of recovery while a univariate and multivariate logistic regression analysis evaluated variables predicting unsatisfactory outcome at 12 months.

Results: At one year unsatisfactory outcome was registered for 17 % of patients, 11 % of all males and 28 % of all females ($p<0.001$). Patients with an unsatisfactory outcome had worse RDQ and VAS scores compared to those who recovered satisfactorily ($p<0.001$). Women had a slower rate of recovery: HR 0.76 (95 % CI 0.59-0.99) and were associated with an unsatisfactory outcome represented by an unadjusted odds ratio of 3.3 (95 % CI 1.7-6.3) compared to males.

Conclusions: Besides a slower recovery rate, female gender was a strong predictor of unsatisfactory outcome at one year for patients with sciatica.

Introduction

The total impact of lumbar spinal disorders on society is high, since they constitute the fifth most expensive disease category as far as hospital care is concerned and are even the most expensive disorder with respect to work absenteeism and disability[77]. Within this group of musculoskeletal disorders sciatica is an important subcategory. The literal translation of the Greek word 'sciatica' is hip pain , which leaves room for dispute about today's use of the word 'sciatica' in scientific communications. Undoubtedly "lumbosacral radicular syndrome" (LSRS) or sciatic neuralgia is a better description of the disease but it is not frequently used in peer-reviewed manuscripts. For this study sciatica is defined as intense leg pain in an area served by one or more spinal nerve roots and is occasionally accompanied by neurological deficit. The natural course of sciatica is generally favourable, since the radiating ache disappears in the majority of cases within 8 weeks of onset[51;79]. Prognostic studies usually focus on "excellent" outcomes at one year. The high indirect costs, however, due to absenteeism from work and disability are mainly caused by patients experiencing a slower pace of recovery and those with an unsatisfactory outcome in the long term. Insight into determinants of outcome is important in order to be able to inform patients and to guide management decisions.

Interestingly, some early studies[169;170] did show gender to be one of the few variables influencing the outcome of sciatica. Female gender compared to male appeared to predict worse outcomes. For unknown reasons this finding seems to have escaped the attention of studies on spinal disorders in the past two decades. Outcome studies of chronic pain management in general have reported that women experience more pain in more parts of the body, with greater frequency and for longer periods compared to men[171;172]. Explanations for such gender differences have included differences in emotional and coping responses to pain between men and women. Women not only report greater emotional distress, but may also use more emotion-focused problem-solving which may cause the less beneficial long-term outcomes[173;174].

Based upon the findings reported in early studies and recent pain intervention effectiveness trials in general, we hypothesized that female patients with sciatica would show (1) a slower rate of recovery in the short term and (2) experience a higher rate of unsatisfactory outcome in the long term compared to males with sciatica. Besides gender we analysed the influence of other demographic, neurological and radiological determinants on rate of recovery from sciatica and estimated the effect of the unsatisfactory outcomes at one year.

Table 1 a. Gender related demographic and clinical characteristics *

Variable	*n*	Gender		
		Male (n=186)	Female (n=97)	p value
Age (yrs)	283	42.4 ± 9.6	42.9 ± 10.1	0.66
Duration sciatica (w)	283	9.4 ± 2.0	9.6 ± 2.5	0.49
Time intake to randomization (w)	283	2.3 ± 1.0	2.4 ± 1.4	0.45
Randomization (%)	283			0.38
Surgery	142	48	54	
Conservative	141	52	46	
Timing of surgery n(%)				0.35
Operated < 4 weeks	116	71(40)	45 (49)	
Operated between 4-26 weeks	44	32(17)	12(12)	
Not operated or later than 26 weeks	123	83(43)	40 (39)	
Absence from work (%)	220	88	84	0.45
Mentally demanding job (%)	167	73	46	<0.001
Physical job (%)	100	41	33	0.13
Spouse/partner				
Yes (%)	215	77	74	0.66
Children				
Yes (%)	193	69	67	0.68
Smoking				
Yes (%)	117	41	42	0.47
Body mass index (kg/m2) †	283	26.0± 3.7	25.1 ± 3.8	0.05
Sciatica provoked by …..				
Sitting (%)	215	80	81	0.74
Coughing, sneeze (%)	206	69	79	0.24
Straight leg raising (degrees)	283	75. ± 24.4	74.9 ± 23.9	0.94
Positive < 60 degrees (%) ‡	207	77	70	0.15
Crossed leg raising positive (%)	167	58	62	0.53
Bragard test positive (%)	83	22	46	<0.001
Preference for surgery (%)				
Strong	111	39	39	0.97
Roland Disability §				
Baseline	283	15.9 ± 4.2	17.3 ± 3.9	0.009
Outcome at one year		2.7± 4.3	5.0 ± 7.0	0.001
VAS legpain in mm ¶				
Baseline	283	63 ± 19.9	72 ± 20.1	<0.001
Outcome at one year		8.0 ± 13.9	16.6± 26.3	<0.001
VAS backpain in mm				
Baseline		29.9 ± 27.4	37.1 ± 30.3	0.042
Outcome at one year		12.7 ± 17.4	20.5 ± 28.4	0.006
Recovery at one year, n (%)				0.001
Good outcome	235	165 (89)	70 (72)	
Unsatisfactory outcome	47	20 (11)	27 (28)	

Table 1b. Pain and disability characteristics per outcome group at 12 months *

	Outcome		
	Good (n=235)	**Unsatisfactory (n=47)**	**p value**
Roland Disability §	1.6 ± 3.1	12.8 ± 5.5	<0.001
VAS leg pain in mm ¶	5.1 ± 10.9	40.7± 25.5	<0.001
VAS back pain	9.3 ± 14.5	45.8 ± 27.9	<0.001

* Plus-minus value are means ± SD.
† Quetelet Index or Body Mass Index is calculated by dividing the weight in kilograms by the squared of the height in meters. Higher scores define overweight.
‡ Lasègue's sign is positive if the examiner observes a typically dermatomal area of pain reproduction and pelvic muscle resistance when the unilateral straight leg is raised below an angle of 60 degrees; it is called crossed positive if the same is noted when the other leg is raised below 90 degrees.
§ The Roland Disability Questionnaire for Sciatica is a disease-specific disability scale that measures the functional status of patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.
¶ The intensity of pain is indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

METHODS

Patients

The Sciatica Trial provided extensive one year follow-up data on 283 patients after one year of follow-up who had suffered a period of 6 to 12 weeks of severe sciatica[129]. Eligible patients were 18-65 years of age, had a radiologically confirmed disk herniation, and had been diagnosed by an attending neurologist with an incapacitating lumbosacral radicular syndrome lasting between 6 and 12 weeks. Correlation of MRI with complaints was confirmed by the neurosurgeon. At the time of enrolment an independent research nurse verified persistence of complaints. Patients presenting with a cauda equina syndrome, muscle paralysis or insufficient strength to move against gravity were excluded. Patients were also excluded if they had had identical complaints in the past twelve months, a history of spinal surgery, bony stenosis, spondylolisthesis, pregnancy or severe comorbidity.

This randomized multicentre trial assessed the effect on outcome during the first year by varying the timing of surgery. Patients aged 18 to 65 years old were allocated randomly to either a strategy of prolonged conservative care, possibly with late surgery or early surgery preferably within two weeks. Independent academic research nurses assessed and recorded baseline sociodemographic factors, clinical symptoms and neurological nerve stretch signs. The individual interviews and physical examinations were performed in a standardized fashion and repeated at each visit to the research nurse.

Table 2. Univariate analysis of variables for rate of recovery by an unadjusted Cox proportional hazard model

Variable	*n*	Univariate Cox Proportional Hazard analysis		
		HR	95 % CI	p value
Randomization				
Surgery	141	1.97	1.72-2.22	< 0.001
Conservative	141	1.00	-	
Gender				
Female	97	0.76	0.58-0.99	0.04
Male	185	1.00	-	
Age				
<40	116	1.00	-	
≥ 40	166	0.87	0.68-1.12	0.28
Mentally demanding job				
No	92	1.00	-	
Yes	166	1.17	0.90-1.53	0.25
Physical job				
No	158	1.00	-	
Yes	100	1.03	0.80-1.34	0.80
Housewife				
Yes	21	0.78	0.47-1.30	0.34
No	255	1.00	-	
Start sciatica				
Acute	170	1.00	-	
Slow increase	111	1.10	0.86-1.42	0.43
Sciatica provoked by …..				
Sitting				
Yes	215	0.72	0.48-1.06	0.098
No	67	1.00	-	
Coughing, sneeze				
Yes	205	1.14	0.86-1.50	0.36
No	77	1.00	-	
VAS leg pain				
< 70 mm	151	1.00	-	
≥ 70 mm	130	1.00	0.79-1.28	0.97
Straight leg raising				
Negative ≥ 60 °	69	1.00	-	
Positive <60°	206	0.96	0.73-1.28	0.80
Crossed leg raising				
Negative	116	1.00	-	
Positive	166	0.78	0.61-1.00	0.047
Kemp's sign				
Positive	121	0.89	0.66-1.10	0.23
Negative	141	1.00	-	

Table 2. *continued*

Variable	*n*	Univariate Cox Proportional Hazard analysis		
Finger-ground in cm				
>30	156	1.10	0.86-1.42	0.45
≤30	119	1.00	-	
Bragard's test				
Positive	83	0.65	0.49-0.86	0.002
Negative	186	1.00	-	
Sensory disturbance				
No	28	1.00	-	
Yes	251	0.95	0.63-1.41	0.79
MRI-level herniation				
L4L5 (and L3L4)	105	1.00	-	
L5S1	166	0.88	0.68-1.11	0.34
MRI-sequester				
No	154	1.00	-	
Yes	107	1.16	0.90-1.50	0.26
MRI-Gadolinium				
No enhancement	71	1.00	-	
Enhancement	138	0.83	0.61-1.11	0.21
Preference surgery				
Strong	111	1.00	-	
Mild	171	0.95	0.74-1.22	0.70

Interventions

Prolonged conservative management was performed by the general practitioner. Ample information was provided about the favorable prognosis. Study participants were offered access to our trial website, exclusively designed to inform patients about the possibility of a successful natural course, irrespective of the initial pain intensity. Treatment was aimed mainly at resuming daily activities. If necessary, the prescription of pain medication was adjusted according to existing clinical guidelines. Patients who had considerable fear of movement were referred to a physiotherapist. If sciatica persisted 6 months after randomization microdiscectomy was offered. Increasing leg pain not responsive to medication or progressive neurological deficit were reasons for performing surgery even earlier than at 6 months.

Early surgery was scheduled within 2 weeks of assignment and only cancelled if spontaneous recovery occurred before the date of surgery. Under either general or spinal anesthesia the symptomatic disc herniation was removed by a minimal unilateral transflaval approach with magnification. The goal of surgery was to decompress the nerve root and reduce the risk of recurrent disc herniation by an annular

Table 3. Univariate and multivariate log rank analysis of predicting factors for unsatisfactory outcome of sciatica.

Variable	*n*	Univariate analysis			Multivariate analysis		
		OR	95 % CI	p value	OR	95% CI	p value
Randomization				0.27			0.05
Surgery	141	0.70	0.37-1.31		0.49	0.24-1.00	
Conservative	141	1.00	-		1.00	-	
Timing surgery after randomization							-
No surgery or later than 26 weeks	116	1.00	-	-	-	-	
< 4 weeks)	121	0.78	0.08-1.48	0.49	-	-	
4-26 weeks	43	1.05	0.13-1.97	0.92	-	-	
Gender							
Female	97	3.29	1.72-6.28	<0.001	2.81	1.38-5.74	0.006
Male	185	1.00	-	-	1.00	-	-
Age				0.10			-
<40	116	1.00	-		-	-	
≥ 40	166	1.76	0.89-3.47		-	-	
Mentally demanding job				0.09			0.89
No	92	1.00	-		1.00	-	
Yes	166	0.56	0.29-1.09		1.06	0.44-2.53	
Physical job				0.67			-
No	158	1.00	-		-	-	
Yes	100	1.16	0.59-2.29		-	-	
Housewife				0.015			0.37
Yes	21	3.26	1.26-8.44		1.72	0.52-5.65	
No	255	1.00	-		1.00	-	
Spouse/partner							
Yes	214	0.69	0.34-1.38	0.29	-	-	-
No	68	1.00	-		-	-	-
Children							
Yes	193	1.26	0.63-2.52	0.52	-	-	-
No	89	1.00	-		-	-	-
Smoking				0.07			0.05
Yes	117	1.81	0.96-3.41		2.01	0.99-4.1	
No	165	1.00	-		1.00	-	
Quetelet index	282	1.03	0.95-1.12	0.50	-	-	-
Start sciatica				0.79			-
Acute	170	1.00	-		-	-	
Slow increase	111	0.91	0.47-1.77		-	-	

Table 3. *continued*

Variable	*n*	Univariate analysis			Multivariate analysis		
		OR	95 % CI	p value	OR	95% CI	p value
Sciatica provoked by …..							
Sitting				0.22			0.63
Yes	215	1.67	0.74-3.78		1.26	0.50-3.20	
No	67	1.00	-		1.00	-	
coughing, sneeze				0.45			-
Yes	205	0.77	0.39-1.52		-	-	
No	77	1.00	-		-	-	
VAS leg pain				0.32			-
< 70 mm	151	1.00	-		-	-	
≥ 70 mm	129	1.39	0.73-2.62		-	-	
Straight leg raising				0.81			-
Negative ≥ 60 °	69	1.00	-		-	-	
Positive < 60°	206	0.91	0.44-1.89		-	-	
Crossed leg raising				0.15			0.15
Negative	116	1.00	-		1.00	-	
Positive	166	1.64	0.84-3.20		1.75	0.82-3.77	
Kemp's sign				0.70			
Positive	121	1.15	0.58-2.27		-	-	
Negative	141	1.00			-	-	
Finger-ground in cm				0.38			-
>30	156	0.75	0.39-1.42		-	-	
≤ 30	119	1.00	-		-	-	
Bragard's test				<0.001			0.006
Positive	83	3.80	1.92-7.50		2.72	1.33-5.58	
Negative	186	1.00	-		1.00	-	
Sensory disturbance				0.39			-
No	28	1.00	-		-	-	
Yes	251	1.73	0.50-6.00		-	-	
MRI-level herniation				0.88			-
L4L5 (and L3L4)	105	1.00	-		-	-	
L5S1	166	0.95	0.49-1.83		-	-	
MRI-sequester				0.61			-
No	154	1.00	-		-	-	
Yes	107	0.84	0.43-1.63		-	-	
MRI-Gadolinium				0.04			0.04
No enhancement	71	1.00	-		1.00	-	
Enhancement	138	2.94	1.07-8.06	0.04	2.88	0.98-8.45	0.05
No gadolinium	73	5.57	1.68-18.4	0.005	4.49	1.44-14.0	0.01
Preference surgery				0.77			-
Strong	111	1.00			-	-	
Mild	171	0.91	0.48-1.73		-	-	

fenestration, curettage and removal of loose degenerated disc material out of the disc space using a rongeur, without any attempt to perform a subtotal diskectomy. The duration of hospitalization depended on the patient's functional ability to mobilize. Normal care was provided according to the protocols of the participating surgical departments. At home the rehabilitation process was supervised by the physiotherapist who used a standardized exercise protocol. Patients were advised to resume their regular jobs when able, depending on the nature of the work.

Follow-up of patients at 2, 4, 8, 12, 26, 38 weeks and at one year was recorded according to the trial protocol[109] and included perceived recovery measured by a 7-point Likert scale, a VAS 100 millimetres intensity of leg pain scale, VAS back pain and disease-specific functional status measured by the Roland Disability Questionnaire for Sciatica (RDQ). The study was approved by all participating institutes and central and local ethics committees. All patients gave informed consent.

The present study included all patients from both groups of this randomized trial. Patients with 6 to 12 weeks of persistent sciatica, with an indication for surgery and eligible for trial participation were included in this analysis, irrespective of their randomization status. Except for the actual procedure and the moment of surgical intervention as a possible determinant, all baseline socio-demographic, neurological and radiological variables were collected shortly before randomization. In order to study the effect of baseline variables on speed of recovery the prescheduled moments of outcome registration during the first year were used, while the one year outcome was used to estimate the performance of these variables as predictors of an unsatisfactory result at one year.

Statistical analysis

Data were analysed with the SPSS package (version 14.0 for Windows; SPSS Inc, Chicago, IL, USA). Fisher's exact test for categorical variables or the t test for continuous variables was used to assess differences between baseline and outcome variables. To analyse time to recovery and the actual state of recovery at one year the 7 point Likert scale was dichotomized. "Complete" and "Near complete" recovery, considered to be indicative of good or favourable outcome, were defined as "recovery", while a score in the remaining 5 categories was concluded to be a poor or unsatisfactory outcome and thus defined as "no recovery".

Descriptive statistics describe the basic properties of "recovered" and "not recovered" patients as well as those of both genders. To answer the first hypothesis a univariate Cox Proportional Hazard model was used to study the influence of each variable on the short-term rate of recovery. The predictive effect of gender and other variables was analysed by univariate logistic regression analysis with "no recovery"

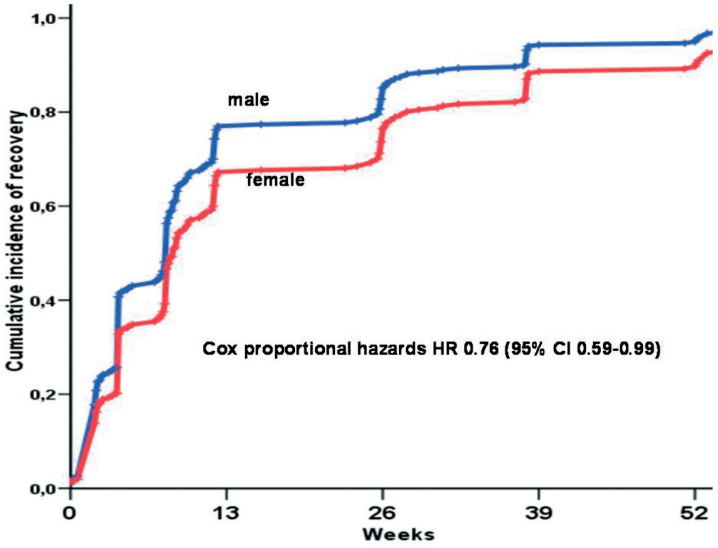


Figure 1. Cox proportional hazard analysis of rate of recovery comparing females to males (p=0.04)

at twelve months as the outcome of interest. The initial list of prognostic factors, chosen in advance by the investigators, was based on potential clinical importance, based on earlier published results[153;163] or current neurological textbooks. Variables were used for multivariate analysis if the univariate effects (Cox Proportional Hazard models and logistic regression, respectively) were significant with a p-value <0.10. The multivariate modelling process itself was a stepwise backward approach starting with the above-mentioned variables, retaining those for which the two-sided p value in the multivariate model remained ≤ 0.05. The result of randomization was always included in the multivariate model, regardless of significance since this factor is the original allocated treatment strategy itself. Repeated measurement analysis of variance was applied in case of continuous outcome measures (disability and pain) with both gender and randomization group as the main effects, while their interaction was assessed and possibly added to the model in a stepwise forward way.

Role of funding source

The sponsor did not influence the study design and had no role in data collection, data analysis or writing of the report. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

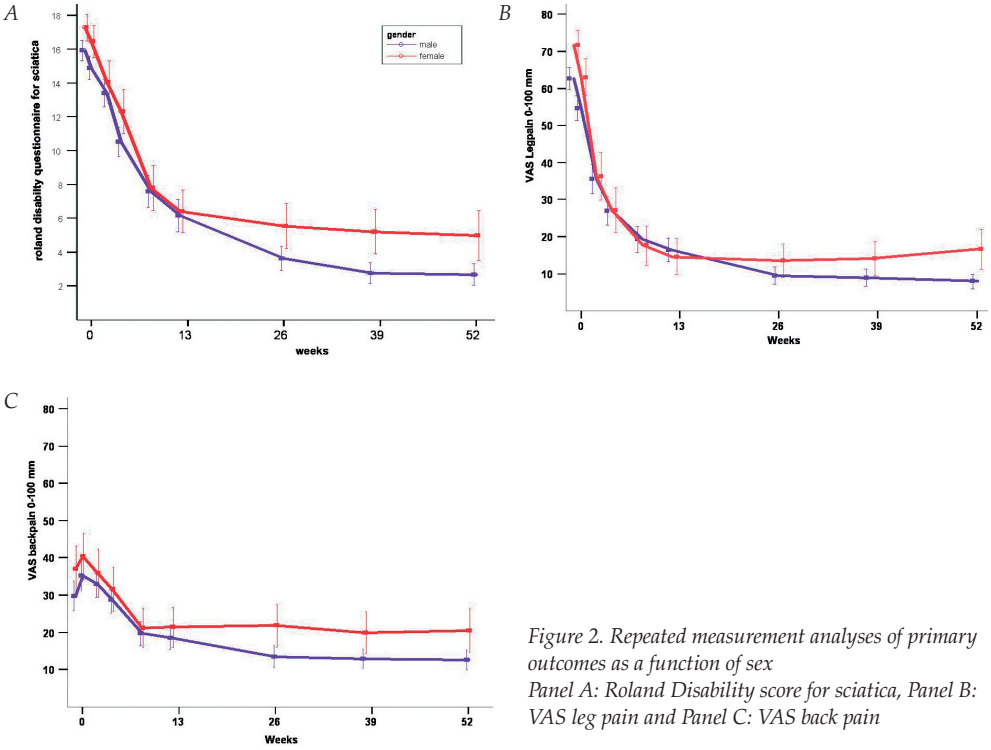


Figure 2. Repeated measurement analyses of primary outcomes as a function of sex
Panel A: Roland Disability score for sciatica, Panel B: VAS leg pain and Panel C: VAS back pain

RESULTS

Allocation of an early surgical strategy resulted in 125 of 141 (89 %) patients who actually underwent lumbar diskectomy after a median period of 1.9 weeks, while of the 142 conservatively managed patients surgery could not be evaded in 55 (39 %) after a median time of 14.6 weeks. At different follow-up moments during the first year 269 of 283 (95 %) patients registered complete recovery. At exactly 12 months, however, 83 % of patients reported complete recovery. The patients with a good outcome at 12 months of follow-up showed a mean RDQ score of 1.6, VAS-leg of 5.1 mm and VAS-back 9.3 mm, while the 17 % of patients with an unsatisfactory outcome had a mean RDQ score of 12.8, VAS-leg 40.7 mm and VAS-back 45.8 mm at 12 months ($p<0.001$) (Table 1b). At intake 97 (34 %) of 283 patients were female. Demographic characteristics of male and female patients were not different at baseline, except for mentally demanding work rated by the patient (Table 1a). Clinical variables, such as disability and pain, showed significantly different baseline values, such that females experienced somewhat worse sciatica at intake. For the patients allocated to conservative treatment, no proportional difference

was noted between genders as far as patients who crossed over to delayed surgery is concerned. Results at 12 months showed a significantly different outcome between genders with 28 % of females exhibiting an unsatisfactory perceived outcome versus 11 % of males (Table 1). The result of the perceived recovery score was consistent with other outcomes such as the mean VAS leg pain, back pain and RDQ functioning scores (Table 1 and Figure 2).

Cox proportional hazard analysis showed a slower rate, HR 0.76 (95 % CI 0.59-0.99) to complete recovery for females as compared to males (Table 2; Figure 1), while interaction with timing of surgery did not influence the result[129]. Other variables with a negative influence on speed of recovery were a positive Bragard's sign and crossed leg raising test.

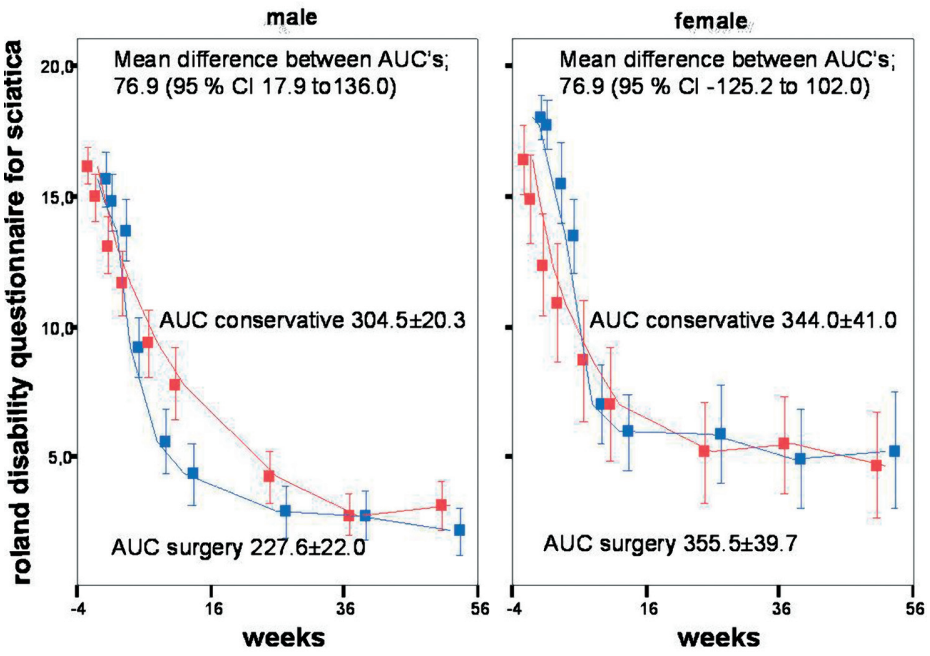
Table 3 shows the results of univariate and multivariate logistic regression analyses of prognostic variables for "no recovery" at 12 months, irrespective of intermediate recovery. In the univariate logistic regression analysis, a clear association between gender and outcome was found. Compared to males, females had a univariate Odds Ratio of 3.29 (95 % CI 1.72-6.28) for an unsatisfactory outcome ($p<0.001$). A positive Bragard test, MRI enhancement by gadolinium, and smoking rendered a significantly higher chance of an unsatisfactory outcome. Likewise did the variable "type of work" after dichotomizing into housewife and other jobs.

Only gender and Bragard's sign were expressed consistently across both analyses. In both logistic regression models and the Cox regression models timing of surgery and neurological, radiological and intensity of pain variables did not have any predictive value for outcome at 12 months, while the effect of gender on outcome was unequivocal.

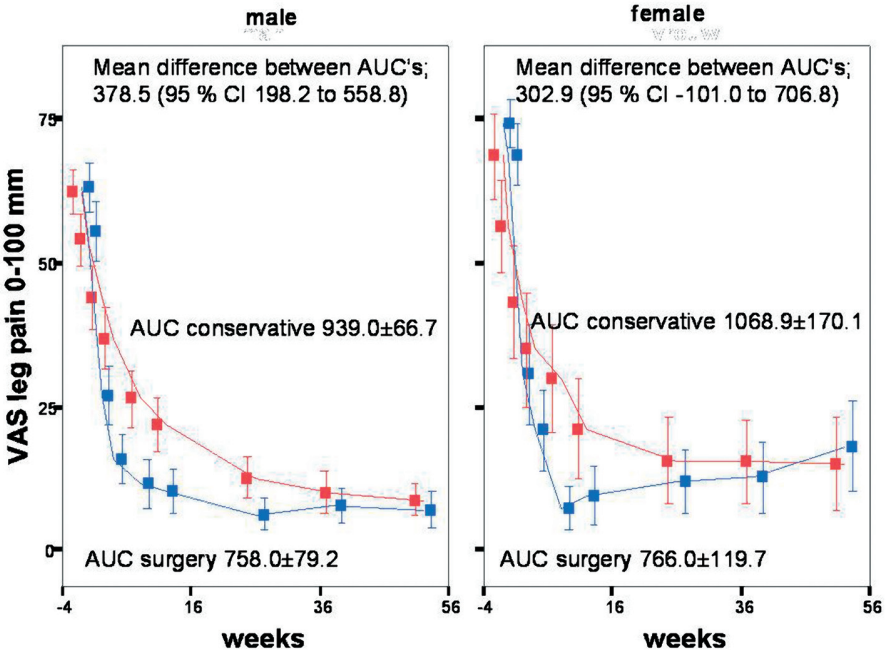
Multivariate analyses showed consistent findings for gender, but also for Bragard sign, gadolinium contrast enhancement and smoking (table 3). Furthermore the risk of unsatisfactory outcome was influenced significantly ($p=0.05$) by the allotted treatment strategy with an odds ratio of 0.49 (95 % CI 0.24-1.00) when corrected for gender in favour of early surgery. The estimated risks for an unsatisfactory outcome for the variables retained by multivariate analysis, vary substantially on specific combinations of risk factor values (Table 4). Figure 3, which illustrates the repeated measurement analysis results for the primary outcomes of the randomized trial stratified for gender, displays a smaller and not significant short-term effect of early surgery on early functional recovery in females. Differences between areas under the curves of all three primary outcomes over the first year after randomization are statistically significant for men in favor of early surgery and not for women.

With regard to experienced relief of disability, leg-pain and back-pain, the early surgery strategy does not seem to be as effective for females compared to men.

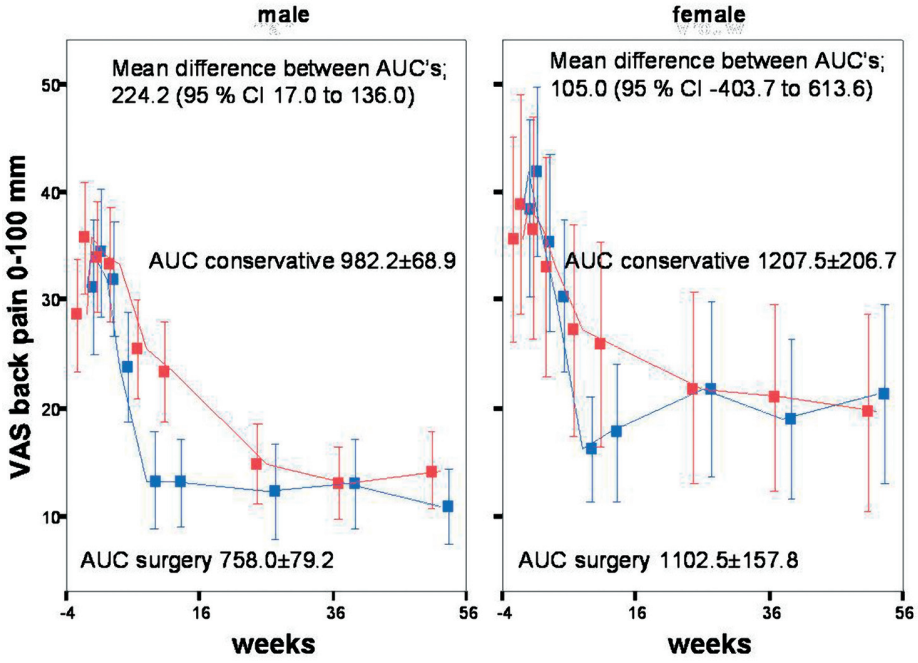
Those males and females who reported recovery at 12 months had similar RDQ



Panel A



Panel B



Panel C

*Figure 3. Repeated Measurement Analysis Curves of Mean scores for Roland Disabilty Questionnaire (Panel A), Leg Pain (Panel B) and Back Pain (Panel C) on a Visual-Analogue Scale. **

All three panels show the 52-week curves with 95 percent confidence intervals represented by vertical bars at consecutive moments of measurement. Red lines represent the conservative treatment group, while the blue lines represent early surgery. Areas under the curve (AUC) are described by their means (SE).

***Panel A** represents the mean disability scores at consecutive moments of measurement stratified by gender.*

The overall difference between the areas under the curves over 12 months is not significant for females (p=0.84) and significant for males (p=0.01) in favor of early surgery.

***Panel B** represents mean visual analogue scores for intensity of leg pain in mm. The difference between the mean AUC's is not significant for females (p=0.14) and significant for males (p<0.001) in favor of early surgery.*

***Panel C** represents mean visual analogue scores for intensity low back pain in mm. Starting with a lower intensity score when compared to leg pain, the mean AUC's exhibit a less strong and not significant difference for females (p=0.68) and significant for males (p=0.03)*

** The mean difference between areas under the curves are expressed by the corresponding 95 percent confidence interval*

Table 4. Estimated risks of unsatisfactory outcome at 12 months, based on a logistic regression model using gender, smoking, Bragard and randomization as main effects.

Variable	Randomization	Gender	
		Male (n=186)	Female (n=97)
Smoking Yes			
Bragard; Positive	Surgery	18 %	38 %
	Conservative	31 %	55 %
Negative	Surgery	7 %	18 %
	Conservative	14 %	31 %
Smoking No			
Bragard; Positive	Surgery	10 %	23 %
	Conservative	18 %	38 %
Negative	Surgery	4 %	10 %
	Conservative	7 %	19 %

and VAS scores (Table 5). Under the unsatisfactory circumstances of not being recovered at one year, however, females scored significantly worse on both the pain and disability scales compared to males. The interaction between gender and perceived recovery on all three symptom outcome scores was significant, implying that the difference between males and females in any of these outcome scores depends significantly on whether they recovered or not.

DISCUSSION

Our study showed unequivocally that female gender is an independent predictive determinant for an unsatisfactory outcome at one year after 6 to 12 weeks of severe sciatica. The estimated unadjusted (crude) odds for a long-term poor outcome was 3.3 higher for female patients with sciatica than for males and this finding was statistically highly significant. In addition females showed a slower perceived recovery from sciatica, but compared to conservative care it was still significantly faster after early surgery. Notwithstanding this important treatment result the early surgery strategy failed to yield any early treatment effects on intensity of leg pain in females compared to the original repeated measurement analysis of the non-stratified study population. Males, however, presented more pronounced early treatment effects which were significantly different in favor of early surgery for all three outcomes scales (Figure 3). Besides a worse initial value on all pain and disability scales for females, the latter also presented with higher pain and disability scores when they

Table 5. Mean disability pain scores according to outcome group and gender at 12 months *

	Gender		
Outcomes	**Male**	**Female**	**p-value †**
Roland Disability			<0.001
Recovered	1.7 (1.2 to 2.3)	1.8 (1.0 to 2.7)	
No recovery	10.6 (9.1 to 12.2)	15.2 (13.9 to 16.6)	
VAS leg pain in mm			<0.001
Recovered	5.4 (3.3 to 7.4)	5.0 (1.8 to 8.2)	
No recovery	27.6 (21.6 to 33.5)	55.9 (50.7 to 61.0)	
VAS back pain in mm			<0.001
Recovered	9.3 (6.7 to 12.0)	8.8 (4.7 to 12.9)	
No recovery	37.1 (29.5 to 44.6)	53.7 (47.2 to 60.2)	

* 12 months mean scores are described with their corresponding 95 % confidence interval (CI)

† P value interaction effect between gender and perceived outcome on Roland and VAS scores.

recorded unsatisfactory perceived recovery in contrast to males with unsatisfactory recovery.

In addition to gender, smoking and Bragard's sign seemed to be predictive of an unsatisfactory outcome too. When adjusted for gender, multivariate analysis resulted in a considerable treatment effect of the early surgery strategy compared to prolonged conservative treatment, such that the odds ratio for unsatisfactory outcome at one year was halved.

Irrespective of treatment the proportion of patients with a good outcome was 83 % at one year. Since this is the actual state of the patients at 12 months, this proportion is lower than the apparently high proportion of 95 % perceived recovery during the first year as indicated by survival analysis[129]. The explanation for this discrepancy is that a considerable proportion of patients had recurrent back or leg pain after initial recovery, which could not be taken into account during Kaplan Meier calculations, since the survival model measures the time until a good outcome occurs for the first time, ignoring any later deterioration of the patient. The results of this trial are comparable to previous prognostic studies[113;151]. Most of these studies focus on good outcome and not on predictions of unsatisfactory outcome. Since prolonged absence from work is influenced by persistent high RDQ scores and VAS pain scores, the mean RDQ and VAS pain scores of patients with an unsatisfactory outcome at one year in this trial represent painful and disabling suffering. Quantification of the degree of failure has not yet been reported.

Notwithstanding the unequivocal findings reported here one must interpret these results carefully. Since this study was not designed primarily to analyse gender influ-

ences on outcome, one might argue that the high odds ratio for poor outcome could be the result of multiple testing. The latter mechanism is quite certainly responsible for the fact that Bragard's sign was also indicated by the analyses as a predictive factor. Although this test was standardized and performed independently by trained research nurses, these positive neurological nerve stretch signs were found previously to be quite unreliable in diagnostic studies. However earlier studies[40;170] also showed less favourable outcomes of treatment of sciatica for females, but these were not quantified and supported by pain and disability scores. Furthermore Kosteljanetz[169] in his famous diagnostic placebo-controlled trial found a good outcome for 90 % of males, compared to only 60 % of females. A good result for 89 % of our males one year after treatment for sciatica is in agreement with information provided by general physicians and spine surgeons for all of their patients, irrespective of gender. The fact that only 72 % of the females in our study and even less in Kosteljantetz's study perceived a good outcome should be taken into account when aiming at the prevention of unsatisfactory outcomes and when informing patients.

In our study population a proportional gender difference was noted with a preponderance of male patients. This is remarkable since extramural epidemiological studies and conservative treatment trials could not detect differences in incidence and prevalence between genders. The baseline characteristics of patients, seeking surgical help in most hospital care intervention trials show a minority for females compared to men. Since utilization of health care sources for sciatica seems to vary between genders, females in surgical populations might differ in baseline characteristics from females in conservative treatment studies and males in surgical series. Although eligibility for surgery, as defined by the general practitioner and medical specialist, is supposed to be the same, female patients might be less willing to request surgery and may only consult the spine surgeon at a higher threshold of pain and disability compared to males. In surgical studies similar to the current trial, this hypothesis is supported by the fact that compared to males females present with higher baseline pain intensity and disability scores. This consistent observation suggests that the differences in perceiving pain severity between genders might be an important factor. Additional investigation is warranted to characterize the nature and practical impact of these effects. During the retrieval of patients, who opted for surgery for sciatica, differential selection bias might have occurred.

In several studies female gender appeared to be a risk factor for chronic pain and disability caused by other musculoskeletal pain disorders as well[175]. Recent basic and clinical research showed biological[176;177], social and behavioural[178;179] factors to contribute to the risk of pain-induced chronic disability in females. Most factors involved are difficult to influence with therapeutic procedures, whereas catastrophizing, more prevalent among females, forms an important prognostic variable for developing

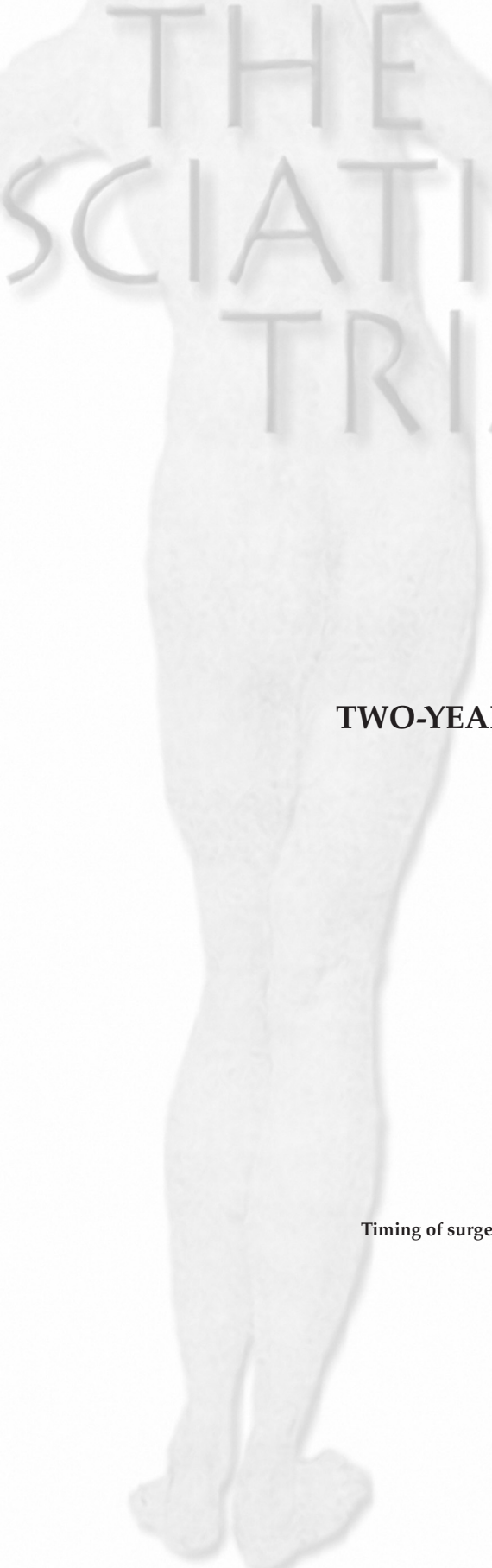
chronic pain disorders and seems to be susceptible to treatment intervention[171;172]. There may be various reasons why females do worse in terms of pain relief. As stated above females in our study as in other surgical trials registered higher baseline values for pain and disability, suggesting a worse start when compared to males. However, baseline pain intensity and disability did not predict outcome at all and the analyses failed to show any confounding or interaction effects with the registered variables.

Minor differences in the low back disability questionnaire reporting as a function of gender have been described before[180;181].

The design of this randomized trial did not allow the investigators to perform an elaborate observational prognostic study. Preferably social-, psychological factors, somatization scores, co-morbidities more prevalent in females (e.g. irritable bowel syndrome and fibromyalgia) and hormone differences should have been registered to account for interaction and confounding effects while estimating the prognostic effect of gender on outcome. Furthermore variables to support the difference in the prevalence of catastrophizing between genders and the theory of social and cognitive behavioural effects were not measured. Despite the prospective nature of a randomized trial, this study has to be considered as a post-hoc subgroup analysis with all the inherent disadvantages, such as lacking registered baseline variables to control for in multivariable regression analyses and possible over-estimation of treatment effects. The findings however concur with some previous sciatica studies and recent biological and social pain theories, but the results of our repeated measurement analyses, with special regard to the randomization effect, need further confirmation by future studies. To improve care for sciatica patients a gender-specific approach might be necessary but these treatment modalities have not been studied yet. Observational studies, starting in an extramural setting, are needed to specify possible gender-specific factors, responsible for differences between utilization of health care services and worse outcomes. Until these data become available discussion about targeted treatment strategies remains highly speculative.

Classical predictive neurological signs and the site or morphology of the disk herniation did not influence results, whereas an unsatisfactory outcome at one year was influenced markedly by gender and smoking, but modified by early surgery in a favourable direction.

Prognosis and treatment of sciatica depend strongly on patient preferences and realistic expectations. The fact that female gender is with a slower rate of perceived recovery and a higher likelihood of unsatisfactory outcome must not be neglected and should be taken into account when informing patients individually.



9

TWO-YEAR RESULTS OF SCIATICA TRIAL

Timing of surgery for sciatica; 2-year results of a randomized controlled trial

Wilco C. Peul
Wilbert B. van den Hout
Ronald Brand
Raph T.W.M. Thomeer
Bart W. Koes

Submitted for publication

ABSTRACT

Study design: A randomized controlled trial with parallel group design comparing "early"surgery, following clinical guidelines, and prolonged conservative care for patients with sciatica.
Objective: To evaluate the effectiveness over a period of 2 years of timing of disk surgery for sciatica .
Summary of Background Data: Lumbar disk surgery is frequently performed on patients after elapse of at least 6 weeks of non abating sciatica, but the optimal timing of surgery is not known. One-year results of a randomized trial showed short-term effects in favor of early surgery. Two-year outcomes have not yet been described.
Methods: We randomized 283 patients with 6-12 weeks of sciatica to early surgery or an intended 6 months of continued conservative treatment, with delayed surgery if needed. Primary outcome measurements were the Roland Disability Questionnaire, Visual-Analogue-Scale for leg pain and Global Perceived Recovery. Repeated measurement analysis according to intent-to-treat was used to estimate the outcome curves for both groups.
Results: Of 141 patients assigned to undergo early surgery, 125 (89 %) underwent microdiskectomy after a mean of 2.2 weeks; of 142 patients designated for conservative treatment, 62 (44 %) were treated surgically after a mean of 18.7 weeks. There was no significant overall difference in disability scores during the first two years ($p=0.25$). Improvement of leg pain was faster for patients randomized to early surgery with a significant difference between areas under the curves over two years ($p=0.05$). Leg pain, back pain, functional disability and perceived recovery in both randomization groups showed similar results at 2 years. Twenty percent of the patients experienced unsatisfactory results at 2 years, as could be concluded from perceived recovery, pain and functional scores.
Conclusions: The two strategies, early surgery and prolonged conservative care, resulted in similar outcomes at two years but early surgery achieved more rapid relief of sciatica.
Summary: To evaluate the timing of lumbar disk surgery, a randomized trial with 283 patients with sciatica for 6 to 12 weeks was conducted, comparing early surgery with prolonged conservative care and possibly delayed diskectomy. Early surgery resulted in faster recovery, but with similar outcomes at 1 and 2 years.

INTRODUCTION

In Western countries surgical removal of the herniated nuclear part of the disk is routinely performed to relieve sciatica. The complex of symptoms encompassing sciatica, more accurately called the lumbosacral radicular syndrome (LSRS), is characterized by radiating pain in an area of the leg typically served by one lumbar or sacral spinal nerve root in combination with motor, sensory or tendon reflex abnormalities. It is estimated that 5 to 10 out of every 1000 inhabitants in western society develop sciatica each year with variable pain intensities and disease courses[127]. During the first 6 weeks the leg pain diminishes in 70 percent of the patients[182]. Most guidelines recommend surgery for the remainder of patients[44;45;47;183]. The unknown number of months needed for spontaneous recovery from pain and the lack of scientifically proven efficacy of alternative therapies, in combination with the personal treatment preference of the attending physician, hinder the patient who must decide about the possibility of surgical treatment. Until a few years ago, only one landmark randomized trial[40] could be retrieved showing that conservative treatment and surgery had similar results after 4 years of follow-up among patients with moderate pain intensities[78]. Patients with intense sciatica fear chronic disability. Without any outlook for short-term pain relief, most of them choose surgery. The continuing uncertainty around the optimal timing of surgery for sciatica probably results in large variations in the frequency of low back surgery between countries[46]. Recently extensive data became available from a randomized trial comparing early surgery with prolonged conservative care and possibly delayed surgery for patients with severe sciatica[129]. While substantially fewer operations were performed during a strategy of prolonged conservative care, early surgery resulted in faster recovery from leg pain but failed to yield higher recovery rates at one year . The 2-year follow-up results of this trial are presented here.

MATERIAL AND METHODS

We conducted a multicenter prospective randomized trial among patients with 6 to 12 weeks of severe sciatica to determine whether a strategy of early surgery leads to better outcomes during the first year compared to a strategy of conservative treatment for an additional 6 months and performing delayed surgery for patients with persisting pain. The medical ethics committee at each of 9 participating hospitals approved the protocol. Written informed consent was obtained from all patients. Details of the design and study protocol have been published previously[118]. The current study evaluates the 2-year follow-up data on these patients and focuses on differences between the long terms results of the two strategies.

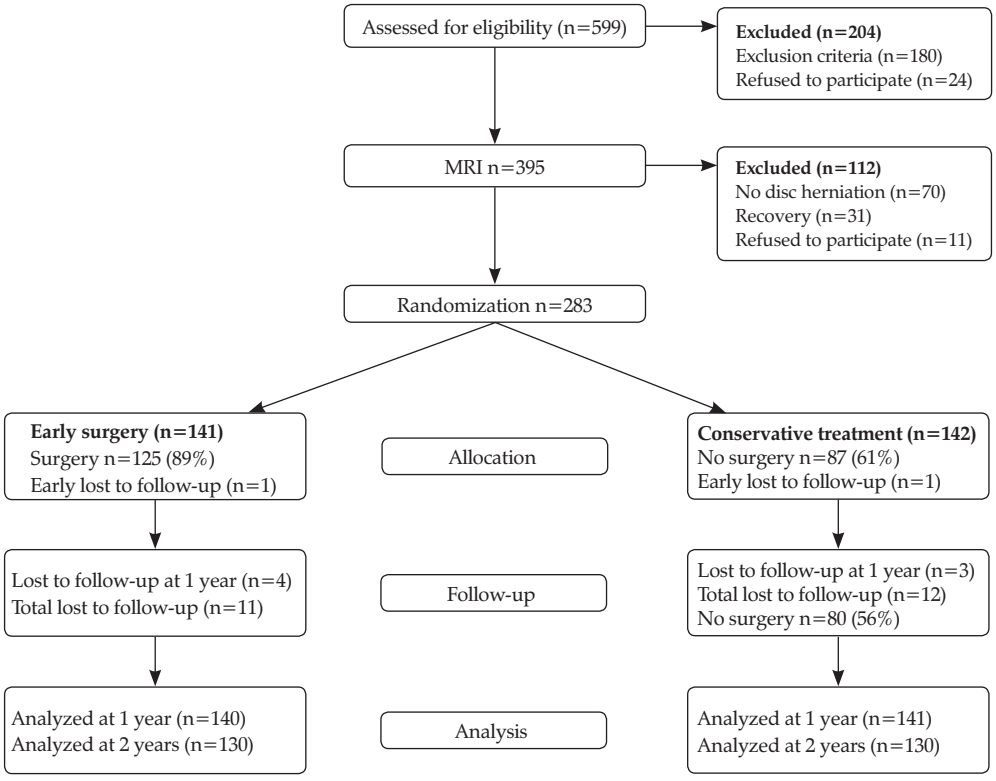


*Figure 1. Flow-diagram for 2 years of follow-up **

** Data of patients lost to follow-up were carried forward for 2 year analysis. No difference was registered between Mantel Haenszel analyses with or without these patients.*

Eligibility and Randomization

Eligible patients were between 18-65 years of age, had been diagnosed with an incapacitating LSRS by an attending neurologist and had a radiologically confirmed disk herniation. Patients presenting with a cauda-equina syndrome or severe paresis (MRC<3) were excluded as well as those with identical complaints in the past twelve months, or a history of spinal surgery, spinal stenosis, deformity or severe comorbidity.

A computer-generated permuted-block scheme was used for randomization, stratified according to center (n=9). One hour before randomization patients were again evaluated by independent research nurses. If at that moment, eligibility criteria were no longer met due to recovery, patients were as yet excluded. Otherwise successive numbered opaque envelopes containing the assigned strategy were opened.

Beforehand patients were notified that they were participating in a study comparing 2 different strategies for timing-of-intervention strategies rather than comparing surgery with non-surgical treatment. Obviously patients could not be blinded to the assigned treatment arm.

Treatment

Early surgery was preferably scheduled within 2 weeks of assignment and only cancelled if spontaneous recovery occurred before the date of surgery. The disk herniation was removed through an unilateral transflaval approach using magnification. Occasionally, at the discretion of the surgeon, a bilateral exploration was performed . After annular fenestration and decompression of the nerve root the risk of recurrent disk herniation was reduced by removal of loose degenerated disk material out of the disk space using curette and rongeur, without striving for a subtotal diskectomy. The duration of the hospital stay depended on the patient's functional ability to mobilize. At home the rehabilitation process was supervised by the physiotherapist. Depending on the nature of their work patients were advised to resume their regular jobs after 6 weeks onwards.

Prolonged conservative management was provided by the family practitioner. Ample information was supplied about the favorable prognosis. Treatment encompassed the prescription of effective painkillers according to prevailing guidelines and the advice to resume daily activities if feasible. A mobilisation scheme, based on time rather than pain, was recommended without checking the compliance. If considerable fear of movement was present, guidance of a physiotherapist was recommended. If sciatica persisted 6 months after randomization microdiskectomy was considered. Increasing leg pain not responsive to medications and progressive neurological deficit were indications to perform surgery earlier, within 6 months.

Outcomes

Primary outcomes were measured by means of the Roland Disability Questionnaire for Sciatica (RDQ)[114], 100 mm visual analogue scale for leg pain (VAS-leg)[109] and a 7-point Likert self-rating scale of global perceived recovery. The questionnaires were assessed at 2, 4, 8, 12, 26, 38, 52, 78 and 104 weeks.

Secondary outcomes, such as a repeated neurological examination, VAS back pain, functional-economic observational assessments (PROLO[104] by the independent Research Nurse, as well as Quality of Life scales[107]were filled out at monitoring visits scheduled at 8, 26, 52, 78 and 104 weeks. Research Nurses observed their own patients at the planned follow-up moments and were aware of the patient's treatment assignment.

Table 1 Baseline and Follow-up Characteristics of Patients with Sciatica*

Table 1 Patient Characteristics	Early Surgery (N=141)	Conservative (N=142)
Age (yr)	41.7 ± 9,9	43.4 ± 9,6
Male sex —no (%)	89 (63)	97 (68)
Quetelet-index†	25.9 ± 4.1	25.8 ± 4.0
Duration of sciatica in weeks	9.43 ± 2.37	9.48 ± 2.11
Took sick leave from work, no (%)	107 (76)	116 (82)
Duration sick leave in weeks	5.32 ± 2.78	5.28 ± 2.62
Radiating pain left leg-no (%)	67 (48)	73 (51)
Positive straight leg-raising test % ‡	100 (71)	104 (73)
Positive crossed straight leg-raising test % ‡	71 (50)	70 (49)
Sensory loss, no (%)	123 (87)	128 (90)
Dermatome anaesthesia, no (%)	31 (22)	33 (23)
Muscle weakness, no (%)	93 (66)	99 (70)
Knee tendon reflex difference, no (%)	54 (38)	51 (36)
Ankle tendon reflex difference, no (%)	75 (53)	107 (75)
Clinically suspected level herniated disk		
Clinically suspected disk level L3-L4 no (%)	6 (4)	5 (4)
Clinically suspected disk level L4-L5 no (%)	69 (49)	57 (40)
Clinically suspected disk level L5-S1 no (%)	66 (47)	83 (58)
Preference conservative treatment-no (%)	42 (30)	43 (30)
Surgical Treatment during follow-up	**Early Surgery**	**Conservative**
Surgery actually performed in first year (%)	125 (89)	55 (39)
Surgeries during 2 years (%)	125 (89)	62 (44)
Mean time to surgery in weeks (CI)	2.2 (1.9-2.5)	18.7 (14.3-23.0)
Median time in weeks (Interquartile Range)	1.9 (1.1-2.4)	14.6 (6.4-26.0)
Recurrent disk surgery (%)	7 (6)	4 (6)
Roland Disabilty Questionnaire Score §	16.5 ± 4.4	16.3 ± 3.9
Score on visual analogue scale ¶		
VAS leg pain	67.2 ± 27.7	64.4 ± 21.2
VAS back pain	33.8 ± 29.6	30.8 ±27.7
Short Form-36 Scores ‖		
SF-36 bodily pain	21.9 ± 16.6	23.9± 18.1
SF-36 physical functioning	33.9 ± 19.6	34.6 ± 19.0

* Plus-minus value are means ± SD. There were no significant differences among the two groups on any of the baseline characteristics.

† Quetelet-Index or Body-Mass Index is calculated by dividing the weight in kilograms by the squared length in meters. Higher scores define overweight.

‡ Lasègue's sign was defined positive if the examiner observed a typically dermatomal area of pain reproduction and pelvic muscle resistance during unilateral provocative straight leg raising below an angle of 60 degrees, and crossed positive if the same experience was noted raising the other leg below 90 degrees.

§ The Roland Disability Questionnaire for Sciatica is a disease specific disability scale that measures functional status in patients with pain in the leg or back. Scores range from 0 to 23, with higher scores indicating worse functional status.

¶ The intensity of pain was indicated on a horizontal 100 mm visual analogue scale, with 0 representing no pain and 100 the worst pain ever experienced.

‖ SF-36 is the abbreviation of Medical Outcomes Study 36-Item Short Form Health Survey (Range 0-100) and is a generic health status questionnaire consisting of 36 items on physical and social functioning delineating 8 domains of quality. Higher score indicates less severe symptoms.

Statistical analysis

The aim of this study was to estimate the difference between the two treatments in disease-specific disability of daily functioning measured with the RDQ. Assuming a mean standard deviation of 10 points[81] over the first year 140 patients were calculated to be required per treatment arm to provide a statistical power of 0.90 with a two-tailed significance level of 0.05 to detect at least three points difference in the RDQ.

Recovery corresponded to "satisfactory outcome" and was defined as complete or nearly complete disappearance of complaints measured by a 7-point Likert scale. The other scores corresponded to "unsatisfactory outcome". The ratio of the respective speeds of recovery was estimated using a Cox Proportional Hazard model, presented as Hazard Ratio with corresponding 95 percent confidence interval. Differences between groups in the Likert-score at two years were evaluated by Fisher's Exact Tests.

Data collection and quality checks were performed with the ProMISe web-based secure data management system of the Department of Medical Statistics & BioInformatics of the LUMC. For all statistical analyses SPSS 14.0 was used[120]. Differences between groups at baseline and after 2 years of follow-up were assessed by comparing means, medians or percentages, depending on the type of variable. Baseline values of variables were used as covariates in the main analyses whenever appropriate to adjust for possible differences between the randomized groups and to increase the power of the analyses. Outcomes of function and pain were analyzed using a repeated measurements analysis of variance with a first order autoregressive covariance matrix. Estimated consecutive scores were expressed as means and 95 % confidence intervals. Point-wise estimates were obtained using models with time as a categorical covariate to allow assessment of systematic patterns. Differences between randomization groups were assessed by estimating either the main effect of the treatment or the interaction between treatment and time. As a second approach to quantification of the differences between the two groups over total follow-up time, "area under the curve" quantities (AUC) were calculated between randomization and week 104 and subsequently compared using Student t-tests. All analyses were performed according to intent-to-treat.

RESULTS

Between November 2002 and February 2005, 599 patients had a surgical indication for treatment of their sciatica according to their family practitioner (Figure 1). After initial consultation with the neurologist, 395 patients met all inclusion criteria and

Table 2. Primary and Secondary Outcomes based on Intent-to-Treat Repeated Measurements Analysis *

	8 weeks			26 weeks		
Primary Outcomes	**Surgery**	**Conservative**	**Treatment effect (95% CI)**	**Surgery**	**Conservative**	**Treatment effect (95% CI)**
Roland Disabilty	6.1 (0.5)	9.2 (0.5)	**3.1 (1.7 to 4.3)**	3.3 (0.5)	3.7 (0.5)	**0.4 (-0.9 to 1.7)**
VAS-Legpain	10.2 (1.9)	27.9 (1.9)	**17.7 (12.3 to 23.1)**	11.0 (1.9)	11.0 (1.9)	**0 (-4.0 to 4.0)**
VAS-Backpain	14.4 (2.1)	25.7 (2.1)	**11.3 (5.6 to 17.4)**	14.2 (2.2)	16.5 (2.1)	**2.3 (-3.6 to 8.2)**
SF-36 bodily pain	62.8 (2.1)	54.4 (2.0)	**-8.4 (-13.5 to -3.2)**	81.2 (2.0)	78.5 (1.9)	**-2.7 (-7.9 to 2.6)**
SF-36 physical functioning	71.2 (1.7)	61.9 (1.9)	**-9.3 (-14.2 to -4.4)**	84.2 (1.8)	82.0 (1.9)	**-2.2 (-7.2 to 2.8)**
Recovered † Patients (%)	36.5	81.2	**44.7**	70.8	77.4	**6.6**

* Results are described by their mean (SE)
† Likert global perceived recovery is defined by a 7-point scale "Worse" to "Complete" recovery. Recovery is

were examined by MRI. At the second visit 283 patients continued to suffer from sciatica and the disk herniation had been visualized; they were allocated to one of two treatment strategies. No significant differences in baseline characteristics between patients were noted for the two study groups (Table 1). Twenty-three patients (8 %) were lost to follow-up. Of 141 patients assigned to receive early surgical treatment, 16 patients recovered before surgery was actually performed. Median time to early surgery for the remaining 125 patients was 1.9 weeks (Table 1) after randomization. Of the 142 patients assigned to the conservative treatment group 55 underwent surgery during the first year (Table 2) after a median period of 14.6 weeks, because of intractable pain expressed by a mean 54 mm VAS-leg score and RDQ of 15.0, measured shortly before deciding to surgery. During the second year after randomization another 7 patients received delayed surgical care because of persistent or intermittent pain, resulting in 62 surgically treated patients in the conservative treatment arm. In both groups 6 percent of operated patients suffered recurrent sciatica leading to a second surgical intervention during the 2 years of follow-up. Complications occurred in 1.6 percent of all surgical patients, involving 2 dural tears and 1 wound haematoma. All complications disappeared spontaneously. None of the patients developed neurological deficit as a result of surgery.

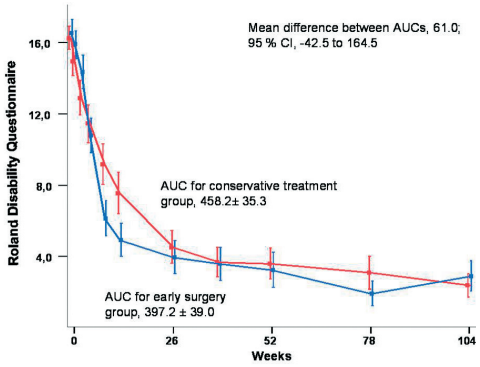
Table 2. Continued

	52 weeks			104 weeks		
Primary Outcomes	**Surgery**	**Conservative**	**Treatment effect (95% CI)**	**Surgery**	**Conservative**	**Treatment effect (95% CI)**
Roland Disabilty	4.0 (0.5)	4.8 (0.5)	**0.8 (-0.5 to 2.1)**	3.1 (0.5)	2.6 (0.5)	**0.5 (-0.8 to 1.8)**
VAS-Legpain	8.4 (1.9)	14.5 (1.9)	**6.1 (2.2 to 10.0)**	11.0 (1.9)	9.0 (1.9)	**-2 (-6.0 to 2.0)**
	15.5 (2.2)	17.8 (2.1)	**2.3 (-3.6 to 8.2)**	15.9 (2.2)	17.3 (2.1)	**1.4 (-4.5 to 6.3)**
SF-36 bodily pain	76.1 (1.1)	72.8 (1.9)	**-3.3 (-8.4 to 1.8)**	78.4 (1.9)	80.7 (1.8)	**2.3 (-2.7 to 7.3**
SF-36 physical functioning	79.1 (1.9)	77.6 (1.7)	**-1.5 (-6.4 to 3.4)**	82.3 (1.9)	83.6 (1.8)	**1.3 (-3.7 to 6.3)**
Recovered † Patients (%)	82.5	85.7	**3.2**	81.3	78.9	**2.4**

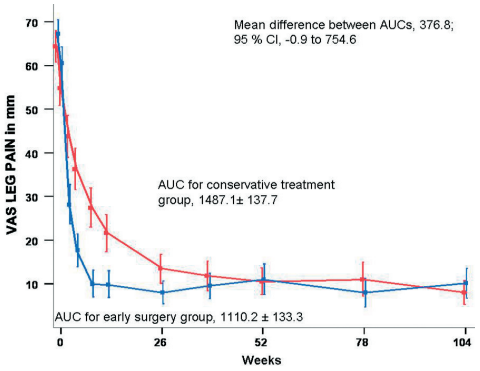
defined as complete or nearly complete recovery using the Likert 7-point scale. Proportions recovered patients between groups at 2 years was not different (p=0.66)

The speed of recovery was statistically different between the groups (Cox model, p<0.001) resulting in an unadjusted hazard ratio of 1.97 (95 % CI 1.72-2.22): recovery was nearly twice as fast for early surgery[129]. Ultimately 95 % of patients of both groups experienced satisfactory recovery by the end of the first year of follow-up. It thus appeared that a slower rate of recovery did not result in a difference in outcome at one year and this lack of a difference between groups was maintained for up to two years. Some patients, however, experienced recurrent low back related complaints after the first year, which resulted in 81.3 % satisfactory results at 2 years for the early surgery group and 78.9 % for the prolonged conservative care group (p=0.66) (Table 2).

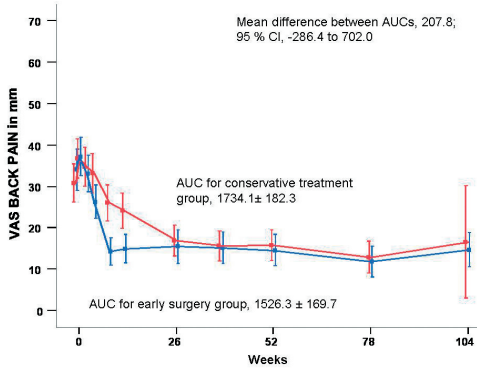
Repeated measurement analysis of continuous outcomes resulted in different courses over time for disability and pain (Table 2; Figure 2). A separation of mean scores exists in favor of early surgery during the first half year after randomization, followed by converging scores. Areas under the curves (AUC) were significantly different over 2 years for VAS leg pain (p=0.05) but without an overall significant difference between AUC's for the RDQ (p=0.25) and VAS back pain (p=0.41). Between 12 and 104 weeks no statistically significant differences were found between randomized groups for any of the primary outcomes at the consecutive fixed follow-up moments.



Panel A



Panel B



Panel C

Figure 2. Repeated Measurement Analysis Curves of Mean scores for Roland Disabilty Questionnaire (Panel A), Leg Pain (Panel B) and Back Pain (Panel C) on a Visual-Analogue Scale.
All three panels show the 2-year curves with 95 percent confidence intervals represented by vertical bars at consecutive moments of measurement. Red lines represent the conservative treatment group, while the blue lines represent early surgery.
Panel A** represents the mean disability scores at consecutive moments of measurement. Although the curves differ, and the short term mean results at 8 and 12 weeks show significantly non-overlapping confidence intervals the overall difference between the areas under the curves (AUC) over 12 months is not significant **(p=0.25).
***Panel B** represents mean visual analogue scores for intensity of leg pain in mm, showing an early effect for leg pain in favour of the surgical group from 2 to 26 weeks, but with near equal scores at one year. The difference between the mean AUC's is significantly different **(p<0.05)**.*
Panel C** represents mean visual analogue scores for intensity of low back pain in mm. Starting with a lower intensity score when compared to leg pain, the mean AUC's exhibit a less strong and not significant difference **(p=0.41)
** Area's under the curve are expressed by their means ± SE, while the mean difference is expressed by the corresponding 95 percent confidence interval*

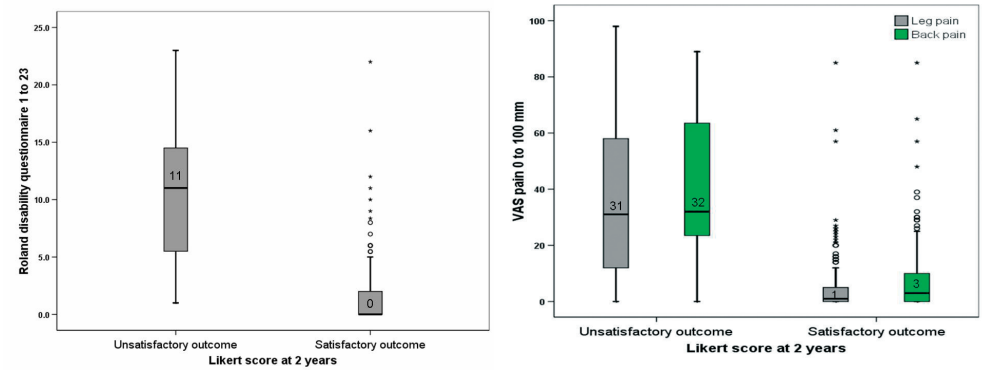
Irrespective of assigned treatment those 56 patients (20 %), who had unsatisfactory results according to the global perceived recovery score at two years, had statistically different RDQ, VAS leg pain, and VAS back pain scores (Table 3) as compared to those with a satisfactory outcome (Mann-Whitney; $p<0.001$). Since these outcome scores had skewed distributions and large standard deviations, box-plots visualizing median, percentiles and outliers are presented instead of 95 % confidence intervals (Figure 3).

DISCUSSION

Although early surgery compared to prolonged conservative care resulted in twice as fast recovery from severe sciatica after a period of six to twelve weeks, one and two year outcome scores for both groups were rather similar. The major advantage of early surgery for patients is rapid relief of leg pain, reassurance of recovery and earlier return to normal activities including work. While a strategy of delayed surgery may cause some additional weeks of suffering, up to 56 % of patients obviated surgery. Remarkably, early surgery did not decrease the risk of an unsatisfactory outcome at 1 or 2 years. Although the risk is relatively low, still 20 % of the patients suffered from recurrent or chronic pain and disability after 1 and 2 years of follow-up. Since 8 % of patients were lost to follow-up for various reasons the study lost some power. Analyses without or including last scores carried forward provided similar results. Furthermore baseline characteristics among drop-outs were comparable to all those providing the 2 year follow-up data. Nevertheless, it remains possible that selective lost-to-follow-up has occurred.

Patients randomized to conservative care were guided by research nurses who supported patients with information and counselling. It is obviously impossible to blind patients and practical limitations prevented the randomization result to be concealed from the independent research nurses. Although this additional support did not prevent the operations of 39 % of patients during the first year it does not reflect usual care. However, this guidance by research nurses has occurred in all cases and therefore may have affected the results in both groups. Obviously research nurses are not present in usual care situations hampering implementation of a strategy of delayed surgery. However, their counselling function may be performed by the recent introduction of nurse-practitioners or physician-assistants, who are quite able to support patients with information and guidance.

The finding that ultimately prolonged conservative care results in outcomes similar to those of early surgery is not new and had already been reported by Weber in 1983[40]. In the latter study, however, patients with severe sciatica were excluded.



Panel A *Panel B*

*Figure 3. Boxplots; primary outcome scores according to perceived recovery at 12 months * †*
** These scores are defined as outliers*
† Medians are presented in interquartile boxes. Mann-Whitney statistics p<0.001

Table 3. Primary outcome scores according to dichotomized perceived recovery at 2 years *

Outcome †	RDQ	VAS leg pain	VAS back pain
Unsatisfactory recovery ‡ (n=56/20 %)	10.8 (5.6)	35.5 (27.0)	**53.3 (106.2)**
Satisfactory recovery ‡ (n=225/80%)	1.5 (2.8)	5.1 (10.3)	**7.4 (11.5)**
Total (n=281)	**3.4 (5.2)**	**11.1 (19.3)**	**16.8 (52.2)**

* Scores of primary outcomes are described by their mean (SD)
† Mann-Whitney nonparametric two-sided test for all three outcome differences between groups (p<0.001)
‡ The 7-point Likert scale was dichotomized. Complete and nearly complete recovery represent "satisfactory" outcome, while the other 5 scores ranging from some recovery to severe worsening of complaints were "unsatisfactory".

Since this landmark randomized trial showed outcome scores to converge after only 4 years, patients with severe sciatica were not easy to convince that postponement of surgery might be effective in the short term for at least some of them and would not be harmful. After the Weber study several high quality observational cohort series presented significantly worse results after prolonged conservative care as compared to surgery. Two studies[163;184] found a threshold of two months of sciatica, after which the risk of an unsatisfactory outcome increases. The present study presents more insight into this topic. Since these otherwise nicely performed studies were not based on randomized cohorts, baseline factors of patients may not be completely comparable and therefore interpretation of the results is hazardous. It may be concluded

that advising early surgery to all patients with the goal to minimize the chance of long-term disability is not justified. Nygaard[185] as well as Ng[186] pointed out in comparable observational studies that delayed surgery after 8 and 12 months of sciatica respectively produced worse results compared to timing of surgery before these limits. These studies do not per se contradict the present trial, but our data do not support their conclusions either. Indeed it is difficult to keep patients with persistent sciatica on a conservative treatment plan for longer than 8-12 months. However, the substructure of a strategy of surgery before 8 months should be base on a randomized controlled trial considering different time windows of complaints. The trend in the studies by Weinstein[49], Osterman[66] and Butterman[126], however, does not point to an unsatisfactory outcome of prolonged conservative care. Because these trials as well as the present study had a randomized design we conclude that early surgery in patients, with 6-12 weeks sciatica, does not lead to markedly improved functioning over the first year. The therapeutic role of surgery is restricted to faster recovery and relief of leg pain, which, however, may yield a valuable gain for a large proportion of patients in Western society, who are not able or willing to await the natural course with possibly delayed surgery. A second conclusion is that prolonged conservative care does not result in an increase in unsatisfactory outcomes at 2 years and disk operations may be reduced by at least 50 % with similar outcomes after 1-2 years of follow-up.

Notwithstanding similar long-term treatment effects presented by four roughly comparable randomized controlled trials, our data unequivocally show that prolonged conservative care with possibly delayed surgery resulted in a significantly slower rate of recovery. If the purpose is to gain fast pain relief, early surgery remains a valuable treatment option for well-informed patients after at least 6 weeks of sciatica.

10

SYNTHESIS & GENERAL DISCUSSION

"The art of medicine consists of comforting the patient for a few months while nature cures the sciatica. "
(Adaptation of Voltaire)

The majority of patients with sciatica recover in 2-3 months. After this period general practitioners refer patients with persistent leg pain to the neurologist or rheumatologist. A considerable proportion of these patients however are not diagnosed with a radicular syndrome or, if diagnosed, do not have a lumbar disk herniation. The exact course of natural recovery from sciatica over the first year is not known.

Several conclusions can be drawn from the randomized controlled trial, presented in this thesis. Undoubtedly early surgery for sciatica more quickly relieved the excruciating leg pain compared to the prolonged 'wait and see' strategy. The positive effect of early surgery on the speed of recovery was present for all subgroups except for patients without 'leg-pain provoked by sitting'. After one and two years the results of early surgery and prolonged 'wait and see' were not different. Female gender was a strong predictor of unsatisfactory outcome, but this finding resulted from post-hoc analysis and therefore affirmation of this finding and its possible implications on an individual and societal level needs future studies.

Timing of surgery was based on today's guidelines. Although not specifically designed for this purpose, one may question to what degree this thesis produces scientific support for the current guideline strategy for the timing of disk surgery. One unequivocal answer is hard to give.

This thesis assesses the efficacy of different timing strategies for surgical treatment of sciatica, caused by a lumbar disk herniation. In the first part of this chapter the implications of the results for patients with 6 to 12 weeks of persistent sciatica are discussed. Is this the appropriate time frame to consider disk surgery? Or is it better to await a finally favorable natural course?

By reviewing the literature (Chapter 2) and conducting a randomized controlled trial (RCT) we now have more knowledge about the results of the current guideline regarding efficient timing of surgery. Did we find the optimal period for 'wait-and-see' before surgery?

In the second part of this chapter new steps to optimize the treatment strategy for sciatica are discussed: comparison in an international context and implementation of a new strategy for timing of surgery based on patient preferences.

The optimal timing of surgery

Although the execution of the classical guideline recommending early surgery after 6 weeks of sciatica resulted in quicker relief of leg pain and gave a feeling of complete recovery sooner, it did not result in a higher proportion of recovery at 1-year follow-up compared to prolonged conservative care[129]. Furthermore our RCT (Chapter 4)

could not detect an overall difference in functional disability at 1 year between those receiving early surgery after a short period of sciatica on the one hand and those who had the intention to delay the execution of surgery on the other. A strong argument for the majority of patients to consider 'early' surgery was the fear of the sciatic pain to become chronic. This fear appears not to be justified, since our search to factors predictive of unsatisfactory outcome (Chapter 8) and the 2-year follow-up analysis (Chapter 9) did not show differences in chronic pain between the two strategies.

Probably surgery after 6 to 12 weeks of sciatica is optimal for those with sciatica provoked by sitting (Chapter 6) and for those with intense pain and high disease-specific disability scores, the baseline values of which predicted a higher probability on late surgery in the conservative treatment cohort (Chapter 7). However, since these results were derived from subgroup analyses these findings have to be addressed carefully. From a societal point of view surgery can be considered to be cost-effective over the first year, when a threshold of $ 50,000 per Quality Adjusted Life Year (QALY) is acceptable and definitely is cost-effective when $ 100,000 is deemed acceptable (Chapter 5). Although significantly different, the overall one-year difference in QALY's was quite low between groups, and early surgery did not yield a more favorable long-term effect on direct and indirect costs compared to prolonged conservative care. Early surgery did not result in the expected benefit in indirect costs.

Early surgery may be preferred by individuals who outweigh the gain of quick recovery against the favorable natural course, which in fact includes a substantial chance of late surgery. Sufficiently informed patients are now able to choose, and based on the new knowledge physicians and certainly society should not 'decide' for them [161].

WAS THE STUDY APPROPRIATELY DESIGNED TO DEFINE THE OPTIMAL WAITING PERIOD BEFORE SURGERY?

We conducted this trial to evaluate the effectiveness of the current guideline recommendation. The major arguments were the varying rates of low back surgery in Western society, with a relatively high one in The Netherlands and combined with doubt regarding the evidence underlying the internationally well accepted 6-week threshold, before surgery is considered. Since previous comparative studies[163;186;187] promoting early surgery had a non-randomized design and the landmark randomized study by Weber[40], advocating prolonged conservative care, did not include patients with severe sciatica, there was a scientific need to study a more representative

population. Since the main advantage of surgery compared to prolonged conservative care was expected to be the gain in time to recovery and prevention of chronic disability, power and design of the study were focused on short-term results of the current guideline and not on a comparison between surgery and non-surgical treatment per se. To evaluate the effect of surgical timing on chronic disability a longer follow-up period is necessary.

In some observational cohort studies delayed surgery after 8 weeks resulted in less favorable outcomes compared to surgery before this period[163;184]. Other studies with a comparable design but another time frame provided data that this threshold might be 8 or 12 months of persistent sciatica after which period the risk of an unfavourable outcome rises significantly[186;187]. Our trial results are not in conflict with the latter conclusions, but do reject the former. Surgical treatment of every patient with 6 weeks of persistent sciatica, with the goal to prevent unfavorable outcome or chronic pain, will result in an unacceptable high rate of interventions for a disease with a favorable natural course. Since our trial does not have the disadvantage of incomparable baseline groups of these observational studies, our results are of a higher level of evidence and support the conclusion that the optimal period of "wait-and-see" can be defined as longer than this attractively clear-cut 6 to 8 weeks period.

For defining the optimal period of 'wait and see' before surgery another study design has to be considered. In order to estimate the specific effects of surgery, theoretically sham surgery for the control group would definitely give the final answer. Obviously execution of such a trial is hampered by ethical objections. In addition only patients with moderate complaints might opt to be included in such a trial, leading to selection bias and a non-representative study population.

On the basis of our study we cannot answer the question: is the optimal period of waiting for surgery 6 weeks or should it be longer? Arguments are lacking to reject the current Dutch guideline recommendation about the timing of surgery. The data of our study, however, do support an "informed" decision strategy for patients and physicians to individually outweigh the advantages and disadvantages of both timing-of-surgery choices. In patients with severe sciatica one would expect individual preferences to present influence on surgical decision making and outcomes, like has been established in other diseases and low back related disorders. With regard to the short-term speed of recovery or 1-year outcomes this trial did not reveal any predictive or interaction effects between personal preferences on the one hand and the randomized treatment strategy on the other. Most patients accrued for participation in this study, however, wanted very urgently to undergo surgery. Patients, who preferred non surgical treatment were not included or hypothetically did not visit the general practitioners or neurologists at all. This variable selection bias inevitably influenced the results of both subgroup analyses of this study. Since ample evidence

presents for the high impact of preferences on surgical strategies and outcome we advise to reject our conflicting finding and to develop shared informed patient decision programs which incorporates individual preferences[168].

RESTRICTIONS IN PERFORMANCE

Although the over-all results of our study are unequivocal, some points of attention need to be highlighted and which may have some implications for future research and the daily care of sciatica patients.

- Since patients were referred by family physicians to neurologists, the eligibility criteria were checked. In order to exactly define how many patients were excluded, all patients should have been registered and reasons for exclusion given by the neurologist. However, compliance to this procedure was not optimal despite repeated requests from the research team. Although the baseline data of our sample of patients does represent severe sciatica, patients might have been excluded selectively.
- Research nurses guided the trial patients included in the randomized trial. Although this affected both randomized groups in the same direction, one might object that the conservative treatment group received more attention, which is not the case in usual care. We do not know what the effect size of this extra attention might be. To reassure future patients about the favorable natural course, attention should be given to sufficient counselling and education.
- Surgery was performed by the conventional microdiskectomy approach, with partial removal of degenerated disk material. Recent data show conflicting evidence regarding minimal conservative removal of the sequestrated protrusion only[123;188]. This might have affected the post-operative course in an unfavorable direction. We intentionally chose for this conventional approach because it involved usual care, and maintains to be the golden standard[64]. So far, microdiskectomy as an effective treatment method has not yet been overshadowed by other approaches.
- Generally it was advised to resume work 6 to 8 weeks postoperatively. As this was regular post surgical care during the execution of the trial, this might have resulted in a relatively small contrast in working disability between the two groups. Thus in favor of the conservative treatment arm during cost-effectiveness analysis since these patients started working again despite their pain (Chapter 5). In contrast during recent years the period of rehabilitation after surgery has been reduced to 2 weeks in most primary care settings.
- Some patients, assigned to the conservative treatment group, received conflicting information, regarding the 'necessity' for surgery, and this might have caused

them to request for surgery sooner. This could have been prevented by better cooperation with physiotherapists and primary care physicians. Hypothetically this may have resulted in a larger proportion of patients who underwent surgery in the conservative treatment arm than reasonably would have been the case if the protocol had been followed strictly.

Variations in outcome definitions

These are perhaps the most important points of concern

- When designing the study, early surgery was deemed to be superior if the Roland disability questionnaire resulted in at least an 3-point average difference during all follow-up moments during the first year[81;114]. Furthermore a perceived recovery difference of more than 20 % at one year would strongly support an early surgery strategy. Both null hypotheses were not rejected and despite this evidence in favor of prolonged conservative care, most reviewers and readers highlighted the difference in quicker recovery rates in favor of early surgery.
- Another hypothesis was time until complete recovery. However, the actual measurement of complete recovery was performed at pre-scheduled visits leading to interval censoring. Indeed it would have been more appropriate, if registration of recovery had been done at the actual (though difficult to observe) moment of perceived recovery. Again, this affected both groups, but hypothetically the prolonged conservative care group had a disadvantage because meetings with research nurses were scheduled at longer intervals in time after 3 months of follow-up, and delayed recovery might have occurred during these intervals.
- Furthermore the methodology of survival analysis does not take into account recurrent sciatica or other low back related complaints. After perceived recovery patients are excluded from analysis and if recurrence of complaints is experienced these patients cannot be re-enrolled. This is a major drawback of pragmatic studies investigating the effectiveness of treatments for disorders which might recur after recovery. For example in both randomization arms 95 % of perceived recovery was registered during the first year according to survival analysis, but at exactly 1 year and 2 years of follow-up 87 % and 80 % of all patients, respectively, reported that they had recovered. Some individuals reported complete recovery but later these same individuals, apparently suffering recurrent symptoms of leg or back pain, experienced no improvement or even deterioration compared to the pre-randomization status. To solve this problem, it may be necessary to redefine “recovery” by absence of symptoms for at least a well demarcated period of time. Unfortunately there are no simple statistical solutions to this problem that

affects not only spinal pathology, but rheumatologic and neurological disorders as well; however the theory of multi state models, currently becoming "popular" as an extension of survival analysis, for example in the framework of bone marrow transplants, may offer a perspective here too. In these (complex) models, the patient may enter a state of "recovery" but then leave that state again and return to it later; the transitions between various states describe the process of falling ill and recovery. It is worthwhile to investigate the application of multi state models in the context of the before mentioned disorders.

Despite these methodological drawbacks "The Sciatica Trial" irrefutably showed that the major advantage of early surgery for patients after 6 to 12 weeks of sciatica is quick recovery of leg pain and quality of life but the outcomes at one year are nearly equivalent to a strategy of prolonged conservative care with delayed surgery.

DOES OPTIMAL SURGICAL TIMING EXIST?

We designed this RCT (Chapter 3) to evaluate the current recommendation to carry out surgery early, i.e. after 6 weeks of sciatica. Previous reports showed a high incidence of low back surgery in the United States and The Netherlands[46]. Since medical opinions from other Western countries do not differ as to in the recommendations to consider surgery after an initial period of 6 weeks of persistent sciatica, it can be assumed that incidences reported in Cherkin's study apparently underreport the surgical prevalence from neighbouring European countries.

A recently published randomized trial by Weinstein et al. comparing surgery with non surgical treatment per se[48;49], included patients with highly variable duration of complaints. Their trial results support a rather conservative approach. A surgical strategy did not lead to significant differences compared to conservative care in the intent-to-treat analysis. In contrast to the main study, their observational cohort study did present some short term advantages of surgery over conservative care. Obviously this finding carries a lower level of evidence than their randomized controlled trial in which they could not reveal any short term superiority of surgery. As in our trial there was considerable cross-over from the conservative treatment arm to the surgical one. In the early surgical treatment arm of "The Sciatica Trial" this intervention was planned prompt after randomization, leading to a mean time of less than 12 weeks of complaints before surgery was executed. The timing of surgery in the Weinstein study, however, was left to the participating hospitals and patients, which resulted in varying periods in time during the first year before surgery was

executed. A substantial part of the patients did not undergo surgery at all, while they were assigned to this intervention. This lack of contrast between treatment groups might have resulted in the absence of differences. Besides the seemingly at random scheduling of surgery after allocation of treatment, patients were amply informed about both strategies by a video which might have changed the preferences of patients and caused them to be reluctant to undergo surgery. Moreover, the choice for primary outcomes of the SPORT study differed from our trial. While relief of pain and speed of global perceived recovery are of primary concern to patients and both issues are quite susceptible to treatment, the SPORT study designers decided to evaluate general perceived quality of life, measured by the Short-Form 36. Furthermore a substantial proportion of their patients had baseline sciatica for at least 6 months, resulting in quite variable duration of complaints as compared to our trial, which, because of the primary objective to evaluate early timing of surgery, only included patients with complaints for less than 12 weeks. In conclusion the apparently similar designs of both trials did have different objectives, analysis methods and patient populations and thus resulted in a more demarcated early treatment effect in "The Sciatica Trial". But the long term results of their trial[49], the Weber trial[40], the smaller Ostermann's study[66]and the present study provide no evidence in favor of surgery at 2 year follow-up. Apart from an early gain in recovery in Ostermann's and our study surgery did not prevent an unsatisfactory outcome better than the control group. This conclusion raises doubts about the role of surgery in the seemingly unaffected natural course of sciatica. One may concur that a RCT is needed to compare microdiskectomy with placebo or sham surgery. At least all these arguments raise doubt on the very existence of an optimal timing for surgery in the disease course applicable to all sufferers from it.

In addition the question arises whether the study offers data supporting an individualized optimal timing of surgery. Our trial protocol (Chapter 3) chose surgery delayed until 6 months after randomization for the conservative treatment arm. Since baseline complaints lasted on average 9 weeks (2 months) this period of 8 months of conservative care was expected. Despite strenuous efforts of patients, research team and physicians, most of the 55 surgical patients of the conservative arm were operated on well before this period resulting in a mean of 27 weeks of sciatica complaints before surgery was performed in the prolonged conservative care group. Therefore our trial results do not contradict the observational study of Nygaard[187], who described worse results for patients with at least 8 months of complaints compared with those experiencing shorter durations of sciatica before surgery was executed. Furthermore in view of the observed difficulties of conservative treatment for this very painful group it might be a hard job to perform a future

randomized trial in this group. However, we cannot state in general that the optimal period is 8 months.

For example, high leg pain intensity and the inability to sit and a confirmed disk herniation, might be good arguments for an individual patient to time surgery early which preference should not be disregarded because of the opinion of treating physicians. On the basis of patient preferences and good information about the alternative natural course combined with registered pain and disability scores (Chapter 7), we can at present conclude that the optimal timing of surgery is an individual question, which cannot be generalized to cover all primary or secondary care patients.

Current status and future research

Implementation of a shared health decision program for sciatica is necessary to improve health care for this specific group of low back disorder patients. Surgery is a safe and cost-effective method to conquer sciatic pain quickly. Most neurological and radiological signs do not predict the course of sciatica. Since pain and disability scores reflect the individual situation, exhibit a predictive value for surgery and can be used to monitor the patient with sciatica, there is a need for implementation of these scores in daily care to improve the quality of treatment. The occurrence of chronic disabling disease after a period of sciatica needs further study. At least early surgery does not prevent its development. More elaborate survival models are designed to evaluate recurrence of disease complaints (Chapter 10). For the purpose of future intervention prognostic spine studies these sophisticated but complex epidemiological calculations will be executed in close cooperation with the Department of Medical Statistics. The baseline data of the present study will be analysed using these multi-state models with the goal to predict unsatisfactory outcome at 2 and 5 years. Finally, in our quest to evaluate invasive treatments for spine disorders by comparative cost-effectiveness studies we have to search for novel more rigorous research methods to be better able to answer clinically important research questions.

Conclusion

The results of this thesis do not contradict, nor do they support the current strategy of early disk surgery after 6 weeks of sciatica. A hypothetical future study to describe the natural course of sciatica during the first year in detail will not change the discussion about the timing of surgery.

Compared to prolonged conservative care, early surgery quickly relieves sciatica,

especially for those unable to sit as a consequence of provoked leg pain. Furthermore those with higher VAS leg-pain en RDQS scores are at a greater risk to suffer prolonged disability and delayed surgery when treated conservatively. On the basis of the information acquired individual patients now are better able to decide for themselves since they can be informed about the expected outcomes of both treatment modalities.

11

SUMMARY & CONCLUSION

Summary

Background
Although sciatica is as old as mankind its cause remained unknown throughout the centuries. The typical symptom complex of a diseased lumbosacral nerve root was not correlated with an anatomical substrate until some 75 years ago. The cause is a disk herniation, an entity which can easily removed be treated surgically but appears susceptible to spontaneous cure as well. Although surgery seemed to be the preferred method of cure for persistent sciatica from 1934 on, the optimal time of execution remained unknown **(Chapter 1)**. A review of literature presented the state of the art in epidemiology, diagnosis, conservative and surgical treatments for sciatica caused by a disk herniation. The clinical diagnosis is based on descriptive criteria and only needs radiological affirmation of nerve root compression before further invasive treatment is discussed. **(Chapter 2)**. The review concluded with uncertainties around the appropriate conservative or surgical treatment for disk herniation related sciatica. For a disease with such a high incidence, societal impact and internationally varying surgery rates, it is amazing to realize that the 6 weeks "wait-and-see" period is based on empirical medicine without any substantial evidence.

Objectives and design of the trial
After evaluation of the existing scientific literature it was clear that, with concern to the superiority of 'relative' early timing of surgery, no evidence supported this strategy for most patients with 6 to 12 weeks of non-remitting sciatica. Besides this fact no prospective trial had been performed yet with the goal to estimate the economic and societal impact of disk surgery compared to prolonged conservative care. For this reason a randomized trial protocol had to be developed, to answer the question whether early surgery would effectively speed up recovery and if this strategy was cost-effective compared to prolonged conservative care. A third objective was to estimate the effect of early surgery on speed of recovery and 1 year outcome for predefined subgroup variables.

The design of The Sciatica Trial with subsequent NWO/ZonMW grant approval lasted 2-3 years, including considerable methodological struggle but with the gain of epidemiological knowledge. Background, methods and design of analysis of this trial were described in detail **(Chapter 3)**. To answer the question whether early surgery, after 6 to 12 weeks of sciatica, is an effective treatment, this strategy would have to be compared randomly with prolonged conservative care and eventual delayed surgery among at least 280 patients. To accrue enough patients with an unequivocal radicular syndrome, 9 regional hospitals in Holland participated in the study after approval of the protocol by the Medical Ethics Committee. The protocol included a

conservative treatment recommendation for participating family practitioners, who guided those patients allocated to prolonged non-surgical treatment group.

Key findings

Although relief of complaints was twice as fast for sciatica patients who underwent early surgery, this multicenter randomized trial (n=283) demonstrated that this strategy did not result in a better overall 1-year functional recovery rate when compared with a policy of prolonged conservative treatment with eventual delayed surgery. During one year 89 percent of patients in the early surgery group and 39 percent of the conservative treatment group underwent microdiskectomy. At one-year follow-up no significant differences were detected in mean scores for any outcome measurements, including leg pain. Thus, the major advantage of early surgical treatment remained the faster relief of sciatica. The study results indirectly provide individual patients with sciatica who are considering disk surgery with information about how early surgery and conservative treatment affect the three separate outcome parameters, i.e. disease-specific disability, intensity of leg pain and time to recovery. **(Chapter 4).**

Faster recovery from sciatica makes early surgery more likely to be cost-effective than prolonged conservative care. The estimated difference in health care costs was acceptable and was compensated by the difference in absenteeism from work. For a willingness to pay $50,000 or more per Quality Adjusted Life Year, early surgery need not be withheld for economic reasons. **(Chapter 5).**

Except for "sciatica provoked by sitting" early surgery compared to prolonged conservative care yielded significantly faster rates of recovery for all investigated variables. If patients were able to sit without provoking sciatica early surgery did not result in faster recovery compared to conservative treatment. In contrast to former beliefs the straight leg raising test and morphology of the disk herniation failed to affect the short-term speed of recovery by early surgery versus prolonged conservative care. **(Chapter 6).** Higher initial disability scores and intensity of leg pain scores were found to have a predictive value for the probability for delayed surgery (39 %) in a cohort of 142 patients during a strategy of prolonged conservative care. Surgery after 6 to 12 weeks of sciatica may continue to be a valuable tool for those patients with continuous pain of high intensity and high disability scores as a sign of severe sciatica **(Chapter 7)**. We have demonstrated unequivocally that female gender is an independent predictive determinant for an unsatisfactory outcome at one year after a 6 to 12-week period of severe sciatica irrespective of surgery. **(Chapter 8).** The estimated odds for a long-term poor outcome were 3.3 higher for female patients with sciatica than for males and this finding was statistically highly significant. In addition females exhibited a slower recovery from sciatica. Irrespective of treatment the pro-

portion of patients with a good outcome was 87 % at one year. Since this is the actual state of the patients at 12 months, this proportion is lower than the 95 % perceived recovery during the first year as indicated by survival analysis. The mean disability and pain scores of patients with an unsatisfactory outcome at one year in this trial represent painful and disabling suffering. Quantification of the degree of failure has not yet been reported before.

During analysis of 2-year follow-up data, both strategies, early surgery and prolonged conservative care, resulted in similar outcomes at two years but early surgery achieved more rapid leg pain relief. Prolonged conservative care for 6-8 months was safe and did not result in a higher proportion of unsatisfactory outcomes at two years. **(Chapter 9).**Remarkably, early surgery did not prevent the risk of an unsatisfactory outcome at 1 or 2 years. In our study 20 % of the patients suffered chronic pain after a first episode of sciatica. Those with unsatisfactory outcomes scored worse on all outcomes corresponding to grave disability.

Conclusions

The optimal timing of surgery for sciatica cannot be defined for all patients, it remains a personal choice. After the classical guideline threshold of 6 to 12 weeks nature is still able to cure sciatica in a considerable proportion (60 %) of patients during the following months. Early surgery resulted in a recovery twice as fast compared to conservative care. From a cost-utility perspective data analysis showed that early surgery is an acceptable treatment. To operate on all patients without recovery in the first 3 months, however, would lead to unnecessary interventions, unless patients are aware of the potential alternatives for a favorable natural course. There were no clinical or imaging predictors of which patients would do better with surgery, although the presence of leg pain provoked by sitting was a potential determinant. Moreover, more intense leg pain and disability resulted in a higher chance on delayed surgery during a strategy of conservative care. Surgery could not prevent grave disability, which cripples 20 % of patients at 2 years irrespective their treatment. Future research will address this problem of chronic disability in this minority of patients, which has received only minimal attention in the past. **(Chapter 10).**

Physicians are now able to provide their patients with realistic data about the different courses of sciatica and thus indirectly to enable them to choose surgery or conservative treatment on an individual basis.

NEDERLANDSE SAMENVATTING

SAMENVATTING

Achtergrond

Hoewel het lumbosacraal radiculair syndroom (LSRS) zo lang bestaat als de geschiedenis van onze mensheid, heeft het tot 75 jaar geleden geduurd voordat de wetenschap een correlatie aantoonde tussen de symptomen van een aangedane lumbale zenuwwortel en het oorzakelijk anatomische substraat. Dit bleek te gaan om een hernia nuclei pulposis (HNP), welke chirurgisch gemakkelijk verwijderd kan worden, maar blijkbaar ook spontaan kan verdwijnen door een gunstig natuurlijk genezingsproces. Terwijl na 1934 chirurgisch ingrijpen de meest effectieve behandeling lijkt te zijn voor een persisterend LSRS, blijft het optimale tijdstip van uitvoering onbekend **(Hoofdstuk 1)**. Een review van de wetenschappelijke literatuur presenteert de huidige stand van zaken van de epidemiologie, diagnostiek, conservatieve en chirurgische behandeling van het LSRS veroorzaakt door een lumbale HNP. De op circumscripte criteria gebaseerde klinische diagnose is helder en hoeft alleen bij die patiënten, waar chirurgische behandeling wordt overwogen, een radiologische bevestiging van zenuw wortel compressie **(Hoofdstuk 2).** De review besluit met de onduidelijkheid die blijft bestaan rondom de juiste conservatieve of chirurgische behandelingsstrategie voor patiënten met een LSRS. Het is op zijn minst verbazingwekkend te noemen dat voor deze, frequent voorkomende aandoening met grote socio-economische consequenties en internationaal sterk variërende operatie aantallen, er geen wetenschappelijk bewijs voor handen is, die het bespreken van chirurgisch ingrijpen na 6 weken afwachtend beleid kan rechtvaardigen. Deze periode van "wait-and-see" is gebaseerd op empirische geneeskunde.

Doelstellingen en onderzoeksopzet

Na evaluatie van de bestaande wetenschappelijk literatuur was duidelijk dat er geen bewijs voor handen was die een beleid van vroege chirurgie kan ondersteunen voor de meeste patiënten met een 6 tot 12 weken durend LSRS. Verder was er nog geen studie uitgevoerd met een doelmatigheids opzet om de economische en sociale impact te kunnen meten. De opzet van het protocol voor de "Sciatica Trial", met vervolgens de NWO/ZonMW doelmatigheidsonderzoek subsidie goedkeuring, heeft 2 tot 3 jaar geduurd en ging gepaard met aanzienlijke methodologische discussies, maar met het voordeel van verkrijgen van epidemiologische kennis. Achtergronden, onderzoeksmethodes en de wijze van analyse zijn in detail beschreven **(Hoofdstuk 3)**. Om de vraag, is vroege chirurgie na minimaal 6 en maximaal 12 weken een effectieve behandeling, te kunnen beantwoorden dient deze behandelingsstrategie in een gerandomiseerd onderzoek te worden vergeleken met een verlengd afwachtend beleid, gevolgd door eventueel later chirurgisch ingrijpen. De te onderzoeken

populatie moest uit tenminste 280 patiënten bestaan. Na goedkeuring van het onderzoeksprotocol door de Medisch Ethische Toetsing Commissie participeerden 9 regionale ziekenhuizen in Holland in deze studie om voldoende patiënten te kunnen includeren met een evident LSRS. Naast de omschrijvingen van klinische diagnostiek en behandeling voorzag het onderzoeksprotocol tevens in een uitgebreid conservatief behandel advies voor de participerende huisartsen. Zij begeleidden de patiënten die waren toegewezen aan een voortgezette conservatieve behandeling.

Resultaten

Hoewel vroege chirurgie voor LSRS patiënten resulteerde in een 2 keer zo snel herstel van klachten in vergelijking met langer afwachten en late chirurgie, liet deze multicenter gerandomiseerde studie (n=283) zien dat dit niet gepaard ging met een proportioneel verschil in het totale aantal herstelde patiënten 1 jaar na randomisatie. Gedurende dit eerste jaar onderging 89 % van de patiënten een hernia operatie indien zij waren geloot voor een vroeg chirurgisch beleid, terwijl 39 % van de patiënten in de conservatieve groep ook niet aan deze behandeling ontkwamen. De gemiddelde 1 jaar pijn-, functionering en kwaliteit-van-leven scores lieten geen significante verschillen zien tussen beide groepen. Het enige, maar wel grote, voordeel van vroeg chirurgisch ingrijpen is dus een snel herstel van het LSRS. Toekomstige individuele LSRS patiënten, die vroege operatie overwegen, kunnen op basis van dit studieresultaat worden voorzien van nuttige keuze informatie over het beloop van de drie gescheiden uitkomst parameters; ziektespecifiek functioneren, intensiteit van beenpijn en tijdsduur tot herstel**(Hoofdstuk 4).**

Het snellere herstel van LSRS klachten na vroeg chirurgisch ingrijpen, resulteert in een hogere waarschijnlijkheid dat dit beleid kosten-effectiever is dan een verlengd conservatieve behandeling. Het geschatte verschil in gezondheidszorg kosten was acceptabel en werd gecompenseerd door een verschil in kosten door afwezigheid van arbeid welke in het voordeel van vroeg chirurgisch ingrijpen waren. Indien men bereid is om 50.000 US dollars te betalen per Quality Adjusted Life Year, zou patiënten vroeg chirurgisch ingrijpen niet moeten worden onthouden om economische redenen **(Hoofdstuk 5).**

Vergeleken met een strategie van conservatieve behandeling resulteerde vroege chirurgie in een significant sneller herstel wat gelijk was voor alle onderzochte variabelen, behalve voor de variabele 'provocatie van beenpijn door zitten'. Indien patiënten in staat waren te zitten zonder provocatie van hun LSRS, resulteerde vroege chirurgie niet in een sneller herstel dan langer afwachten. In tegenspraak met klassieke neurologische gedachten hadden de proef van Lasègue en de morfologie van de discushernia geen invloed op het resultaat van beide behandelingsstrategieën met betrekking tot de snelheid van herstel **(Hoofdstuk 6).** Hogere initiële functione-

ring en beenpijn intensiteit scores bleken een voorspellende waarde te hebben op de kans op late chirurgie in de conservatieve behandelgroep. Chirurgie na 6 tot 12 weken beenpijn blijft een waardevolle behandeling voor patiënten met persisterend hoge pijn intensiteit en functionering scores als teken van een ernstig LSRS **(Hoofdstuk 7).** We hebben onlosmakelijk vastgesteld dat, met betrekking tot patiënten met een 6 tot 12 weken bestaand ernstig LSRS, het vrouwelijke geslacht een onafhankelijke voorspellende determinant is voor een slecht resultaat na 1 jaar. Dit resultaat ontstaat onafhankelijk van het ondergaan van chirurgie**(Hoofdstuk 8).**. De geschatte odds op een slecht lange termijn resultaat waren 3.3 maal hoger voor vrouwelijke patiënten met LSRS dan voor mannen en deze bevinding was sterk significant. Tevens blijkt dat vrouwen een langzamer herstel van LSRS vertoonden. Onafhankelijk van de ondergane behandelingsstrategie registreerden 87 % van de patiënten op 1 jaar een goed ervaren herstel. Omdat dit de actuele toestand van de patiënten weergeeft op 1 jaar is deze proportie lager dan het 95 % ervaren herstel die werd geregistreerd in de Kaplan Meier overlevingsanalyse gedurende het eerste jaar. De gemiddelde functionering en pijn scores van patiënten met een slecht resultaat op 1 jaar zijn representatief voor pijnlijk en invaliderend lijden. Kwantificering van de mate van falen van behandeling is nog niet eerder op deze manier gepubliceerd.

De 2-jaars data lieten zien dat beide behandelingsstrategieën, vroege chirurgie en langer afwachten, resulteerden in identieke uitkomsten, maar dat een vroeg chirurgisch beleid, ondanks de langere follow-up nog steeds resulteerde in een significant sneller herstel van beenpijn **(Hoofdstuk 9)**. Langer afwachten gedurende 6 tot 8 maanden bleek echter veilig te zijn en resulteerde niet in een hogere proportie van slecht herstel op 2 jaar. Het is opmerkelijk dat vroege chirurgie de kans op een slechte uitkomst op 1 en 2 jaar niet beïnvloedde. Uit onze studie blijkt dat 20 % van de patiënten chronisch pijnlijk bleven na een eerste episode van LSRS. De patiënten met een slecht resultaat scoorden slecht op alle uitkomst schalen, corresponderend met ernstige invaliditeit.

CONCLUSIES

Gezien het feit dat het optimale tijdstip van chirurgie niet voor alle patiënten gedefinieerd kan worden, blijft dit een persoonlijke keuze. Na de klassieke richtlijn termijn van 6 tot 12 weken geneest de natuur het LSRS alsnog bij een aanzienlijke hoeveelheid (60 %) van alle patiënten gedurende de volgende maanden. Indien al deze patiënten die in de eerste 3 maanden niet herstelden, geopereerd zouden worden, zou dat leiden tot veel onnodige ingrepen, tenzij patiënten goed op de hoogte zijn van de potentiële kans op een herstel door een gunstig natuurlijk beloop. Een vroege

operatie resulteerde in een 2 maal sneller herstel van LSRS vergeleken met langer afwachten, maar kon ernstige invaliditeit in 20 % van de patiënten na 2 jaar niet voorkomen. Toekomstig onderzoek zal aandacht schenken aan het ontstaan van het probleem bij deze chronisch pijnlijke patiënten. Wellicht, omdat ze de minderheid vormen, heeft dit in het verleden relatief weinig aandacht gehad **(Hoofdstuk 10)**.

Artsen zijn nu in staat om patiënten te voorzien van realistische data met betrekking tot de verschillende herstelkansen van LSRS in de tijd en kunnen dus indirect de patiënten in staat stellen om een individuele keuze te maken met betrekking tot het moment van operatie ten opzichte van een langer afwachtend beleid.

REFERENCE LIST

(1) Oxford dictionary of English. Second edition (revised). Oxford University Press; 2005.
(2) Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: a systematic review. J Spinal Disord 2000; 13(6):463-469.
(3) Weber H, Holme I, Amlie E. The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. Spine 1993; 18(11):1433-1438.
(4) Mixter WJ, Barr J. Rupture of the Intervertebral Disc With Involvement of the Spinal Canal. N Engl J Med 1934; 211:210-215.
(5) Parisien RC, Ball PA. William Jason Mixter (1880-1958). Ushering in the "dynasty of the disc". Spine 1998; 23(21):2363-2366.
(6) Marketos SG, Skiadas P. Hippocrates. The father of spine surgery. Spine 1999; 24(13):1381-1387.
(7) Knoeller SM, Seifried C. Historical perspective: history of spinal surgery. Spine 2000; 25(21):2838-2843.
(8) Sonntag VKH. History of degenerative and traumatic disease of the spine. In Samuel H. Greenblatt (Ed); T. Forcht Dagi and Mel H. Epstein, contributing editors. A history of neurosurgery: in its scientific and professional contexts. Park Ridge: American Association of Neurological Surgeons. 1997. Ref Type: Generic
(9) Aurelianus Caelius. Acute diseases and chronic diseases. 1950.
(10) Gurunluoglu R, Gurunluoglu A. Paul of Aegina: landmark in surgical progress. World J Surg 2003; 27(1):18-25.
(11) Naderi S, Acar F, Arda MN. History of spinal disorders and Cerrahiyetul Haniye (Imperial Surgery): a review of a Turkish treatise written by Serefeddin Sabuncuoglu in the 15th century. Historical vignette. J Neurosurg 2002; 96(3 Suppl):352-356.
(12) Vesalius A. de humani corporis fabrica. Basileae ex off Ioannis Oporini. 1543.
(13) van Alphen HA. [Andreas Vesalius' 'De Humani Corporis Fabrica Libra Septem' 450 years]. Ned Tijdschr Geneeskd 1993; 137(51):2632-2637.
(14) Cotunnius [Cotugnius]D. De ischiade nervosa commentarius. Neapoli apud frat Simonios. 12 ed. Viennæ: 1764.
(15) Niederstadt D. [In memory of Domestico Cotugno and his work on sciatica.]. Z Rheumaforsch 1951; 10(11-12):396-400.
(16) Androutsos G. Giovanni-Battista Morgagni (1682-1773): creator of pathological anatomy. J BUON 2006; 11(1):95-101.
(17) Walton GL, Paul WE. Contribution to the study of spinal surgery: one successful and one unsuccessful operation for the removal of tumor. Bost Med Surg J 153, 114-117. 1-1-1905. Ref Type: Generic
(18) Kocher T. Die Verletzungen der Wirbelsäule zugleich als Beiträg zur Physiologie des menschlichen Rückenmarks. Mitt Grenzgeb Med Chir 1, 415-480. 1896. Ref Type: Generic
(19) Virchow R. Untersuchungen über die Entwicklung des Schadelgrunde. Reimer, Berlin; 1857.
(20) Stookey B. Compression of the spinal cord due to ventral extradural cervical chondromas: diagnosis and surgical treatment. Arch Neurol Psychiatry 20, 275-291. 1928. Ref Type: Generic
(21) De SS. [Small history of an important sign: Lasegue's sign.]. Sem Hop 1958; 34(13/3):815-7SP.
(22) Wartenberg R. Lasegue sign and Kernig sign; historical notes. AMA Arch Neurol Psychiatry 1951; 66(1):58-60.
(23) Welfling J. [An inconspicuous birth, that of the Lasegue sign.]. Rev Rhum Mal Osteoartic 1954; 21(3):269-271.
(24) Oppenheim H, Krause F. Über Einklemmung bzw. Strangulation der cauda equine. Dtsch Med Wochenschr 35, 697-700. 1909. Ref Type: Generic
(25) Robinson JS. Sciatica and the lumbar disk syndrome: a historic perspective. South Med J 1983; 76(2):232-238.
(26) Goldthwait JE. The lumbosacral articulation. An explanation of many cases of "lumbago", "sciatica" and paraplegia. Boston Med Surg J 1911; 164:365-601.
(27) Midleton GS, Teacher JH. Injury of the spinal cord due to rupture of an intervertebral disc during muscular effort. Glasgow Med J 76, 1-6. 1911. Ref Type: Generic
(28) Elsberg CA. Extradural ventral chondromas (ecchondroses), their favorite sites, spinal cord and root symptoms they produce, and their surgical treatment. Bull Neurol Inst NY 1, 350-388. 1931. Ref Type: Generic

(29) Elsberg CA. Tumors of the spinal cord and the symptoms of irritation and compression of the spinal cord and nerve roots: pathology, symptomatology, diagnosis and treatment. New York: Paul B Hoeber , 195-198. 1-1-1925. Ref Type: Generic
(30) Dandy WE. Loose cartilage from intervertebral disk simulating tumor of the spinal cord. Arch Surg 19, 660-672. 1929. Ref Type: Generic
(31) Sicard A. [Examination of the epidural space with lipiodol in the diagnosis of lumbosciatica.]. Mem Acad Chir (Paris) 1950; 76(20-21):596-597.
(32) Glorieux P. [Putti's vertebral syndrome.]. J Belge Radiol 1953; 36(4):467-480.
(33) Putti V. New conceptions in the pathogenesis of sciatic pain. Lancet 2, 53. 1927. Ref Type: Generic
(34) Alajouanine T, Nick J, Contamin F, Brevart P. [Trophic ulcers of the foot during radicular S1 sciatica.]. Bull Mem Soc Med Hop Paris 1959; 75(5-6):217-219.
(35) Mishra R, Kaw R. Foix-Alajouanine syndrome: an uncommon cause of myelopathy from an anatomic variant circulation. South Med J 2005; 98(5):567-569.
(36) Patwardhan RV, Hadley MN. History of surgery for ruptured disk. Neurosurg Clin N Am 2001; 12(1):173-9, x.
(37) Schmorl G. Über die pathologische Anatomie der Wirbelbandscheiben. Beitr Klin Chir 151, 360-368. 1931. Ref Type: Generic
(38) de Vet AC. Behandeling van de hernia nuclei pulposi. (S. prolaps van den discus intervertebralis). Ned Tijdschr Geneeskd 1947; 91.1:493-504.
(39) Lenshoek CH. hernia van de tusschenwervelschijf met verschijnselen van druk op ruggemerg en wortels. Ned Tijdschr Geneeskd 1937; 81(3):4435-4443.
(40) Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. Spine 1983; 8(2):131-140.
(41) Yoshida M, Nakamura T, Sei A, Kikuchi T, Takagi K, Matsukawa A. Intervertebral disc cells produce tumor necrosis factor alpha, interleukin-1beta, and monocyte chemoattractant protein-1 immediately after herniation: an experimental study using a new hernia model. Spine 2005; 30(1):55-61.
(42) Stafford MA, Peng P, Hill DA. Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. Br J Anaesth 2007; 99(4):461-473.
(43) Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren K-A, Jarvinen S et al. The treatment of disc herniation-induced sciatica with infliximab: Results of a randomized, controlled, 3-month follow-up study. Spine Vol 30(24)()(pp 2724-2728), 2005 2005;(24):2724-2728.
(44) Stam J. [Consensus on diagnosis and treatment of the lumbosacral radicular syndrome. Dutch Society for Neurology]. Ned Tijdschr Geneeskd 1996; 140(52):2621-2627.
(45) Vader JP, Porchet F, Larequi-Lauber T, Dubois RW, Burnand B. Appropriateness of surgery for sciatica: reliability of guidelines from expert panels. Spine 2000; 25(14):1831-1836.
(46) Cherkin DC, Deyo RA, Loeser JD, Bush T, Waddell G. An international comparison of back surgery rates. Spine 1994; 19(11):1201-1206.
(47) Koes BW, van Tulder MW, Peul WC. Diagnosis and treatment of sciatica. BMJ 2007; 334(7607):1313-1317.
(48) Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA 2006; 296(20):2451-2459.
(49) Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. JAMA 2006; 296(20):2441-2450.
(50) Weinstein JN, Lurie JD, Olson PR, Bronner KK, Fisher ES. United States' trends and regional variations in lumbar spine surgery: 1992-2003. Spine 2006; 31(23):2707-2714.
(51) Vroomen PC, de Krom MC, Knottnerus JA. Diagnostic value of history and physical examination in patients suspected of sciatica due to disc herniation: a systematic review. J Neurol 1999; 246(10):899-906.
(52) Deville WL, van der Windt DA, Dzaferagic A, Bezemer PD, Bouter LM. The test of Lasegue: systematic review of the accuracy in diagnosing herniated discs. Spine 2000; 25(9):1140-1147.
(53) Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994; 331(2):69-73.

(54) Miranda H, Viikari-Juntura E, Martikainen R, Takala EP, Riihimaki H. Individual factors, occupational loading, and physical exercise as predictors of sciatic pain. Spine 2002; 27(10):1102-1109.
(55) Modic MT, Ross JS, Obuchowski NA, Browning KH, Cianflocco AJ, Mazanec DJ. Contrast-enhanced MR imaging in acute lumbar radiculopathy: a pilot study of the natural history. Radiology 1995; 195(2):429-435.
(56) Modic MT, Obuchowski NA, Ross JS, Brant-Zawadzki MN, Grooff PN, Mazanec DJ et al. Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome. Radiology Vol 237(2)()(pp 597-604), 2005 2005;(2):597-604.
(57) Awad JN, Moskovich R. Lumbar disc herniations: surgical versus nonsurgical treatment. Clin Orthop Relat Res 2006; 443:183-197.
(58) Govind J. Lumbar radicular pain. Aust Fam Physician 2004; 33(6):409-412.
(59) Jarvik JG, Deyo RA. Diagnostic evaluation of low back pain with emphasis on imaging. Ann Intern Med 2002; 137(7):586-597.
(60) Luijsterburg PA, Verhagen AP, Ostelo RW, van Os TA, Peul WC, Koes BW. Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review. Eur Spine J 2007.
(61) Hagen KB, Jamtvedt G, Hilde G, Winnem MF. The updated cochrane review of bed rest for low back pain and sciatica. Spine Vol 30(5)()(pp 542-546), 2005 Date of Publication: 01 MAR 2005 2005;(5):542-546.
(62) Health Council of the Netherlands. Management of the lumbosacral radicular syndrome (sciatica). 1999/18. 1999. Ref Type: Generic
(63) Mens JMA, Chavannes AW, Koes BW, Lubbers WJ, Ostelo RWJG, Spinnewijn WEM et al. NHG-Standaard Lumbosacraal radiculair syndroom. Huisarts Wet 2005 48, 178. 2005. Ref Type: Generic
(64) Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev 2007;(2):CD001350.
(65) van Tulder MW, Koes B, Seitsalo S, Malmivaara A. Outcome of invasive treatment modalities on back pain and sciatica: an evidence-based review. Eur Spine J 2006; 15 Suppl 1:S82-S92.
(66) Osterman H, Seitsalo S, Karppinen J, Malmivaara A. Effectiveness of microdiscectomy for lumbar disc herniation: a randomized controlled trial with 2 years of follow-up. Spine 2006; 31(21):2409-2414.
(67) Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P. Pathophysiology of disk-related low back pain and sciatica. II. Evidence supporting treatment with TNF-alpha antagonists. Joint Bone Spine 2006; 73(3):270-277.
(68) Koes BW, van Tulder MW, Ostelo R, Kim BA, Waddell G. Clinical guidelines for the management of low back pain in primary care: an international comparison. Spine 2001; 26(22):2504-2513.
(69) Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P. Pathophysiology of disk-related sciatica. I.--Evidence supporting a chemical component. Joint Bone Spine 2006; 73(2):151-158.
(70) Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990; 72(3):403-408.
(71) Waddell G. The back pain revolution. Edinburgh: Churchill Livingstone . 1998. Ref Type: Generic
(72) Egger M, Smith GD. Bias in location and selection of studies. BMJ 1998; 316(7124):61-66.
(73) Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. J Clin Epidemiol 2000; 53(2):207-216.
(74) van de Velden J, de Bakker DH. Basisrapport: Morbiditeit in de huisartsenpraktijk. Utrecht Nivel . 1990. Ref Type: Generic
(75) van den Bosch JH, Kardaun JW. Ziekten van het zenuwstelsel in Nederland. SDU uitgeverij, Den Haag . 1993. Ref Type: Generic
(76) Gegevens uit de landelijke registratie van Nederlandse Ziekenhuizen. SIG Zorginformatie, Utrecht. 1996. Ref Type: Generic
(77) van Tulder MW, Koes BW, Bouter LM. A cost-of-illness study of back pain in The Netherlands. Pain 1995; 62(2):233-240.
(78) Weber H. Lumbar disc herniation. A prospective study of prognostic factors including a controlled trial. Part II. J Oslo City Hosp 1978; 28(7-8):89-113.
(79) Hofstee DJ, Gijtenbeek JM, Hoogland PH, van Houwelingen HC, Kloet A, Lotters F et al. Westeinde sciatica trial: randomized controlled study of bed rest and physiotherapy for acute sciatica. J Neurosurg 2002; 96(1 Suppl):45-49.

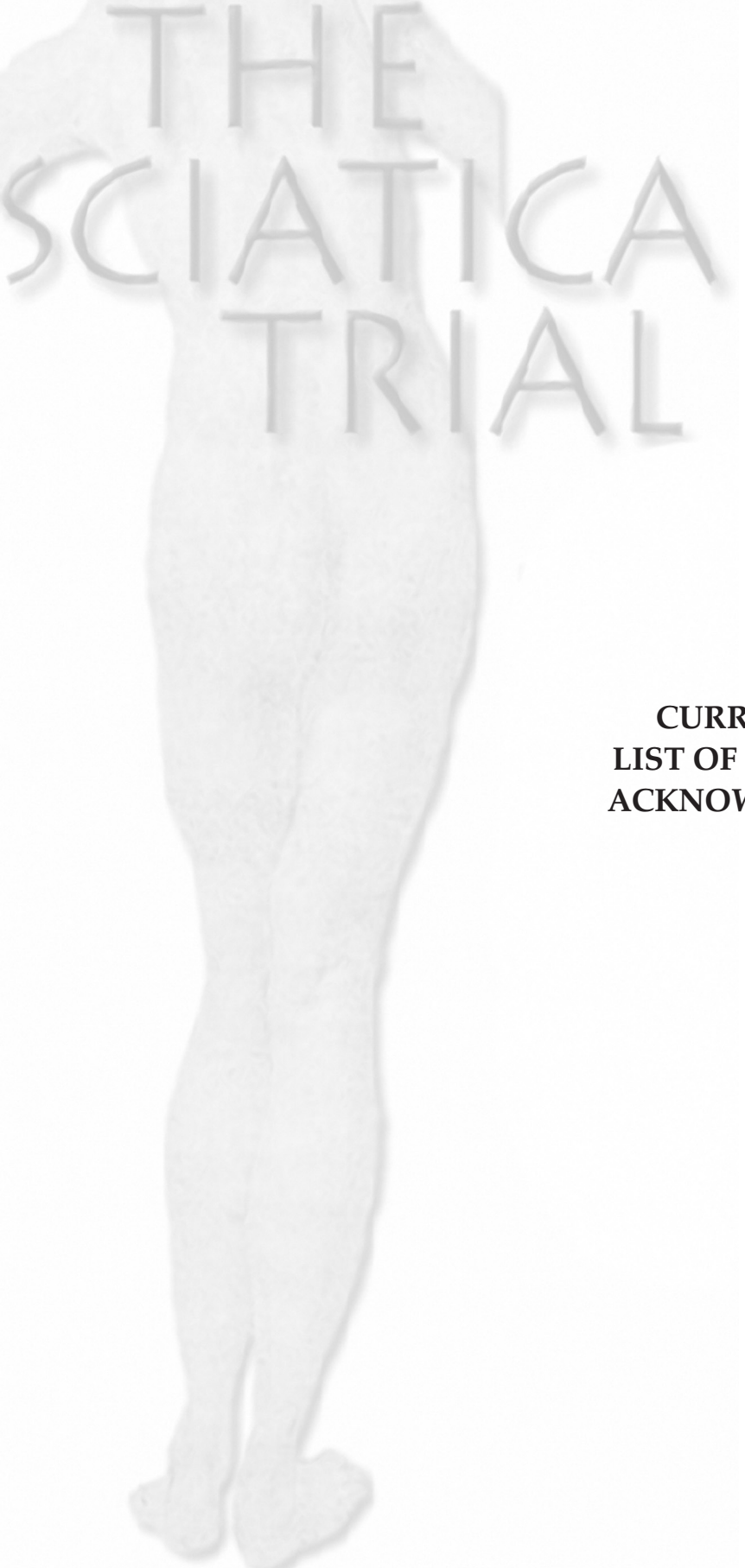
(80) Vroomen PC. The diagnosis and conservative treatment of Sciatica. 1998. Ref Type: Generic
(81) Atlas SJ, Deyo RA, Keller RB, Chapin AM, Patrick DL, Long JM et al. The Maine Lumbar Spine Study, Part II. 1-year outcomes of surgical and nonsurgical management of sciatica. Spine 1996; 21(15):1777-1786.
(82) Hakelius A. Prognosis in sciatica. A clinical follow-up of surgical and non-surgical treatment. Acta Orthop Scand Suppl 1970; 129:1-76.
(83) Malter AD, McNeney B, Loeser JD, Deyo RA. 5-year reoperation rates after different types of lumbar spine surgery. Spine 1998; 23(7):814-820.
(84) Saal JA. Natural history and nonoperative treatment of lumbar disc herniation. Spine Vol 21(24 SUPPL)()(pp 2S-9S), 1996 1996;(24 SUPPL.):2S-9S.
(85) Spanfort EV. Lumbar disc herniation: a computer aided analysis of 2504 operations. Acta Orthopaedica Scandinavica suppl: 142. 1972. Ref Type: Generic
(86) Bessette L, Liang MH, Lew RA, Weinstein JN. Classics in Spine. Surgery literature revisited. Spine 1996; 21(3):259-263.
(87) Saal JA, Saal JS. The natural history of lumbar intervertebral disc extrusions treated non-operatively. Spine 15, 683-686. 1989. Ref Type: Generic
(88) Gibson JN, Grant IC, Waddell G. Surgery for lumbar disc prolapse. Cochrane Database Syst Rev 2000;(3):CD001350.
(89) Gibson JNA, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. Spine Vol 24(17)()(pp 1820-1832), 1999 Date of Publication: 01 SEP 1999 1999;(17):1820-1832.
(90) Tubach F, Beaute J, Leclerc A. Natural history and prognostic indicators of sciatica. J Clin Epidemiol 2004; 57(2):174-179.
(91) Smeele I.J., van den Hooghen JM, Mens JMA, e.a. NHG-Standaard Lumbosacraal Radiculair Syndroom. Huisarts Wet 1996 39, 78-89. 1996. Ref Type: Generic
(92) Gezondsheidraad. Diagnostiek en behandeling van het lumbosacraal radiculair syndroom. 1999/18. 1999. Ref Type: Generic
(93) Malter AD, Larson EB, Urban N, Deyo RA. Cost-effectiveness of lumbar discectomy for the treatment of herniated intervertebral disc. Spine 1996; 21(9):1048-1054.
(94) Gatchel RJ, Turk DC. Psychological approaches to painmanagement: a practitioner's handbook. The Guilford Press . 1996. Ref Type: Generic
(95) Aaronson NK, Acquadro C, Alonso J, Apolone G, Bucquet D, Bullinger M et al. International Quality of Life Assessment (IQOLA) Project. Qual Life Res 1992; 1(5):349-351.
(96) Stansfeld SA, Roberts R, Foot SP. Assessing the validity of the SF-36 General Health Survey. Qual Life Res 1997; 6(3):217-224.
(97) Main CJ, Wood PL, Hollis S, Spanswick CC, Waddell G. The Distress and Risk Assessment Method. A simple patient classification to identify distress and evaluate the risk of poor outcome. Spine 1992; 17(1):42-52.
(98) Deyo RA, Battie M, Beurskens AJ, Bombardier C, Croft P, Koes B et al. Outcome measures for low back pain research. A proposal for standardized use. Spine 1998; 23(18):2003-2013.
(99) Fordyce WE. Behavioral methods for chronic pain and illness. St.Louis: CV Mosby Company . 1976. Ref Type: Generic
(100) Huskisson EC. Measurement of pain. Lancet 1974; 2(7889):1127-1131.
(101) Joyce CR, Zutshi DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol 1975; 8(6):415-420.
(102) Scott J, Huskisson EC. Graphic representation of pain. Pain 1976; 2(2):175-184.
(103) Gommans I, Koes BW. Validity and responsiveness of the Dutch adaptation of the Roland Disability Questionnaire. Low Back Pain. EMGO 1996 , 57-70. 1996. Ref Type: Generic
(104) Prolo DJ, Oklund SA, Butcher M. Toward uniformity in evaluating results of lumbar spine operations. A paradigm applied to posterior lumbar interbody fusions. Spine 1986; 11(6):601-606.
(105) EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990; 16(3):199-208.
(106) Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095-1108.
(107) Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992; 305(6846):160-164.

(108) Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30(6):473-483.
(109) Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997; 72(1-2):95-97.
(110) Melzack R, Katz J. Pain measurement in persons in pain. Textbook of Pain . Ref Type: Generic
(111) College voor zorgverzekeringen. Richtlijnen voor farmaco-economisch onderzoek. CvZ, afdeling FO/G&s . 1999. Ref Type: Generic
(112) Oostenbrink JB, Koopmanschap MA, Rutten FF. Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg. CVZ, 2000 . 2000. Ref Type: Generic
(113) Atlas SJ, Keller RB, Chang Y, Deyo RA, Singer DE. Surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: five-year outcomes from the Maine Lumbar Spine Study. Spine 2001; 26(10):1179-1187.
(114) Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB. Assessing health-related quality of life in patients with sciatica. Spine 1995; 20(17):1899-1908.
(115) Dolan P. Modelling valuations for health states: the effect of duration. Health Policy 1996; 38(3):189-203.
(116) Vroomen PC, de Krom MC, Wilmink JT, Kester AD, Knottnerus JA. Lack of effectiveness of bed rest for sciatica. N Engl J Med 1999; 340(6):418-423.
(117) Andersson GB, Brown MD, Dvorak J, Herzog RJ, Kambin P, Malter A et al. Consensus summary of the diagnosis and treatment of lumbar disc herniation. Spine 1996; 21(24 Suppl):75S-78S.
(118) Peul WC, van Houwelingen HC, van der Hout WB, Brand R, Eekhof JA, Tans JT et al. Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disc herniation: rationale and design of a randomized trial [ISRCT 26872154]. BMC Musculoskelet Disord 2005; 6:8.
(119) Promise version 2, Project Manager Internet Server, developed by the dept of Medical Statistics and Bioinformatics, Section Advanced Data Management, Leiden University Medical Center, the Netherlands [1900.
(120) SPSS version 12.0, SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th floor, Chicago, Illinois 60606 [2006.
(121) Balderston RA, Gilyard GG, Jones AA, Wiesel SW, Spengler DM, Bigos SJ et al. The treatment of lumbar disc herniation: simple fragment excision versus disc space curettage. J Spinal Disord 1991; 4(1):22-25.
(122) Carragee EJ, Spinnickie AO, Alamin TF, Paragioudakis S. A prospective controlled study of limited versus subtotal posterior discectomy: short-term outcomes in patients with herniated lumbar intervertebral discs and large posterior anular defect. Spine 2006; 31(6):653-657.
(123) Thome C, Barth M, Scharf J, Schmiedek P. Outcome after lumbar sequestrectomy compared with microdiscectomy: a prospective randomized study. J Neurosurg Spine 2005; 2(3):271-278.
(124) Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-1194.
(125) Weber H. The effect of delayed disc surgery on muscular paresis. Acta Orthop Scand 1975; 46(4):631-642.
(126) Buttermann GR. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy. A prospective, randomized study. J Bone Joint Surg Am 2004; 86-A(4):670-679.
(127) Frymoyer JW. Back pain and sciatica. N Engl J Med 1988; 318(5):291-300.
(128) Luijsterburg PA, Verhagen AP, Braak S, Avezaat CJ, Koes BW. Do neurosurgeons subscribe to the guideline lumbosacral radicular syndrome? Clin Neurol Neurosurg 2004; 106(4):313-317.
(129) Peul WC, van Houwelingen HC, Van Den Hout WB, Brand R, Eekhof JA, Tans JT et al. Surgery versus prolonged conservative treatment for sciatica. N Engl J Med 2007; 356(22):2245-2256.
(130) Launois R, Henry B, Marty JR, Gersberg M, Lassale C, Benoist M et al. Chemonucleolysis versus surgical discectomy for sciatica secondary to lumbar disc herniation. A cost and quality-of-life evaluation. Pharmacoeconomics 1994; 6(5):453-463.
(131) McKinley DS, Shaffer LM. Cost effectiveness evaluation of ADCON-L adhesion control gel in lumbar surgery. Neurol Res 1999; 21 Suppl 1:S67-S71.
(132) Ozkose Z, Ercan B, Unal Y, Yardim S, Kaymaz M, Dogulu F et al. Inhalation versus total intravenous anesthesia for lumbar disc herniation: comparison of hemodynamic effects, recovery characteristics, and cost. J Neurosurg Anesthesiol 2001; 13(4):296-302.

(133) Stevenson RC, McCabe CJ, Findlay AM. An economic evaluation of a clinical trial to compare automated percutaneous lumbar discectomy with microdiscectomy in the treatment of contained lumbar disc herniation. Spine 1995; 20(6):739-742.
(134) Karppinen J, Ohinmaa A, Malmivaara A, Kurunlahti M, Kyllonen E, Pienimaki T et al. Cost effectiveness of periradicular infiltration for sciatica: subgroup analysis of a randomized controlled trial. Spine 2001; 26(23):2587-2595.
(135) Lafuma A, Bouvenot G, Cohen C, Eschwege E, Fagnani F, Vignon E. A pragmatic cost-effectiveness study of routine epidural corticosteroid injections for lumbosciatic syndrome requiring inhospital management. Rev Rhum Engl Ed 1997; 64(10):549-555.
(136) Ostelo RWJG, Goossens MEJB, De Vet HCW, van den Brandt PA. Economic Evaluation of a Behavioral-Graded Activity Program Compared to Physical Therapy for Patients Following Lumbar Disc Surgery. Spine Vol 29(6)()(pp 615-622), 2004 Date of Publication: 15 MAR 2004 2004;(6):615-622.
(137) Price C, Arden N, Coglan L, Rogers P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. Health Technology Assessment (Winchester, England) Vol 9(33)()(pp iii-46), 2005 2005;(Winchester, England):iii-46.
(138) Hansson E, Hansson T. The cost-utility of lumbar disc herniation surgery. Eur Spine J 2007; 16(3):329-337.
(139) Carragee E. Surgical treatment of lumbar disk disorders. JAMA 2006; 296(20):2485-2487.
(140) Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005; 43(3):203-220.
(141) Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002; 21(2):271-292.
(142) Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, De Haes HJ. The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? Int J Technol Assess Health Care 1996; 12(2):291-298.
(143) OECD. Purchasing Power Parities (PPPs) for OECD Countries 1980-2006 (accessed July 3, 2007 at www.oecd.org/dataoecd/61/56/1876133.xls). 2007. Ref Type: Generic
(144) Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. Health Econ 2003; 12(5):377-392.
(145) Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. Pharmacoeconomics 2002; 20(7):443-454.
(146) Oostenbrink JB, Koopmanschap MA, Rutten FF. Manual for cost analyses, methods and standard prices for economic evaluations in health care (in Dutch). Amstelveen: Dutch Health Insurance Executive Board . 2004. Ref Type: Generic
(147) Dutch Health Insurance Executive Board. Pharmacotherapeutic Compass (in Dutch). www.fk.cvz.nl. 2006. Ref Type: Generic
(148) van den BB, Brouwer W, van EJ, Koopmanschap M. Economic valuation of informal care: the contingent valuation method applied to informal caregiving. Health Econ 2005; 14(2):169-183.
(149) Zethraeus N, Johannesson M, Jonsson B, Lothgren M, Tambour M. Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. Pharmacoeconomics 2003; 21(1):39-48.
(150) Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med 2003; 163(14):1637-1641.
(151) Lutz GK, Butzlaff ME, Atlas SJ, Keller RB, Singer DE, Deyo RA. The relation between expectations and outcomes in surgery for sciatica. J Gen Intern Med 1999; 14(12):740-744.
(152) Ito T, Takano Y, Yuasa N. Types of lumbar herniated disc and clinical course. Spine 2001; 26(6):648-651.
(153) Vroomen PC, Wilmink JT, de KM. Prognostic value of MRI findings in sciatica. Neuroradiology 2002; 44(1):59-63.
(154) Carragee EJ, Kim DH. A prospective analysis of magnetic resonance imaging findings in patients with sciatica and lumbar disc herniation. Correlation of outcomes with disc fragment and canal morphology. Spine 1997; 22(14):1650-1660.
(155) Carragee EJ, Han MY, Suen PW, Kim D. Clinical outcomes after lumbar discectomy for sciatica: the effects of fragment type and anular competence. J Bone Joint Surg Am 2003; 85-A(1):102-108.

(156) Autio RA, Karppinen J, Kurunlahti M, Haapea M, Vanharanta H, Tervonen O. Effect of periradicular methylprednisolone on spontaneous resorption of intervertebral disc herniations. Spine 2004; 29(15):1601-1607.
(157) Komori H, Okawa A, Haro H, Muneta T, Yamamoto H, Shinomiya K. Contrast-enhanced magnetic resonance imaging in conservative management of lumbar disc herniation. Spine 1998; 23(1):67-73.
(158) Dvorak J, Gauchat MH, Valach L. The outcome of surgery for lumbar disc herniation. I. A 4-17 years' follow-up with emphasis on somatic aspects. Spine 1988; 13(12):1418-1422.
(159) Junge A, Frohlich M, Ahrens S, Hasenbring M, Sandler A, Grob D et al. Predictors of bad and good outcome of lumbar spine surgery. A prospective clinical study with 2 years' follow up. Spine 1996; 21(9):1056-1064.
(160) Vroomen PC, de Krom MC, Knottnerus JA. When does the patient with a disc herniation undergo lumbosacral discectomy? J Neurol Neurosurg Psychiatry 2000; 68(1):75-79.
(161) Deyo RA. Back surgery--who needs it? N Engl J Med 2007; 356(22):2239-2243.
(162) Caspar W, Campbell B, Barbier DD, Kretschmmer R, Gotfried Y. The Caspar microsurgical discectomy and comparison with a conventional standard lumbar disc procedure. Neurosurgery 1991; 28(1):78-86.
(163) Hurme M, Alaranta H. Factors predicting the result of surgery for lumbar intervertebral disc herniation. Spine 1987; 12(9):933-938.
(164) Hurme M, Alaranta H, Einola S, Falck B, Kallio V, Knuts LR et al. A prospective study of patients with sciatica. A comparison between conservatively treated patients and patients who have undergone operation, Part I: Patient characteristics and differences between groups. Spine 1990; 15(12):1340-1344.
(165) Keller RB, Atlas SJ, Singer DE, Chapin AM, Mooney NA, Patrick DL et al. The Maine Lumbar Spine Study, Part I. Background and concepts. Spine 1996; 21(15):1769-1776.
(166) Lauridsen HH, Hartvigsen J, Manniche C, Korsholm L, Grunnet-Nilsson N. Responsiveness and minimal clinically important difference for pain and disability instruments in low back pain patients. BMC Musculoskelet Disord 2006; 7:82.
(167) Porchet F, Wietlisbach V, Burnand B, Daeppen K, Villemure JG, Vader JP. Relationship between severity of lumbar disc disease and disability scores in sciatica patients. Neurosurgery 2002; 50(6):1253-1259.
(168) Deyo RA, Cherkin DC, Weinstein J, Howe J, Ciol M, Mulley AG, Jr. Involving patients in clinical decisions: impact of an interactive video program on use of back surgery. Med Care 2000; 38(9):959-969.
(169) Kosteljanetz M, Espersen JO, Halaburt H, Miletic T. Predictive value of clinical and surgical findings in patients with lumbago-sciatica. A prospective study (Part I). Acta Neurochir (Wien) 1984; 73(1-2):67-76.
(170) Thomas M, Grant N, Marshall J, Stevens J. Surgical treatment of low backache and sciatica. Lancet 1983; 2(8365-66):1437-1439.
(171) Edwards RR, Doleys DM, Lowery D, Fillingim RB. Pain tolerance as a predictor of outcome following multidisciplinary treatment for chronic pain: differential effects as a function of sex. Pain 2003; 106(3):419-426.
(172) Fillingim RB, Doleys DM, Edwards RR, Lowery D. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. Spine 2003; 28(2):143-150.
(173) Keogh E, McCracken LM, Eccleston C. Do men and women differ in their response to interdisciplinary chronic pain management? Pain 2005; 114(1-2):37-46.
(174) Keogh E, McCracken LM, Eccleston C. Gender moderates the association between depression and disability in chronic pain patients. Eur J Pain 2006; 10(5):413-422.
(175) Wijnhoven HA, de Vet HC, Picavet HS. Sex differences in consequences of musculoskeletal pain. Spine 2007; 32(12):1360-1367.
(176) Hyyppa MT, Alaranta H, Lahtela K, Nykvist F, Hurme M, Nyberg F et al. Neuropeptide converting enzyme activities in CSF of low back pain patients. Pain 1990; 43(2):163-168.
(177) Takeuchi H, Kawaguchi S, Ohwada O, Kobayashi H, Hayakawa M, Takebayashi T et al. Plasma neuropeptides in patients undergoing lumbar discectomy. Spine 2007; 32(2):E79-E84.
(178) den Boer JJ, Oostendorp RA, Beems T, Munneke M, Evers AW. Continued disability and pain after lumbar disc surgery: the role of cognitive-behavioral factors. Pain 2006; 123(1-2):45-52.

(179) Hasenbring M, Ulrich HW, Hartmann M, Soyka D. The efficacy of a risk factor-based cognitive behavioral intervention and electromyographic biofeedback in patients with acute sciatic pain. An attempt to prevent chronicity. Spine 1999; 24(23):2525-2535.
(180) Hakkinen A, Kautiainen H, Jarvenpaa S, Arkela-Kautiainen M, Ylinen J. Changes in the total Oswestry Index and its ten items in females and males pre- and post-surgery for lumbar disc herniation: a 1-year follow-up. Eur Spine J 2007; 16(3):347-352.
(181) Pietrobon R, Taylor M, Guller U, Higgins LD, Jacobs DO, Carey T. Predicting gender differences as latent variables: summed scores, and individual item responses: a methods case study. Health Qual Life Outcomes 2004; 2:59.
(182) Vroomen PC, de Krom MC, Knottnerus JA. Predicting the outcome of sciatica at short-term follow-up. Br J Gen Pract 2002; 52(475):119-123.
(183) Mayer HM. [The delayed OP--indications for surgery of lumbar disc herniations]. Z Orthop Ihre Grenzgeb 2005; 143(3):287-291.
(184) Rothoerl RD, Woertgen C, Brawanski A. When should conservative treatment for lumbar disc herniation be ceased and surgery considered? Neurosurg Rev 2002; 25(3):162-165.
(185) Nygaard OP, Kloster R, Solberg T. Duration of leg pain as a predictor of outcome after surgery for lumbar disc herniation: a prospective cohort study with 1-year follow up. J Neurosurg 2000; 92(2 Suppl):131-134.
(186) Ng LC, Sell P. Predictive value of the duration of sciatica for lumbar discectomy. A prospective cohort study. J Bone Joint Surg Br 2004; 86(4):546-549.
(187) Nygaard OP, Romner B, Trumpy JH. Duration of symptoms as a predictor of outcome after lumbar disc surgery. Acta Neurochir (Wien) 1994; 128(1-4):53-56.
(188) Spengler DM. Lumbar discectomy. Results with limited disc excision and selective foraminotomy. Spine 1982; 7(6):604-607.



CURRICULUM VITAE
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Curriculum Vitae

Willem Cornelis Peul was born on October 20, 1963 in Rotterdam, The Netherlands. He obtained his Athenaeum diploma at the Marnix College in Rotterdam in June 1983. In august 1983 he entered Medical School at the Erasmus University of Rotterdam and received his Medical Doctor degree in july 1989. During the following 2.5 years he subsequently worked at the departments of Neurosurgery of AZR Dijzigt, Rotterdam, and AMC, Amsterdam, as a medical doctor. In Rotterdam his epidemiological interest for spine surgery related research started during medical training, under the supervision of professor Reinder Braakman.

In February 1992 he began his training as a resident in Neurosurgery at the Westeinde Hospital in The Hague (Chairman: Hans Wurzer). In 1994 at the same hospital he was for one year trained in Neurology (Chairman: Joseph Tans) and in 1995 in General Surgery (Chairman: Bob Koumans). From 1996 until 1997 he worked as a resident at the Neurosurgical Department of the Leiden University Medical Center (Chairman: professor Raph Thomeer) where his interest in spine surgery and related research was intensified. In February 1998 he finished his residency program as a neurosurgeon in The Hague.

He subsequently started working as a Neurosurgeon at the Leiden University Medical Center. From that time on the research questions and design of the protocol for the presented thesis started, a NWO (ZonMW) grant was successfully pursued for the present study and an epidemiological training was followed at the EMGO institute (Chairman; professor Lex Bouter) of the VU Medical Center Amsterdam, practical supervision (professor Bart Koes) and finished successfully with a Master of Epidemiology degree in April 2005. Subsequently he became a member of the editorial board of Cochrane Back Review group and participated as a post-graduate trainer in spinal surgery for the European Association of Neurological Surgeons (EANS). Since september 2004 he works as a Neurosurgeon in the Medical Center The Hague and is principal investigator of the Leiden-The Hague Spine-Intervention-Prognostic-Study (SIPS) Group of the department of Neurosurgery at the Leiden University Medical Center.

List of publications

Peul WC, Brand R, Thomeer RT, Koes BW.
Influence of gender and other prognostic factors on outcome of sciatica; a post-hoc analysis of a randomized trial.
Accepted for publication by Pain (in press 2008)

Luijsterburg PA, Verhagen AP, Ostelo RW, van den Hoogen HJ, Peul WC, Avezaat CJ, Koes BW.
Physical therapy plus general practitioners' care versus general practitioners' care alone for sciatica: a randomised clinical trial with a 12-month follow-up.
Eur Spine J. 2008 Jan 3

Peul WC, Van Houwelingen HC, Van den Hout WB, Brand R, Eekhof JA, Tans JT, Thomeer RT, Koes BW.
[Early surgery or a wait-and-see policy in lumbosacral radicular syndrome: a randomized study]
Ned Tijdschr Geneeskd. 2007 Nov 10;151(45):2512-23.

Arts MP, Nieborg A, Brand R, Peul WC.
Serum creatine phosphokinase as an indicator of muscle injury after various spinal and nonspinal surgical procedures.
J Neurosurg Spine. 2007 Sep;7(3):282-6.

Bartels RH, Peul WC.
Mini-thoracotomy or thoracoscopic treatment for medially located thoracic herniated disc?
Spine. 2007 Sep 15;32(20):E581-4.

Luijsterburg PA, Lamers LM, Verhagen AP, Ostelo RW, van den Hoogen HJ, Peul WC, Avezaat CJ, Koes BW.
Cost-effectiveness of physical therapy and general practitioner care for sciatica.
Spine. 2007 Aug 15;32(18):1942-8.

Koes BW, van Tulder MW, Peul WC.
Diagnosis and treatment of sciatica.
BMJ. 2007 Jun 23;334(7607):1313-7. Review.

Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, Thomeer RT, Koes BW; Leiden-The Hague Spine Intervention Prognostic Study Group.
Surgery versus prolonged conservative treatment for sciatica.
N Engl J Med. 2007 May 31;356(22):2245-56.

Boszczyk B, Timothy J, Peul W, Casey AT.
Neurosurgical training and the spine: reflections on EANS winter meeting Luxembourg, February, 2006.
Acta Neurochir (Wien). 2007;149(4):339.

Luijsterburg PA, Verhagen AP, Ostelo RW, van Os TA, Peul WC, Koes BW.
Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review.
Eur Spine J. 2007 Jul;16(7):881-99.

Nandoe Tewarie RD, Bartels RH, Peul WC.
Long-term outcome after anterior cervical discectomy without fusion.
Eur Spine J. 2007 Sep;16(9):1411-6.

Arts MP, Peul WC, Brand R, Koes BW, Thomeer RT.
Cost-effectiveness of microendoscopic discectomy versus conventional open discectomy in the treatment of lumbar disc herniation: a prospective randomized controlled trial.
BMC Musculoskelet Disord. 2006 May 13;7:42.

Arts M, Pondaag W, Peul W, Thomeer R.
Nerve root decompression without fusion in spondylolytic spondylolisthesis: long-term results of Gill's procedure.
Eur Spine J. 2006 Oct;15(10):1455-63.

de Graaf I, Prak A, Bierma-Zeinstra S, Thomas S, Peul W, Koes B.
Diagnosis of lumbar spinal stenosis: a systematic review of the accuracy of diagnostic tests.
Spine. 2006 May 1;31(10):1168-76.

van Rijn JC, Klemetso N, Reitsma JB, Bossuyt PM, Hulsmans FJ, Peul WC, den Heeten GJ, Stam J, Majoie CB.
Observer variation in the evaluation of lumbar herniated discs and root compression: spiral CT compared with MRI.
Br J Radiol. 2006 May;79(941):372-7.

Wolfs JF, Peul WC, Boers M, van Tulder MW, Brand R, van Houwelingen HJ,Thomeer RT.
Rationale and design of The Delphi Trial--I(RCT)2: international randomized clinical trial of rheumatoid craniocervical treatment, an intervention-prognostic trial comparing 'early' surgery with conservative treatment. BMC Musculoskelet Disord. 2006 Feb 16;7:14.

Schenk B, Brouwer PA, Peul WC, van Buchem MA.
Percutaneous laser disk decompression: a review of the literature.
AJNR Am J Neuroradiol. 2006 Jan;27(1):232-5.

van Rijn JC, Klemetso N, Reitsma JB, Majoie CB, Hulsmans FJ, Peul WC, Bossuyt PM, Heeten GJ, Stam J.
Symptomatic and asymptomatic abnormalities in patients with lumbosacral radicular syndrome: Clinical examination compared with MRI.
Clin Neurol Neurosurg. 2006 Sep;108(6):553-7.

Peul WC, van Houwelingen HC, van der Hout WB, Brand R, Eekhof JA, Tans JT, Thomeer RT, Koes BW.
Prolonged conservative treatment or 'early' surgery in sciatica caused by a lumbar disc herniation: rationale and design of a randomized trial.
BMC Musculoskelet Disord. 2005 Feb 11;6:8.

van Rijn JC, Klemetsö N, Reitsma JB, Majoie CB, Hulsmans FJ, Peul WC, Stam J, Bossuyt PM, den Heeten GJ.
Observer variation in MRI evaluation of patients suspected of lumbar disk herniation.
AJR Am J Roentgenol. 2005 Jan;184(1):299-303. Erratum in: AJR Am J Roentgenol. 2005 Mar;184(3):1027.

Luijsterburg PA, Verhagen AP, Ostelo RW, van den Hoogen HJ, Peul WC, Avezaat CJ, Koes BW.
Conservative treatment in patients with an acute lumbosacral radicular syndrome: design of a randomised clinical trial.
BMC Musculoskelet Disord. 2004 Nov 9;5(1):39.

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APPENDIX

Study Group, Recruitment and Data Collection and Management—M. Nuyten, P. Bergman, G. Holtkamp, S. Dukker, A. Mast, L. Smakman, C. Waanders, L. Polak and A. Nieborg; *Participating Hospitals and coordinating physicians—Medical Center Haaglanden, The Hague*—J.Th.J. Tans and R. Walchenbach; *Diaconessen Hospital, Leiden*—J. van Rossum and P. Schutte; *Groene Hart Hospital, Gouda*—G.A.M. Verheul, J.E. Dalman and J.A.L. Wurzer; *Reinier de Graaf Hospital, Delft/Voorburg*—J.W.A. Sven and A. Kloet; *Spaarne Hospital, Heemstede/Haarlem*—I.S.J. Merkies and H. van Dulken; *Bronovo Hospital, The Hague*—P.C.L.A. Lambrechts and J.A.L. Wurzer; *Haga Hospital, The Hague*—R.W.M. Keunen and C.F.E. Hoffmann; *Rijnland Hospital, Leiderdorp/Alphen ad Rijn*-J. Haan and H. van Dulken; *Lange Land Hospital, Zoetermeer*—R. Groen and R.R.F. Kuiters; *Leiden University Medical Center, Leiden*—R.A.C. Roos, and, J.H.C. Voormolen; General Practioners, Leiden/ Oegstgeest/ Leiderdorp/ Zoetermeer/ Gouda/ Delft/ Heemstede/ Voorburg/ Wassenaar/ The Hague—J.A.H. Eekhof and the neurologists, radiologists and surgical theatres of these regional hospitals.

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