THE ACUTE LUMBOSACRAL RADICULAR SYNDROME

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1 CHAPTER

General Introduction

BACKGROUND

Case description

An everyday situation at the Outpatient Neurology Clinic: Robert is a 45 years old man presenting with severe pain radiating into the left leg, all the way down to his little toe. By the time he presents to his neurologist, he already has symptoms for almost 8 weeks. Robert visited his General Practitioner first who diagnosed him with a lumbosacral radicular syndrome and prescribed Tramadol, an opioid, and physiotherapy as a treatment, unfortunately to no effect.

Robert works as a construction worker, a physically demanding job, but cannot work at the moment due to disabling pain. He has no relevant medical history. At neurological examination, there is a diminished sensation of the lateral side of the left foot together with the absence of the Achilles tendon reflex. His neurologist decides to make an MRI of the lower spine, which shows a herniated disc at the left L5-S1 level thereby confirming the diagnosis. Back at the neurologist's office, Robert and his neurologist discuss possible treatments to reduce his pain and to improve his functioning. Is there a need for surgery? Or should he try a corticosteroid injection at the Pain Department first? Robert's wife told him the latter might be successful and even replace 'risky surgery'.

This case story is the starting point of this PhD-thesis.

Definition and terminology

Sciatica, or lumbosacral radicular syndrome, is a disabling condition that is characterized by radiating leg pain, with or without low back pain. In the Netherlands, the term 'sciatica' (or '*ischias*' in Dutch) has been largely replaced by 'lumbosacral radicular syndrome'. However, in (American-)English 'sciatica' is the more common term. As this thesis originates from the Netherlands, but contains articles that have been published internationally, both terms are used.

Patients with a lumbar radicular syndrome may experience tingling or pricking in the dermatomal distribution of a nerve root, but sensory symptoms are usually minor[1]. Paresis, such as foot drop due to weakness of the anterior tibial muscle (in case of L5 radiculopathy), is present in less than half of patients[1]. In more than 85% of cases, lumbar radicular syndrome is caused by a herniated lumbar disc where the nerve root is compressed by disc material that has ruptured through its surrounding annulus[2]. Rarer causes of 'radiculopathy' include spondylolisthesis, lumbar stenosis, foraminal stenosis, and malignancy[1]. The common denominator of all of these causes is the fact that the lumbar nerve root is irritated, which may in turn resulted in inflammation. The latter is evidenced by a range of pro- and anti-inflammatory proteins that have been found in serum, cerebrospinal fluid (CSF) and biopsies of patients with lumbosacral radicular syndrome, including interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α[3-5]. Evidence suggests that it is not so much the pressure on the nerve root that causes lumbosacral radicular syndrome, but a combination of pressure-related, inflammatory, and immunological processes[6,7].

Epidemiology

The prevalence and incidence of the lumbosacral radicular syndrome, as reported in the literature, vary widely due to different definitions and methods of data collection[8]. The yearly incidence of lumbosacral radicular syndrome in the Netherlands has been estimated at 9 per 1000 patient-years[9] and the yearly prevalence has been estimated at 17.2 per 1000 patient-years[9]. In a recently published Danish study, the prevalence of lumbosacral radicular syndrome among primary care patients with low back pain ranged from 2 to 11% in chiropractic clinics and general practices, respectively[10].

The consensus is that the prognosis of the lumbosacral radicular syndrome is favourable. That is, within three months, circa 75% of patients are expected to reach bearable pain levels and to be able to resume their work without surgery[11]. Nonetheless, a recent

UK-based study of patients seeking primary care for back-related leg pain, including the lumbosacral radicular syndrome, showed that only 55% of the patients with a lumbosacral radicular syndrome had more than 30% reduction in disability 1 year later[12].

Economic Burden

The economic burden of neck and back pain in general is substantial. In the Netherlands, the direct total costs for neck and back pain together were estimated at €905 million in 2019, which included the cost of 24,000 surgeries. Indirect costs (e.g. productivity losses) should be added to this number[13]. There is limited research on the economic burden of the lumbosacral radicular syndrome in particular. In a British cohort from 2019, containing 609 adults, the mean annual total societal cost per patient with a lumbar radicular syndrome was estimated to be £1106. The largest proportion (65%) of these costs incurred were due to productivity losses[14].

History and examination

Patients with a lumbosacral radicular syndrome are primarily diagnosed and treated by general practitioners (GPs)[15]. No single symptom reported during history taking or result on a physical test is sensitive or specific enough to conclusively diagnose a lumbosacral radicular syndrome. Therefore, clinical guidelines recommend a combination of history taking and physical tests in order to come to a final diagnosis[7].

Symptoms and signs that should be addressed during history taking are[7,16]: the dominance of leg pain (more leg pain than back pain); the radiation pattern of the leg pain (according to one or more dermatomes); the presence of tingling and/or sensory loss (roughly) according to the dermatomes of the affected spinal root; weakness and/or reflex changes in a myotomal distribution; and an increase in leg pain with coughing, sneezing, and/or taking a deep breath.

The physical examination of the patient with suspected lumbosacral radicular syndrome usually includes: testing the strength of the leg muscles using the Medical Research Council (MRC) scale; sensory examination: tests for perception of light touch, pin prick, and vibration sense of the lower extremities; reflex examination: tests for reflexes of the patella (L3,L4) and ankle (S1); straight leg raise test: with the patient laying on the back, one extended leg is lifted upwards. The straight leg raise test or Lasègue is positive if the patient experiences radicular pain when the leg is at an angle between 30 and 70°. A finger-floor distance of more than 25 cm, absence of knee or ankle tendon reflex, leg

paresis and a positive straight leg raise test are an indication for a herniated disk with nerve compression on MRI[16]. However, it is important to realize that the additional value of the neurological examination is limited, because most of the relevant information revealed by physical testing has been demonstrated by during the neurological history taking[7].

Diagnostic procedures

Magnetic resonance imaging (MRI) is considered the imaging procedure of choice for patients, in whom lumbar-disc herniation is suspected[17,18], and is frequently performed in patients with persistent or recurrent symptoms of a lumbosacral radicular syndrome. However, the association between findings on an MRI and symptoms is controversial, with several studies showing a high prevalence of disc herniation, ranging from 20 to 76%, in persons without any symptoms[19,20]. Therefore, an MRI is not recommended as a standard procedure in the Dutch clinical guidelines[15,21] but is recommended to be reserved for candidates for invasive treatment (surgery or epidural corticosteroid injection) or patients with so called 'red flags' that may indicate underlying serious pathology. While most guidelines recommend screening for 'red flags', there is variation regarding the red flags that are endorsed, and heterogeneity exists with respect to the precise definitions of the red flags. To illustrate, *Verhagen et al* identified 46 different 'red flags' in 16 different guidelines[22]. Well-known red flags are nocturnal back pain (that suggests an underlying tumour) or fever (that suggests an infection).

Other diagnostic procedures in patients with a lumbosacral radicular syndrome are needle electromyogram (EMG) and selective diagnostic nerve blocks. The EMG is carried out by a clinical neurophysiologist (within the hospital setting) and can aid to the diagnosis by revealing a topographic distribution of muscular denervation corresponding to a nerve root[23]. However, its role in a lumbosacral radicular syndrome has not been established and the latest Dutch multidisciplinary guideline[21] does therefore not recommend an EMG. Another option would be a selective diagnostic nerve block. Selective diagnostic nerve blocks are performed by anaesthesiologists to determine if a specific, isolated nerve root is the source of pain[24,25]. Similar to the EMG, however, they have limited value and are not recommended by the same Dutch multidisciplinary guideline[21].

Treatment

According to the Dutch GP's guideline[15] treatment of the lumbosacral radicular syndrome preferably consists of pain treatment by taking analgesics if needed, referral to physiotherapy, and the advice to maintain, or resume, normal daily activities as much as possible. If patients do not recover within six weeks, they are referred to secondary care for further diagnosis and treatment. In the Netherlands, 16% of lumbosacral radicular syndrome patients are referred to secondary care (hospital), of which 70% to a neurologist and 14% to an anaesthesiologist[26].

Within the secondary care setting, there are two treatment modalities, invasive procedures in the Pain Department (epidural corticosteroids or pulse radio frequency) and disc surgery. With regard to surgery, there is international consensus that surgery should only be offered if symptoms persist after a period of conservative treatment[27]. However, there is no agreement on how long conservative therapy should last before surgery. The Dutch multidisciplinary guideline[21] recommends offering the patient the option of surgery if symptoms do not improve after three months of conservative treatment. It is important to mention that patients with severe pain, irresponsive to pain medication or epidural corticosteroid injections, or patients with neurological deficits, such as cauda syndrome or paresis, will be operated immediately regardless of the duration of these complaints.

Epidural corticosteroid injections are increasingly used as an alternative to pain medication in patients with lumbosacral radicular syndrome, especially in acute patients with severe pain. In the United Kingdom, for example, the number of epidural injections increased with 49%, from 47,803 in 2000 to 70,967 in 2010[28]. Moreover, in a retrospective US cohort, epidural corticosteroid injections were found to have increased by 609% from 2000 to 2014[29].In spite of their increasing popularity, however, the role of epidural steroids is much-debated and therefore the main topic of this thesis.

Epidural Corticosteroids

Epidural corticosteroid injections against the lumbosacral radicular syndrome were first introduced around 1900[30]. There are currently three different techniques for epidural injection: 1) caudal, 2) interlaminar and 3) transforaminal. The caudal approach is the oldest technique, performed by inserting a needle through the sacral hiatus to gain entrance into the sacral epidural space, and has largely been replaced by the other two methods. Of them, most pain physicians in the Netherlands prefer a transforaminal

approach (transforaminal epidural steroid injections or TESIs), because it is regarded as more effective than the interlaminar technique[31]. However, more recent data show equivalence between the two[32,33]. Moreover, a wide variety of injection fluids is used, including local anaesthetics (e.g. Procaine or Levobupivacaine) and glucocorticosteroids or 'steroids' (e.g. methylprednisolone and triamcinolone)[34].

During recent years, the effectiveness and safety of epidural steroids against the lumbosacral radicular syndrome have been widely discussed within the international medical community. A meta-analysis that was based on six systematic reviews, and was a part of the Dutch multidisciplinary guideline[21,35-40], found a statistically significant, but small, short-term (<3 months) effect for leg pain of epidural corticosteroids versus placebo; i.e. an improvement of 0.94 on a 10-point visual analogue scale (VAS).

In 2014, the American Food and Drug Administration (FDA) issued a safety warning after several neurologic events had been reported in patients undergoing epidural corticosteroids, including some fatal events of spinal cord infarction and stroke[41]. However, serious complications of injections below conus-level (L2) appear to be rare and are usually limited to nausea, headache, dizziness, vasovagal attacks, and flushing of the face[42-46].

Given the above, it is important to carefully select patients that are likely to benefit most from epidural steroids (not only in terms of symptoms, but also in terms of costs), while closely monitoring their safety. Because patients with lumbosacral radicular syndrome present acutely, the hypothesis underlying this thesis is that early adequate pain management with epidural steroids might be helpful against pain and to improve functioning. Early intervention might possibly also prevent chronification and possibly surgery. The acute stage of the lumbosacral radicular syndrome has hardly been addressed by randomized controlled trials (RCTs) before and therefore we* decided for a trial that specifically addresses patients with short lasting symptoms (< 8 weeks), i.e. the STAR-(STeroids Against Radiculopathy)-trial.

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* *'We' refers to the STAR-research team consisting of neurologists, anesthesiologists and radiologists of the OLVG Teaching Hospital, Amsterdam and Zaans Medical Center, Zaanstad, the Netherlands along with researchers of the Amsterdam Movement Sciences research institute.*

AIM OF THIS THESIS

With regard to epidural corticosteroid injections, there are several knowledge gaps worth investigating:

- How are transforaminal epidural steroid injections used in daily practice given the current scientific evidence and safety data?
- Is there an underlying inflammatory substrate in patients with lumbosacral radicular syndrome, justifying the use of (epidural) corticosteroids?
- Would an early intervention (<8 weeks) with transforaminal epidural steroid injections be (cost-)effective in patients with a lumbosacral radicular syndrome compared with usual care?

Therefore, this thesis aims to answer the following questions:

Question 1 *What is the historical evolution of epidural corticosteroid injections from ancient times to present?*

Question 2 *How do neurologists and anaesthesiologists in The Netherlands diagnose and treat patients with an acute lumbosacral radicular syndrome in daily practice?*

Question 3a *What inflammatory biomarkers have been identified in patients with* a *lumbosacral radicular syndrome in the literature so far?*

Question 3b *Is there an association between the level of inflammatory activity and clinical symptoms?*

Question 4 *What is the effectiveness of transforaminal epidural steroid injections in patients with acute lumbosacral radicular syndrome due to a herniated disc, compared to usual care and compared to a transforaminal injection wil local anesthetic and saline solution?*

Question 5 *What is the cost-effectiveness of transforaminal epidural steroid injections in patients with acute lumbosacral radicular syndrome due to a herniated disc, compared to usual care and compared to a transforaminal injection wil local anesthetic and saline solution from a societal perspective?*

OUTLINE OF THIS THESIS

The overall goal of this thesis was to contribute to best clinical practice during the acute stage of the lumbosacral radicular syndrome, defined as the first 8 weeks. The main focus is on transforaminal epidural steroid injections, which are increasingly used as an alternative to pain medication in patients with lumbosacral radicular syndrome, especially in acute patients with severe pain. This thesis consists of three different research themes. The three themes are briefly described below.

Theme 1 is entitled *'Diagnosis and treatment of the acute lumbosacral radicular syndrome'* and contains a historical overview of the use of epidural steroids against lumbosacral radicular syndrome (**chapter 2**) followed by a cross sectional survey among neurologists and anaesthesiologists assessing lumbosacral radicular syndrome (**chapter 3**).

Theme 2 is entitled *'Inflammation'* and contains a systematic review on inflammation as an underlying pathogenic mechanism in lumbosacral radicular syndrome (**chapter 4**).

Theme 3 is entitled '*(Cost-)effectiveness of transforaminal epidural steroid injections'* and contains the design (**chapter 5**), statistical analysis plan (**chapter 6**), effectiveness results (**chapter 7**), and cost-effectiveness results (**chapter 8**) of the 'steroids against radiculopathy' (STAR)-trial. The STAR-trial is a randomized controlled trial evaluating the (cost-)effectiveness of transforaminal epidural steroid injections against acute lumbosacral radicular syndrome.

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1

GUIDELINE

Diagnosis and treatment of the lumbosacral radicular syndrome

Eur Neurol. 2016;75(1-2):58-64.

2 CHAPTER

The epidural treatment of sciatica its origin and evolution.

Ter Meulen BC, Weinstein H, Ostelo R,
Koehler PJ.

ABSTRACT

Epidural injection with corticosteroids is a common treatment option for patients with low back pain or sciatica. In this paper we review its history. The first injections were given around 1900 in Paris by Jean Sicard (1872-1929) and Fernand Cathelin (1873-1945), who worked independently. They both injected small volumes of cocaine into the sacral hiatus. After a slow start, the epidural treatment of back pain and sciatica gradually spread to other parts of Europe and Northern America. In the early 1950s corticosteroids were introduced for epidural use. Since the 1970s there have been numerous clinical trials that show a significant, although small, effect of epidural corticosteroid injections compared with placebo for leg pain in the short term. Despite an ongoing debate about effectiveness and safety epidural injections remain popular.

INTRODUCTION

Epidural injection with corticosteroids is a common treatment option for patients with low back pain or sciatica[1]. The injections may offer rapid relief from pain in acute patients and may be a good treatment alternative for patients, who for some reasons, technically or motivationally, can or will not undergo spinal surgery. There is even a category of chronic pain patients who visit the pain clinic every couple of weeks to get repeated injections.

The first epidural injections were given around 1900 in Paris, not with corticosteroids, but with cocaine. In this paper we trace the history of the injections. Our interest is not so much in historical facts and figures for their own sake (out of curiosity), but to see how a common medical treatment evolved from a modest laboratory to a booming worldwide practice[2], despite an ongoing debate about effectiveness and safety. We refer to **Table 1** for a chronological overview.

TABLE 1 Timeline of the epidural treatment of sciatica

Year	Country	Description
1885	USA	First spinal puncture by Corning
1895	Germany	Intrathecal infusion of cocaine by Bier
1901	France	First caudal epidural injections by Sicard and Cathelin
1925	Canada	Viner uses Novocain to treat sciatica.
1930	UK	Evans successfully treats 24/40 patients with Procaine.
1952	Italy	Robecchi and Capra use corticosteroids for the first time.
1953	France	Lièvre et al publish a series of patients treated with epidural corticosteroids
1961	USA	Goebert et al: first series in the USA
1960s-1970s		Uncontrolled studies
1970s-now		Randomized, controlled trials

TWO MINDS BUT WITH A SINGLE THOUGHT?

We are not sure who was the first to treat a patient with an epidural pain injection in the lower back. There are two claims. It is true that Jean Anasthase Sicard (1872-1929) was the first to mention the injections publicly, when he addressed the members of the *Societé de Biologie* in Paris on April 20th, 1901[3]. However, at the time Sicard gave

his speech, Fernand Cathelin (1873-1945), also from Paris, had been treating patients with epidural injections for some months already. See **Figure 1** for their portraits. It is important to realize that both men were not inventors in the true sense: they simply perfected anesthetic techniques that had been described before, most notably by the American James Corning (1855-1923) and the German August Bier (1861-1949).

FIGURE 1 Two minds but with a single thought? Sicard (left) and Cathelin presented their data on epidural injections against low back pain and sciatica almost at the same time.

The first direct spinal puncture in a living person is often credited to Corning, who in 1885 injected a cocaine solution into the epidural space at the T11-T12 level of a man, who was habituated to masturbation and suffered from "spinal weakness and seminal incontinence"[4,5]. In 1895, Bier successfully anesthetized the lower body of one of his residents by injecting a cocaine solution into the intrathecal space. Unfortunately, the procedure was complicated by severe headache due to intracranial hypotension lasting for more than one week[6].

Bearing the work of Corning and Bier in mind, Sicard started his research on the spine in 1896, when he became an intern at the laboratory of the neurologists Fulgence Raymond (1844-1910) and Edouard Brissaud (1852-1909) at the famous *Hôpital de La Salpetrière*. At the beginning of his project, his goal was twofold: 1) to regard the spine from a clinical point of view, rather than from a mere anatomical or physiological perspective; 2) to administer medicinal fluids into the spine, instead of withdrawing cerebrospinal fluid by lumbar puncture[7].

Sicard experimented on animals first. He was able to anesthetize the lower body of several dogs easily by injecting a small amount of cocaine, not between the lumbar vertebrae, as Bier had done, but by using, what has since been known as, the "caudal route". Sicard passed a needle through the (first) dorsal sacral foramen to gain access to the sacral roots. Hereby he left the outermost layer of the meninges intact, carefully confining himself to the epidural space. After his experiments with dogs, Sicard performed similar injections in human cadavers to improve his skill, and finally injected patients suffering from pain[3,7].

On April 20th 1901, Sicard presented the data of 9 of his patients during a weekly meeting of the *Societé de Biologie* in Paris. Two suffered from syphilitic myelopathy, two had low back pain and four had sciatica. The treatment was painless, safe and (most importantly) successful:

> *Tous nos malades ont été immédiatement soulagés. Il est vrai que les deux tabétiques n'ont vu leurs douleurs fulgurantes disparaître que pour douze à vingt heures, mais, par contre, la guérison s'est maintenue depuis quatorze jours chez les deux maladies atteints de lumbago, ainsi que dans deux des cas de sciatique rebelle. Les deux autres malades atteints de sciatique sont toujours très soulagés durant deux à trois jours à chaque nouvelle injection[3].*

[All our patients were relieved immediately. It is true that the two patients with tabes only saw their fierce pains disappear for 12 to 20 hours, but, to the contrary, recovery has been maintained for 14 days in the two patients with low back pain as well as in 2 resistant cases of sciatica. The two other patients with sciatica have been relieved for 2 to 3 days after each new injection].

Only a week after Sicard had presented his data, Fernand Cathelin, who worked as a resident in urology, was quick to come up with similar data. In front of the same audience at the *Societé de Biologie*, he made a clear statement:

> *Toute question de priorité étant écartée, nous avons expérimenté, M. Sicard et moi, simultanément et indépendamment l'un de l'autre[8].*

[Let's not talk about priority, Mr. Sicard and I, have experimented simultaneously and independently from one another].

Cathelin also used the caudal approach with cocaine to anesthetize his patients, but unfortunately his results were not as positive as those by Sicard. Four patients that needed inguinal repair were anesthetized only partly. Cathelin suggested he should have increased the dosage. With our current knowledge we can conclude that Cathelin probably injected "too low" and should have injected a higher, lumbar level of the spine, in order to anesthetize the inguinal region.

In his PhD-thesis, published in 1903, Cathelin was far less tactful when it came to priority[9]. In a lengthy argumentation, he left no doubts that he was the first and only one to have introduced the caudal epidural injection. According to Cathelin, Sicard had absolutely "no right" to claim any priority.

> *Nous restons donc le premier à avoir expérimenté cette méthode sur l'animal et le seul à avoir fourni un protocole complet, le premier et le seul à en avoir donné un théorie, le premier…[9].*

[So we remain the first to have experimented with this method in animals and the only to have provided a complete protocol, the first and only to have given a theory, the first to…].

In the years to follow, Sicard would become famous as "pain doctor". In particular during World War I, he performed numerous alcoholizations for painful peripheral nerve injuries, in particular causalgia[10,11]. Sicard is also known as the founder of contrast radiology. In 1921 Sicard and Jacques Forestier (1890-1978) made the first epidurogram by injecting

contrast fluid in the epidural space, followed by examination of the subarachnoid space and myelography[12,13]. Cathelin became chief surgeon at the Hôpital d 'Urologie, Paris, and was primarily interested in surgery and related anesthetic techniques, rather than pain management.

SOME IDEAS ARE QUICK, OTHERS SLOW

Some innovations in the history of medicine spread quickly. For example the discovery of ether to anesthetize patients in 1846 spread across the Atlantic from Boston to Paris and London in only 4 weeks[14]. Other possibly good ideas, on the contrary, travel slowly: major, international publications about the epidural treatment of sciatica appeared only 2-3 decades after the initial descriptions by Sicard and Cathelin.

In 1925 Viner from Montreal, also employed the caudal approach, but used Novocain instead of cocaine[15]. See **Figure 2**. He repeated the injections in patients with sciatica three to four times at weekly intervals, with good outcome. He wrote: "this method is very effective in giving relief in intractable (and ordinary) sciatica. In most cases it restores the patient to his occupation and in practically all cases speedily gives marked relief from pain". The adjective "Intractable"' referred to the often unknown origin of the pain. It should be noted that the herniated disc that is currently known as the most frequent cause of sciatica was not widely known until 1934 by Mixter and Barr[16].

FIGURE 2 The caudal approach according to Viner (1925).

In 1930 Evans reported treating 40 patients with “idiopathic sciatica” by caudal injection of normal saline and procaine hydrochloride[17]. Sciatica was relieved completely in 24 patients and “considerable benefit” occurred in 6 patients. Evans was the first to inject large volumes. He demonstrated that injection of 100 ml of fluid into the epidural space at the base of the sacrum caused diffusion of the fluid throughout the spinal canal.

COMPOUND E AND THE QUEST FOR EVIDENCE

In the early 1920s, animal research at the Mayo Clinic led to the discovery of cortisone or “compound E”[18]. Shortly after the World War II the first patients with rheumatoid arthritis were treated[19]. The results were spectacular, almost like an “awakening”, making corticosteroids the cornerstone of rheumatism treatment ever since. In 1952, Robecchi and Capra, two Italian rheumatologists from Torino, speculated that not only rheumatic disease, but low back pain as well as sciatica were also caused by inflammation, an important hypothesis that still holds today. Their first description (in Italian) was of a woman with sciatica, who reported successful pain relief after ”periradicular” infiltration with hydrocortisone of the first sacral nerve root[20]. Hydrocortisone or “compound F” is a steroid with a longer lasting effect that was discovered in the early 1950s. Soon, more articles followed, most of them in French and Italian. *Lièvre et al.* treated 46 patients with sciatica with hydrocortisone. Of these 8 had a very good response, 15 good and 8

mediocre[21]. *Goebert et al.* were the first to report the use of epidural corticosteroids against sciatica in the United States: three injections of procaine and hydrocortisone caused greater than 60% relief of symptoms in 58% of patients (N=239)[22].

The most important uncontrolled trials between 1950 and 1990 are summarized in the table, adapted from Nelson and Landau (**Table 2**)[21-29]. The reader should be aware that the table only shows data from epidural administration of corticosteroids. Intrathecal injections were popular for a short period during the 1960s[30,31], but the risk of meningitis has made this approach uncommon in modern pain management. Apart from being uncontrolled, the studies mentioned in the table have various other methodological shortcomings. Most of them are unblinded, contain small numbers of patients, and have a retrospective design. However, despite their often poor quality, the older studies contributed to wide acceptance and worldwide use of corticosteroids against sciatica.

TABLE 2 The most important uncontrolled studies[23]

First author, year	N	Study design	Patients with pain relief (%)*
Lièvre, 1953	20	retrospective	25 at 3 weeks
Brown, 1960	20	retrospective	100 at 52 weeks
Goebert, 1960	239	retrospective	6 at 12-130 weeks
Goebert, 1961	113	retrospective	83 at> 12 weeks
Winnie, 1972	10	Prospective	100 at 2-104 weeks
Rosen, 1988	40	retrospective	25 at 1-32 weeks
Power, 1992	16	retrospective	6 at 1 week
Bowman, 1993	35	retrospective	43 at 12 weeks

*Definition of “pain relief” = excellent+ good + moderate + “not severe”

The first randomized controlled studies date from the 1970s and yielded conflicting results. For example: *Dilke et al.* investigated 100 consecutive patients with sciatica in a randomized blinded trial (epidural corticosteroids versus cutaneous saline injections) [32]. The results were labelled “striking”: patients who received epidural corticosteroids experienced less pain than controls, needed surgery less often and returned back to work sooner. *Snoek et al.,* on the contrary, showed that “extradural injection of methyl prednisolone (80 mg) is no more effective than a placebo injection in relieving chronic symptoms due to myelographically demonstrable lumbar disc herniation”[33]. A good, consistent positive response to epidural corticosteroids in patients with sciatica has not been described yet.

CURRENT STATE OF THE ART

Over the past few decades, the technique and indications for epidural injections have been changing constantly. A variety of anesthetics have been used (procaine, lidocaine, bupivacaine), as well as a number of glucocorticoids (hydrocortisone, methylprednisolone, triamcinolone). The caudal approach, originally described by Sicard and Cathelin, has largely been replaced by interlaminar and transforaminal injections that are usually given under fluoroscopical guidance. With the interlaminar approach the needle is placed in the posterior epidural space comparable to epidural catheter placement in surgery. With the transforaminal approach the needle is placed in one of the intervertebral foramina, where the spinal nerve root exits the spinal canal. Most pain physicians prefer transforaminal injections, as studies showed superiority compared to the interlaminar technique with regard to pain relief and functional status[34].

Huge numbers of epidural corticosteroids are administered every year for a variety of spine conditions manifesting with back pain and/or sciatica: herniated disk, end-stage degenerative disc disease, spinal or foraminal stenosis and failed back surgery. For patients there are two major concerns about the injections: “do they work?” and “are they safe?” The respective answers are “no” and “yes”.

The evidence in favor of epidural injections against sciatica is hardly convincing. Pinto et al analyzed the data of 23 trials (since 1984)[35]. The overall quality of evidence according to the GRADE classification was rated as high[36]. The pooled results showed a significant, although small, effect of epidural corticosteroid injections compared with placebo for leg pain in the short term (mean difference, -6.2 on a 0-100 visual analogue pain scale [95% CI, -9.4 to -3.0]) and also for disability in the short term (mean difference, -3.1 [CI, -5.0 to -1.2]). “Short term” was defined as 2-12 weeks. The long-term (> 3 months) pooled effects were smaller and not statistically significant[35].

Several studies have been conducted with regard to side-effects and safety of epidural steroid injections[37-40]. Common side-effects include nausea, headache, dizziness, vasovagal attacks, and flushing of the face. Unintentional dural puncture might cause post-spinal tap headache. Abram and O’Connor looked at 53 series of descriptions of epidurals (66 thousand patients)[41]. They only found two cases of epidural abscess, one case of bacterial meningitis, and one case of aseptic meningitis following epidural steroid injections. Other complications reported in the literature are Cushing’s syndrome due

the use of corticosteroids, dural leak in case of an accidental intrathecal puncture, air embolus and allergy. Severe complications, including spinal cord infarction and cerebral ischemia, are very rare and have only been described as case reports[42-45]. Several cases of fungal meningitis have been reported from the injection of contaminated methylprednisolone acetate[46].

To address concerns related to medication-related risks, the U.S. Food and Drug Administration (FDA) created its Safe Use Initiative (SUI) in 2009 to establish and facilitate public and private collaborations within the healthcare community. The SUI facilitated the organization of a multidisciplinary expert working group created to review the existing evidence regarding neurologic complications associated with epidural corticosteroid injections and produce consensus procedural clinical considerations aimed at enhancing the safety of these injections. Seventeen clinical considerations aimed at improving safety came out that should lead to a reduction of neurologic injuries following epidural corticosteroid injections[47,48].

Despite the rarity of severe complications, the FDA issued a letter in April 2014, warning for “loss of vision, stroke, paralysis, and death” as a result of epidural corticosteroid injections[49].The FDA advice was later countered by a number of experts in the field, who requested the FDA to modify its statement[50,51]. In their opinion the FDA should spread an evidence-based warning, emphasizing the off-label use of epidural steroids, which can cause rare, but serious neurologic problems following cervical and thoracic injections and also an increased risk with lumbar injections when performed without appropriate precautions.

The risks associated with epidural steroid injections were discussed at a meeting of the FDA’s Anesthetic and Analgesic Drug Products Advisory Committee in November 2014. Some committee members noted that the current class warning should be removed for lumbar epidural injections; however, others stated that the class warning should be continued and removal at this point would be misleading and falsely indicate that there is evidence of safety[52].

CONCLUSIONS

We identified 5 successive stages in the development of epidural corticosteroids against sciatica: 1. Pioneer stage; 2. Globalization; 3. Introduction of corticosteroids; 4. Uncontrolled trials; 5. Randomized controlled trials.

It is interesting that the first descriptions came from two different laboratories in Paris at the same time. This seems too much of a coincidence: in our opinion either Sicard or Cathelin must have "heard it through the grapevine". The fact that there are two pioneers is hardly a surprise: scientific discoveries can rarely be attributed to a single individual. The dispute between Sicard and Cathelin is just one of a long list of claims and conflicts about originality from the history of medicine[53].

Contrary to other ideas in the history of medicine, it took a long time for the epidural injections to spread around the world. This might have to do with language (French), or with the fact that the effects of caudal injections with cocaine were just not spectacular enough.

The introduction of corticosteroids in the 1950s as a panacea against all kind of pain conditions, and a number of uncontrolled, positive clinical trials during the 1960s and 1970s, contributed to wide acceptance and popularization of epidural corticosteroids against back pain and sciatica. However, the popularity of the injections seems irrational to us: the scientific proof that epidural corticosteroids are effective against back pain and sciatica is hardly convincing. More prospective data in selected populations, for example acute patients only, are needed in support of epidural corticosteroids. There are also important safety issues that have been addressed by the FDA. However, severe complications of lumbar epidural injections against back pain and sciatica are very rare.

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3

CHAPTER

Diagnosis and treatment of sciatica in the Netherlands: a survey among neurologists and anesthesiologists.

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ABSTRACT

Background

This study aimed to assess how Dutch neurologists and anesthesiologists diagnose and treat people with sciatica in secondary care and to evaluate their adherence to the newest guidelines.

Methods

We conducted a cross-sectional survey. Respondents were asked about their current clinical practice related to sciatica. Three authors rated the respondents' adherence to the guidelines on a three-point Likert scale.

Results

Eighty neurologists and 44 anesthesiologists completed the questionnaire. Neurologists diagnose their sciatica patients primarily using an MRI (89%). Selective diagnostic nerve blocks are considered useful by 81% of the neurologists. Neurologists primarily treat patients with pain medication and 40% thinks epidural steroid injections are effective in 40-60% of injected patients. Twenty-nine percent of neurologists refer patients to a neurosurgeon after 4 months. Anesthesiologists consider a selective diagnostic nerve root block to have a higher diagnostic value than mapping. The most reported side effect of epidural injections is exacerbation of pain (82%). Pulse radio frequency is applied in 9-11% of acute cases. The results also indicate that Dutch neurologists and anesthesiologists follow an evidence-based approach that is strictly or broadly in line with the guideline.

Conclusions

Neurologists treat sciatica patients initially with pain medication and physiotherapy, followed by epidural steroid injections and referral for surgery. Anesthesiologists treat sciatica patients with one or more steroid injections or may perform a selective nerve root block. Imaging, selective nerve root blocks, medication, physiotherapy and pulse radio frequency are topics of further research.

INTRODUCTION

Sciatica, or lumbosacral radiculopathy, is defined as pain, radiating from the back into the leg. Patients may also report sensory symptoms or weakness[1]. In about 85% of cases, sciatica is caused by a herniated lumbar disc with nerve root compression[2]. In the Netherlands, the mean incidence rate and prevalence rate of sciatica have been estimated at 9.4 and 17.2 per 1000 person years, respectively [3]. About half of the patients with sciatica recover within a year[4,5].

In the Netherlands, patients with sciatica are primarily treated by general practitioners (GPs). According to the Dutch GP's guideline[6], treatment of sciatica consists of pain treatment by taking analgesics if needed, referral to physiotherapy, and the advice to maintain, or resume, normal daily activities as much as possible. If patients do not recover within six weeks, they are referred to secondary care for further diagnosis and treatment. In the Netherlands, 16% of sciatica patients are referred to secondary care, of which 70% to a neurologist and 14% to an anesthesiologist[7]. In secondary care diagnostic procedures include magnetic resonance imaging (MRI) and selective diagnostic nerve root blocks. Treatments include medication, therapeutic epidural corticosteroid injections, and surgery in case of long-lasting and severe pain or dysfunction.

The management of sciatica in secondary care varies considerably within and between countries. For example, there is significant variation in the use of epidural steroid injections between different US states[8] and referral to physiotherapy between Denmark and The Netherlands[9]. These differences may be due to a paucity of evidence on the value of interventions and a lack of clear clinical guidelines, or they may reflect differences in healthcare and insurance systems[10].

We aimed to assess how Dutch neurologists and anesthesiologists diagnose and treat patients with sciatica. Our study coincides with the launch of the updated Dutch multidisciplinary guideline on sciatica[11]. This study might therefore identify important gaps between the updated evidence-based recommendations and daily practice, thereby identifying important areas for future clinical studies.

METHODS

Design

We conducted a cross-sectional survey among Dutch neurologists and anesthesiologists. The results of our study were reported in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES)[12].

Participant recruitment

From February 27th, 2020 to April 1st, 2020, neurologists and anesthesiologists were recruited: 1) by contacting the program directors of the major neurology residency programs in the Netherlands directly and asking them and (through them) their residents and staff members and their colleagues from the anesthesiology (pain) department to participate in the current study; 2) through the 12 members of the Pain Section of the Dutch Society for Neurology, all of whom were asked to participate and to invite their direct in-hospital colleagues; 3) through 'snowballing', meaning that participants were asked to invite other neurologists and anesthesiologists for participation.

For neurologists to be eligible, they had to see at least one patient with sciatica a week. This inclusion criterion was not applied for anesthesiologists, because they were assumed to treat more than one sciatica patient a week. Eventually, 260 general neurologists (including 68 residents) and 75 anesthesiologists specialized in pain medicine were invited to participate. This was done through email. We sent two reminders, including a reminder one week after the initial invitation and another one after two weeks. The total period during which the questionnaires could be completed was five weeks.

Content of the questionnaire

The survey was developed using a 3-step procedure: first, separate provisional questionnaires were developed for neurologists and anesthesiologists by a neurologist (BTM), an anesthesiologist (JWK), and an epidemiologist (RO). The survey for neurologists contained 32 general questions and three hypothetical cases with 64 questions. The survey for anesthesiologists contained 25 general questions and three hypothetical cases with 52 corresponding questions; second, the provisional questionnaires were pilot-tested and modified where necessary; third, the final questionnaires were administered using Castor Electronic Data Capture (EDC). The final questionnaires can be found in **supplementary file 1** (https://doi.org/10.6084/m9.figshare.14482848.v1). There were no incentives offered to the participants.

Analyses

The findings of the surveys were analyzed using descriptive statistics. Continuous variables were described using means and standard deviations and categorical data were described using frequencies and percentages.

To assess guideline adherence three authors (BTM, MT, BB) compared the respondents' answers to the survey to 1) the multidisciplinary guideline on sciatica ('Richtlijn lumbosacraal radiculair syndroom')11 and 2) the recommendations on the safety of epidural steroid injections for anesthesiologists in Belgium, Luxemburg and The Netherlands (WIP Benelux work group)[13]. The respondents' adherence was rated a 3-point Likert scale ('not in line with guideline'- 'broadly in line with guideline' – 'strictly in line with each guideline').

Ethical consideration and funding statement

This study was approved by the Institutional Review Board of OLVG Hospital Amsterdam, the Netherlands (January 22nd, 2020, WO 19.177). Potential respondents were informed about the study objectives as well as the fact that personal information would be protected according to General Data Protection Regulation. Clicking the link to the online survey served as informed consent. To rule out the possibility of multiple entries a uniquely generated link was generated. There was no funding.

RESULTS

Demographic characteristics

Ninety-eight neurologists (38%) and 44 anesthesiologists (59%) completed the survey. Of them, eighty neurologists met the required criterion of seeing at least one patient with sciatica a week. Characteristics of the respondents are presented in **Table 1**. In short, 75% of anesthesiologists (33/44) and 51% of neurologists (41/80) were male. Of the neurologists, 83% (66/80) were specialists and 18% (14/80) were residents. Neurologists indicated to have different sub-specialties, with 24% (16/66) focussing on pain and/or headache. The majority of both neurologists and anesthesiologists worked at a teaching hospital (60% and 53%, respectively). Neurologists treated on average four sciatica patients per week (range; 2-30), whereas anesthesiologists treated on average 11 sciatica patients per week (range; 1-50).

TABLE 1 Demographics of participants

Male sex – no. (%)	Anesthesiologists (44) 33 (75%)	Neurologists (80) 41 (51.2%)
Experience as a specialist – no. (%)	**Pain specialists**	**Neurologists – 66/80 (82.5%)**
0-5 years	10 (23%)	16/66 (24%)
6-10 years	9 (21%)	14/66 (21%)
11-15 years	9 (21%)	12/66 (18%)
15-20 years	5 (11%)	5/66 (8%)
>20 years	11 (25%)	19/66 (28.8%)
Residents – no. (%)		14/80 (18%)
Year 0[1] – year 3	-	10/14 (71%)
Year 4 – year 6		4/14 (29%)
Sub-specialty[2]		
None / general neurologist	-	16/66 (24%)
Vascular		15/66 (23%)
MS		9/66 (14%)
Pain / headache[3]		16/66 (24%)
Cognitive disorders		8/66 (12%)
Movement disorders		17/66 (26%)
Sleep disorders / epilepsy/ clinical neurophysiology		14/66 (21%)
Oncology		8/66 (12%)
Neuromuscular disorders		6/66 (9%)
Other[4]		8/66 (12%)
Main deployment – no. (%)		
Academic hospital	6 (14%)	8 (10%)
Teaching hospital	23 (52%)	48 (60%)
General hospital	9 (21%)	22 (28%)
Private practice	6 (14%)	2 (2%)

1. Year 0 meant the respondent was not a resident (yet).
2. Some neurologists had multiple sub-specialties, leading to a total of >100%.
3. Including 'radiculopathy' and 'spinal'.
4. Including: child neurology, ICU, acute neurology, vertigo, infectious neurological diseases and sports.

Neurologists: general questions

Of the neurologists, 49% (39/80) reported to follow a protocol, 44% (17/39) of whom indicated to follow a local protocol and 56% (22/39) a national guideline.

Diagnosis

Nine out of the 80 neurologists (11%) indicated that they always ordered an MRI for acute sciatica patients. Neurologists that only ordered an MRI under specific circumstances

(89%; 71/80) mostly did so in case of an abnormal neurological examination (65%; 46/71), including cauda syndrome. See **Table 2**.

Selective diagnostic nerve blocks are typically performed at a specific, isolated nerve root to determine if that particular nerve root is the source of pain. Most neurologists (81%; 65/80) considered selective diagnostic nerve blocks useful. Their main reasons for ordering a selective diagnostic nerve blocks were a mismatch between a patient's clinical symptoms and MRI (24%; 18/75) or more than one level of herniation on the MRI and a doubt about which one is symptomatic (27%; 20/75).

TABLE 2 Ordering an MRI in patients with acute sciatica (symptoms <8 weeks)

I always order an MRI for these patients, because:	11% (9/80)
I follow the wish/request of the patient	33% (3/9)
I need an MRI for confirmation of the diagnosis and reassurance	44% (4/9)
I do not want to waste time waiting for an MRI	22% (2/9)
An MRI is part of a hernia outpatient clinic	22% (2/9)
I order an MRI for these patients under the following circumstances:[1]	89% (71/80)
An abnormal neurological exam, including cauda syndrome and/or severe weakness	65% (46/71)
A history of malignancy, current B-symptoms, or 'higher age'[2]	28% (20/71)
A longer period of symptoms[3] or severe pain	61% (43/71)
An indication for surgery or epidural steroid injection	25% (18/71)
On a patient's request	27% (19/71)
In case of uncertainty about a patient's diagnosis	16% (11/71)
In case of no reaction to pain killers	9% (6/71)
Trauma	1% (1/71)
Standard MRI as part of a hernia outpatient clinics	1% (1/71)
Use of anticoagulants	1% (1/71)

[1] These numbers do not add up to 71, as respondents were allowed to give more than one answer.

[2] Mostly not specified.

[3] 'Long' being specified as >4 weeks up to >3 months

Treatment

Neurologists indicated to prescribe different kinds of oral pain medication: i.e. 65% (52/80) acetaminophen, 76% (61/80) non-steroidal anti-inflammatory drugs (NSAIDs), 59% (47/80) weak opioid analgesics, 71% (57/80) strong opioid analgesics, and 45% (36/80) neuropathic painkillers.

Thirty three percent (26/80) of neurologists indicated that they referred 0-20% of patients to a physiotherapist, 23% (18/80) indicated to refer 20-40%, 16% (13/80) indicated to refer 40-60%, and 19% (15/80) indicated to refer 60-80%. Ten percent (8/80) of neurologists indicated that they referred nearly all of their patients to a physiotherapist (i.e. 80-100%).

The most important reasons for referring sciatica patients to the Pain Department were pain severity (31%; 28/80) and insufficient pain reduction with oral painkillers (13%; 29/80). Five percent of neurologists (4/80) reported to never refer patients for the Pain Department.

Forty percent (32/80) think that epidural steroid injections are effective in 40-60% of injected patients in terms of pain reduction (69%; 55/80), improvement in functioning (16%; 13/80), and reduction in the use of painkillers (5%; 4/80) (see **Figure 1** for all other responses).

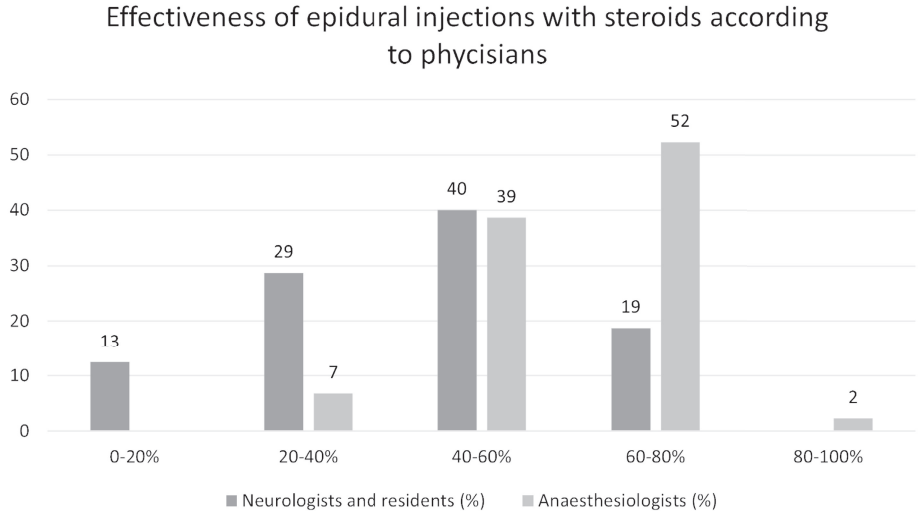

FIGURE 1 Answers to the question: 'In your experience, in which percentage of patients with sciatica are epidural injections effective?'

Of the neurologists, 58% (46/80) considered epidural steroid injections to be a short-term solution, whereas 15% (12/80) considered them to be a long-term solution.

Neurologists considered epidural steroid injections to be safe (98%; 78/80), which was mostly based on their personal experience. Other arguments are presented in **Figure 2**.

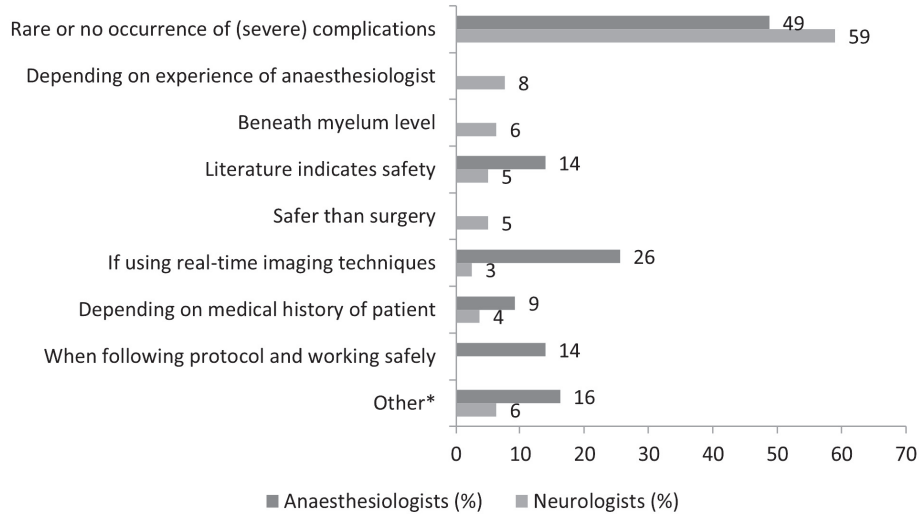

FIGURE 2 Answers to the open-ended question "Please elaborate on why you think epidural nerve blocks of the lumbar spine (L2 and below) are safe."

Of the neurologists, 60% (48/80) indicated to refer 0-20% for surgery, 29% (23/80) indicated to refer 20-40%, and 11% (9/80) indicated to refer 40-60%.

Cases

An overview of the neurologists' responses in relation to the case studies is given in **Table 3.** In summary, the neurologists' responses suggest that in the 'acute case' (case 1) neurologists' mainly focus on the adjustment of pain medication (91%), whereas imaging was only considered by 45% of the respondents. Moreover, there were hardly any referrals to a neurosurgeon (3%) and epidural corticosteroids were only considered by 14% of neurologists. For the 'sub-acute case' (case 2), 99% of respondents would order an MRI. In terms of treatment, 44% would adjust pain medication, 10% would refer the patient for an epidural steroid injection, and 33% would refer for surgery. For the 'chronic case' (case 3), almost all of the neurologists (98%) would order an MRI. In terms of treatment, 62% would adjust pain medication, 41% would refer the patient for epidural steroid injections, and 29% would refer for surgery. In all three cases, 95% of the neurologists would do follow-ups themselves. Patient-reported outcome measures, such as numerical rating scales (NRS) or visual analogues scores (VAS) scores for pain, would be used by 33-48% of the respondents.

TABLE 3 Numbers and percentages of the answers to some of the questions about the clinical cases for neurologists.

	Case 1	Case 2	Case 3
I would perform patient reported outcome measures	27/80 (33%)	36/80 (45%)	38/80 (48%)
- NRS	15/27 (56%)	19/36 (53%)	19/38 (50%)
- VAS	11/27 (41%)	17/36 (47%)	19/38 (50%)
- Other[1]	2/27 (7%)	2/36 (6%)	2/38 (5%)
I would order imaging	36/80 (45%)	79/80 (99%)	78/80 (98%)
- MRI lumbosacral spine	36/36 (100%)	79/79 (100%)	78/78 (100%)
- X-ray lumbosacral spine	-	1/79 (1%)	-
I would adjust the pain medication	73/80 (91%)	35/80 (44%)	49/80 (61%)
I would refer the patient for physical therapy	25 (31%)	-	33/80 (41%)
I would refer the patient to the Pain Department for ESI	14/80 (14%)	8/80 (10%)	33/80 (41%)
I would refer the patient to a neurosurgeon	2/80 (3%)	26/80 (33%)	23/80 (29%)
Follow-up is done by the:			
- Neurology department	76/80 (95%)	79/80 (99%)	78/80 (98%)
- Pain Department	-	-	1/80 (1%)
- General practitioner	2/80 (3%)	-	-
- Other	2/80 (3%)	1/80 (1%)[2]	1/80 (1%)[3]

(1) Quebec Back Pain Disability Scale (QBPDS), Hospital Anxiety and Depression Scale (HADS) or Pain Catastrophizing Scale (PCS). (2) Submitting the patient to the neurology ward. (3) Neurosurgeon. NRS: Numerical Rating Scale. VAS: Visual Analogue Scale (VAS).

TABLE 4 Answers to multiple choice question 'In your experience, which complications occur after epidural injections of the lumbosacral spine?'

Reported complications by anaesthesiologists	Number of answers – no. (%)
Exacerbation of pain	36 (82%)
Pain at the injection site	31 (71)
Vasovagal syncope	31 (71%)
Accidental puncture of the dura	22 (50%)
(post dural puncture) headache	18 (41%)
Infection (arachnoiditis, (aseptic) meningitis, epidural abscess)	11 (25%)
Epidural hematoma	9 (21%)
Fever the night after the procedure	5 (11%)
Persisting numbness	4 (9%)
Nausea and vomiting	3 (7%)
Other[1]	
Flushing	3 (7%)
High blood sugars in diabetic patients	2 (5%)

[1] 'Other' was an open field.

Anesthesiologists: general questions

Twenty-eight of the 44 anesthesiologists (64%) indicated to follow a protocol, of which four (14%) indicated to follow a local hospital protocol and 24 (86%) a national guideline.

Diagnosis

When asked whether they considered selective diagnostic nerve root block or mapping to be most useful, 25% (11/44) considered mapping to be most useful, whereas 61% (27/44) considered a selective diagnostic nerve root block to have the highest diagnostic value. Mapping concerns the sensory stimulation of the suspected- and adjacent nerve roots and asking the patient for recognizable paraesthesias in their painful area. Twenty-nine (66%) anesthesiologists typically perform a single selective diagnostic nerve root block, four (9%) a double selective diagnostic nerve root blocks, and 11 (25%) answered not to perform selective diagnostic nerve root blocks.

Treatment

In case of a confirmed lumbar disc herniation, 21% (9/44) of anesthesiologists would perform a single and 78% (35/44) would perform multiple epidural steroid injections. Thirty four percent (11/32) indicated that they would perform the second injection after 3-6 weeks, 22% (7/44) after 6 weeks till 3 months, and 44% (14/44) after 3-6 months. The maximum number of epidural steroid injections within 1 year ranged between 2 and 5.

Forty-two (96%) anesthesiologists inject an average amount of 2.6mL (0.75mL-5.0mL). Eighty percent (32/44) uses a combination of a corticosteroid and a local anesthetic (50% (22/44) uses lidocaine and 30 % (13/44) bupivacaine).

Fifty-two (23/44) of anesthesiologists think that epidural steroid injections are effective in 60-80% of injected patients (for all other responses see **Figure 1**). All of the anesthesiologists indicated that follow-up is done by themselves.

Safety / complications

Ninety-eight % 43 (/44) of anesthesiologists considered injections of the low lumbar spine to be safe (**Figure 2**).

The following complications of epidural steroid injections were mentioned: *'exacerbation of pain'* (36/44) and 71% responded *'pain at the injection site'* or *'vasovagal syncope'* (31/44) (**Table 4**).

Cases

An overview of the anesthesiologists' responses to the three case studies is given in **Table 5.** In summary, for both the 'acute case' (case 1) and the 'sub-acute case' (case 2), all respondents would perform an epidural steroid injection. For the 'acute presentation without imaging' (case 3), 66% (33/44) would perform an epidural steroid injection. Pulse radio frequency blockade was preferred as the first treatment by 9-11% of the respondents in all three cases. If neurologists had already ordered an MRI (as with case 1 and 2), anesthesiologists would hardly order any additional tests, whereas if neurologists had not performed an MRI (case 3), 68% (30/44) of the respondents would order an MRI themselves.

TABLE 5 Numbers and percentages of the answers to some of the questions about the clinical cases for anesthesiologists.

	Case 1	Case 2	Case 3
Imaging			
I would order imaging before invasive pain treatment	3/44 (7%)	4/44 (9%)	34/44 (77 %)
Treatment with ESI			
I would offer the patient treatment with ESI	44/44 (100%)	44/44 (100%)	25/44 (66 %)
Treatment with PRF			
I would initially treat the patient with epidural steroids, and subsequently consider PRF	31/44 (70.5%)	29/44 (66%)	24/44 (55%)
I would start with PRF treatment, before considering ESI	4/44 (9%)	4/44 (9%)	5/44 (11%)
I would not treat this patient with PRF	7/44 (16%)	9/44 (21%)	7/44 (16%)

Guideline adherence

An overview of the neurologists' and anesthesiologists' adherence to the two guidelines is shown in **Table 6**.

Results suggest that neurologists tend to follow the multidisciplinary guideline broadly when it comes to imaging. With regard to selective diagnostic nerve blocks there seems to be a mismatch: i.e. though not recommended, diagnostic nerve blocks are generally considered useful in clinical practice. It should be noted, however, that we do not know from our survey how often neurologists refer for selective diagnostic nerve blocks. With regard to medication, the answers of the respondents were broadly in line with the guidelines, as neurologists typically follow the WHO pain ladder (from the guideline), with the exception of neuropathic pain medication. With regards to referring to physiotherapy, there seems to be a partial mismatch as well: i.e. even though the guideline contains a weak recommendation for referring patients to a physiotherapist, only 19% of neurologists reported to refer 60-80%

of patients to a physiotherapist. With regards to epidural steroid injections, the guideline states that *'epidural steroid injections can be considered in sciatica patients in case of severe pain despite pain medication'*, a recommendation that is rather strictly followed. Disc surgery is recommended by the guideline in case of a herniated disc causing severe pain, prolonged symptoms or neurological deficits, for example cauda syndrome: this is also strictly followed.

TABLE 6 Adherence to the most recent multidisciplinary guideline (1) and the WIP Benelux safety recommendations (2).

Category	According to guideline 1	According to guideline 2
Neurologists		
Imaging	broadly in line	X
Diagnostic injections	not in line	X
Medication	broadly in line	X
Therapeutic injections	strictly in line	X
Surgery	strictly in line	X
Physiotherapy	broadly in line	X
Anaesthesiologists		
Imaging	not line	not in line
Diagnostic injections	not in line	X
Therapeutic injections (type)	X	broadly in line
Therapeutic injections (safety)	X	strictly in line
Pulse radio frequency	not in line	X

For anesthesiologists, we see that the WIP recommendations on the safety of epidural injections are strictly followed. This does not apply to imaging: even though imaging is considered necessary before an epidural injection, about 1/3 of the anesthesiologists does not do so in daily practice (see case study 3). With regards to selective diagnostic nerve blocks, there seems to be a mismatch between the guideline and the opinion of most anesthesiologists. That is, though selective diagnostic nerve blocks are not recommended, they are generally considered useful. With regard to the type and quantity of the injected fluids, there is considerable variation between the different injections fluids that are used (therefore 'broadly in line'). With regard to pulsed radio frequency, we concluded that the results are not in line with multidisciplinary guideline: though not recommended by the multidisciplinary guideline in the treatment of (sub)acute sciatica, 9-11% of our the respondents would use pulse radio frequency in the acute phase of sciatica.

DISCUSSION

The results of our survey suggest that two patterns of diagnosis and treatment can be distinguished ('established facts'): (A) neurologists diagnose their sciatica patients primarily with an MRI, that is ordered in case of severe pain, prolonged symptoms or presence of symptoms, and signs that suggest an etiology other than a herniated disc. Selective (diagnostic) nerve blocks are considered useful. Patients are treated with a wide variety of medication first and referred for epidural steroid injections as a second step if they fail to respond to pain medication. Patients may also be referred to a physiotherapist with the aim to improve movement and the provision of interventions against kinesiophobia. As a third step, patients will be referred to a surgeon, increasing from 3% at 3 weeks (painful sciatica not responsive to medication) to 29% at 4 months. (B) anesthesiologists treat 100% of their sciatica patients with epidural corticosteroids upon referral from the neurologist. This percentage drops to 66% if no imaging has been performed before. There is considerable variation in the type and quantity of the injection fluid and the number of injections when performing epidural steroid injections. The anesthesiologists' most reported side effects of these injections were in accordance with international literature[14,15]. Pulse radio frequency is mostly applied as a secondary step, if epidural steroid injections lack a good long-term response. A minority (9-11%) of the anesthesiologists indicated to uses pulse radio frequency as a primary treatment in the acute phase of sciatica (<3 months). Selective nerve root blocks are considered useful. This applies to a lesser extent to mapping, which is a relatively new diagnostic tool[16,17].

Our survey coincides with the launch of the new Dutch multidisciplinary guideline on sciatica[11]. Therefore, it is interesting to see how well clinicians currently follow these guidelines[19]. In their 2018 article that was part of the Lancet 'Back pain series', *Foster et al* concluded that: 'despite many clinical guidelines with similar recommendations for the management of low back pain, the gap between evidence and practice is pervasive' [18]. Our survey is in line with this when it comes to imaging before an epidural injection, referral to physiotherapy and pulse radio frequency in the acute stage (<3 months). That is, these treatments and/or diagnostic procedures are used in daily practice despite a poor (physiotherapy) or moderate recommendation (pulse radio frequency) to apply them or because they were not performed despite being recommended (imaging before epidural steroid injection). The same applies to selective diagnostic nerve blocks: though not recommended, these are considered useful. Moreover, there is partial discordance ('broadly followed') between daily practice and the guidelines when it comes to medication

and imaging by neurologists. For medication, the new multidisciplinary guideline advices to use the WHO pain ladder[19]. We saw that the ladder is used, but that neurologists also prescribe neuropathic pain medication that lacks good evidence (e.g. pregabaline)[20]. It should be noted that the guideline advices MRIs only in selected cases, including patients with severe pain irresponsive to pain medication (and therefor candidates for epidural injection or surgery) or patients with neurological deficits (cauda syndrome and severe paresis <MRC 4) that are candidates for an urgent surgical procedure. This an advice is followed by most of the neurologists (89%), but to a lesser extent by anesthesiologists performing an epidural steroid injection (66 %). For other domains (including epidural steroid injections, surgery and safety measures) there is good accordance between practice and guidelines. It is noteworthy that contrary to only a small but significant short-term (< 3 months) effect for leg pain of epidural corticosteroids versus placebo (<1 point on a 10 points pain scale) shown by recent systematic reviews and meta-analyses [21-24], epidural injections are considered rather effective by both neurologists and anesthesiologists (**Figure 1**). However in daily practice epidural corticosteroid injections are used only in case of ineffective pain medication (as recommended).

Our survey has several strengths, including its combination of general questions and case studies, which provides valuable insight into the way neurologists and anesthesiologists think. Moreover, surveys on sciatica have been published before, but those were restricted to surgeons [25,26], whereas ours addresses neurologists and anesthesiologists.

This survey also has some limitations. First, the use of semi-structured interviews, would have provided more detailed information about the respondents' clinical reasoning than a survey. Second, there might be some level of selection bias. As we approached respondents primarily through residency program directors and members of the Pain Section of the Dutch Society of Neurology, this survey was mainly focused on hospital-based specialists and therefore specialists working in private practice might be underrepresented (see **Table 1**). On the other hand, it is important to take into account that in the Netherlands the majority of neurologists and anesthesiologists work in a hospital setting and only very few work in private practices. Therefore, for the Dutch situation this survey looks to be an adequate representation. Another factor that needs attention is that the kind of specialists treating sciatica patients might differ between countries. In the Netherlands, the overwhelming majority of sciatica patients in secondary care is treated by neurologists and anesthesiologists (i.e. 84%[27]). The remainder is treated by orthopedic surgeons and a few other specialists such as rheumatologists

(<2 %). In other countries, such as the United States of America, however, a large share of sciatica patients is treated by the latter. Hence, the results of our survey might not be relevant to all other healthcare systems. Third, the number of respondents was somewhat limited and consequently our data may not be generalizable to all neurologists and anesthesiologists in The Netherlands. However, the number of surveyed physicians as well as the response rate were almost equal to similar types of surveys[28,29].

Please note that this survey was finished just before the arrival of the COVID-pandemic in the Netherlands in March 2020, which had huge implications for the Dutch healthcare sector. Amongst others, there were less opportunities to see patients in the outpatient setting, because of a limited availability of doctors and resources and because of safety issues, e.g. epidural steroids are were not recommended to reduce the risk of COVID-infection[30].

Based on the current findings ('novel insight'), we think that various areas of (partial) discordance between daily practice and guidelines are topics for further research (e.g. selective nerve root blocks or medication). Moreover, we think that the use of patient reported outcome measures (PROMS) should be implemented more broadly to focus on a patient's individual health goals.

CONCLUSION

Neurologists treat sciatica patients initially with pain medication and physiotherapy, followed by epidural steroid injections and referral for surgery if patients fail to respond to conservative treatment. Anesthesiologists treat sciatica patients with steroid injections or may perform a selective nerve root block or mapping in case of doubt about the origin of radicular pain. Imaging, medication, referral to physiotherapy and pulse radio frequency in the acute stage (< 3 months) are considered topics of further research. This also applies to selective nerve root blocks. Imaging before epidural steroid injections is not always performed but should be from the perspective of safety.

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2

THIEME

Inflammation

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4

CHAPTER

Inflammatory biomarkers in patients with sciatica: a systematic review.

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ABSTRACT

Background

This systematic review focusses on inflammation as an underlying pathogenic mechanism in sciatica. We addressed two questions in particular: (1) what inflammatory biomarkers have been identified in patients with sciatica in the literature so far? 2) is there an association between the level of inflammatory activity and clinical symptoms?

Methods

The search was conducted up to December 19th 2018 in MEDLINE, EMBASE, CENTRAL and Web of Science. The study selection criteria: (1) observational cohort studies, cross-sectional studies and randomized clinical trials (RCT), (2) adult population (≥ 18 years) population with sciatica, (3) concentrations of inflammatory biomarkers measured in serum, cerebrospinal fluid (CSF) or biopsies, and (4) evaluation of clinically relevant outcome measures (pain or functional status). Three reviewers independently selected studies and extracted data regarding the study characteristics and the outcomes. Risk of Bias was evaluated using an adjusted version of the Quality in Prognosis Studies (QUIPS) tool.

Results

In total 16 articles fulfilled the criteria for inclusion: 7 cross sectional observational studies and 9 prospective cohort studies that included a total of 1212 patients. With regard to question 1) the following markers were identified: interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IL-21, tumor necrosis factor-α (TNF-α), phospholipase A2, high sensitivity C-reactive protein (hsCRP), C-X-C motif chemokine 5 (CXCM5), CX3CL1, CCL2, epidermal growth factor (EGF), and monocyte chemotactic protein 4 (MCP-4). With regard to question 2) several positive correlations were found in longitudinal studies: a strong positive correlation between inflammatory mediators or byproducts and pain (measured by visual analogue scale, VAS) was found for IL-21 in two studies ($r > 0,8$), and moderate positive correlations for TNF-a in both serum ($r = 0,629$) and biopsy ($r = 0.65$); severe pain (VAS >4) is associated with increased hsCRP levels among patients with sciatica (adjusted OR = 3.4 (95% CI, 1.1 to 10).

Conclusion
In this systematic review there was considerable heterogeneity in the type of biomarkers and in the clinical measurements in the included studies. Taking into account the overall risk of bias of the included studies there is insufficient evidence to draw firm conclusions regarding the relationship between inflammation and clinical symptoms in patients with sciatica.

BACKGROUND

Sciatica or lumbosacral radicular syndrome is characterized by pain radiating into the leg along the course of one of the lumbar nerve roots[1]. Sometimes there is numbness or tingling in the dermatomal distribution of a nerve root. Paresis is present almost half of patients, for example weakness of plantar flexion in S1 radiculopathy. Most patients experience back pain also. The incidence of sciatica in The Netherlands is 9.4 cases per 1000 adults per year[2]. Sciatica is a major cause of costs of hospital care and costs resulting from absenteeism from work[3].

Sciatica is considered having different pathogenic components. First, there is a mechanic component that consists of compression of the nerve root by a herniated disc. Neuroradiologic studies confirm that approximately 90% of cases of sciatica are associated with a disc disorder[4,5]. Second, it has been hypothesized that inflammation may play a role in patients with low back pain[6] and sciatica[7], the elderly in particular[8] A range of pro- and anti-inflammatory proteins has been found in serum, CSF and biopsies of patients with sciatica, including interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor (TNF)-α[7]. Third, in patients with sciatica there possibly is also a neuropathic component caused by neural damage at the level of the nerve root[9].

In this systematic review we focus on the role that inflammation may play in lumbosacral radicular syndrome. We conducted this review as an inflammatory substrate in patients with sciatica could be a potential target for anti-inflammatory therapy, specifically non-steroidal anti-inflammatory drugs (NSAIDs) or transforaminal epidural corticosteroids. We address two questions in particular: (1) what inflammatory biomarkers have been identified in patients with sciatica 2) Is there an association between the level of inflammatory activity and clinical symptoms?

METHODS

Criteria for inclusion and exclusion

A study must fulfill the following inclusion criteria to be included in this review:

Types of studies

Observational cohort studies (with and without control group), cross-sectional studies and randomized clinical trials (RCT). Studies should contain both laboratory and clinical information. Animal studies were excluded.

Types of participants

Adults, older than 18years, with sciatica. Inflammatory activity is measured in serum, cerebrospinal fluid (CSF) or in tissues obtained through biopsy.

Types of outcome measures

For question 1) regarding the presence of biomarkers, the primary outcome was presence of inflammatory proteins in serum, biopsies or CSF. There was no restriction to laboratory methods, including ELISA and Western Blotting for serum and CSF, and messenger RNA qualitative polymerase chain reaction (mRNA qPCR) for biopsy studies.For question 2) regarding clinical features, the outcomes were pain and physical functional status. The following self-reported outcome measures were assessed: pain intensity (e.g. visual analogue scale (VAS)), back-specific disability (e.g. Roland Morris, Oswestry Disability Index), and perceived recovery (e.g. overall improvement).

Search methods

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement[10]. Studies were identified by searching PubMed, Embase.com, Cochrane Central Register of Controlled Trials/Wiley and Web of Science/Clarivate Analytics from inception up to 19 December 2018. The following concepts, including synonyms and closely related words, were used as index terms or free-text words: 'sciatica', 'inflammation' and 'cytokines'. The full search strategy for all databases can be seen in **Additional file 1**. References of retrieved articles and relevant overview articles were checked to identify additional studies.

Methods of review

Study selection

Three authors (MJ/BTM/TVO) independently screened the abstracts and titles retrieved by the search strategy and applied the inclusion criteria. Duplicate articles were excluded. Full texts were obtained if the abstract fulfilled the inclusion criteria and were subsequently screened on inclusion criteria by the authors, independently following the PRISMA guidelines. The checklist can be seen in **Additional file 2**. Any disagreements between the authors were resolved by discussion and consensus.

Risk of bias assessment

Two authors (MJ and TVO) independently conducted the risk-of-bias assessment. Risk of Bias (ROB) was evaluated using the Quality in Prognosis Studies (QUIPS) tool[11]. The reason to choose for QUIPS is that in this review we included observational studies assessing the (longitudinal) association between the level of inflammatory activity and clinical symptoms. This resembles very closely a prognostic model and therefore we used the QUIPS tool that supports a systematic appraisal of such studies. It is based on recommendations from a comprehensive review of quality assessment in prognosis systematic reviews and is informed by basic epidemiologic principles. Independently developed and modified versions of the tool have been successfully used by several research groups, with moderate to substantial interrater reliability.

The QUIPS tool considers the following 6 domains of bias: (1) bias due to patient selection (2) attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding (6) statistical analysis and reporting. Items and operationalization are given in **Additional file 3**. Due to the explorative nature of this review, only the first four domains were included in the risk of bias assessment. The items of these four domains were each scored to assess the overall risk of bias of the included study. For each item within a domain the responses can be: `yes', `partial', `no' or `unsure'. The responses on these items were combined to assess the risk of bias per domain. The risk of bias for each domain was scored as `high' (+), `moderate' (+/–) or `low' (–) risk of bias. In line with *Den Bakker et al.*[12], a study was considered to be of low overall risk of bias when the domain scores were rated as low or moderate on all of the 4 domains, with at least 2 rated as low (including the outcome measurement domain). We scored a study as having high overall risk of bias if 2 or more of the domains were judged as high. A study was scored as moderate if the criteria for 'low' or 'high' were not met. Low overall risk of bias implies that the associations found in this study are unlikely to be different for

participants and eligible nonparticipants, not to be different for completing and non completing participants, not to be different for different levels of the outcome of interest, and unlikely to be different related to the baseline level of the prognostic factor[11].

Data extraction

Data were extracted independently by two review authors (MJ, TVO). The following data were extracted: (1) characteristics of the studies: number of participants, gender, age; (2) characteristics of inflammatory activity (what biomarkers and how they were measured); (3) characteristics of the outcomes: outcome measures, instruments, and scores (e.g. mean, median, standard deviation, and confidence interval). Any disagreements were discussed between the two authors and a third review author (BTM) was consulted if necessary.

Data analysis and statistics

Due to the heterogeneous data our approach was merely descriptive. For question 1) regarding the presence of biomarkers the type and material (serum/CSF/biopsy) were extracted. For question 2) the measures of association that were presented in the included papers were extracted. For example, the correlation between pain measured by a VAS score and biomarker expression. We present the results of the cross-sectional studies and the longitudinal studies separately. In terms of interpretation we used the following guidance: a correlation coefficient of −1 or+1 indicates a perfect linear relation[13]. When Odds Ratio's (OR) were presented these were extracted, including the *p*-value or the 95% CI and the magnitude of the OR was interpreted as follows: OR = 1.68, 3.47, and 6.71 are equivalent to Cohen's d = 0.2 (small), 0.5 (medium), and 0.8 (large)[14]. For other measures of association the p-value was used to assess if the association was statistically significant.

RESULTS

Description of studies

The electronic search initially yielded 3761 articles: 980 in PubMed, 1435 in EMBASE, 41 in CENTRAL and 1305 in Web of Science. After de-duplication 2076 articles were left. Of these, 948 were excluded. The main reasons for exclusion were use of animals or conference abstracts. One study by *Schistadt et al.*[15] was identified through

the reference list of *Pedersen et al.*[26]. Eventually 19 articles fulfilled the criteria for inclusion, of which 16 were analyzed and 3 were excluded. The 16 studies that were analyzed consisted of 7 cross sectional observational studies[16–22] and 9 prospective cohort studies[15, 23–30]. The studies of *Kraychete et al., Weber et al.* and *Miao et al.* were excluded because clinical information was lacking[31] or no correlation between biomarkers and clinical outcomes was described[32, 33]. The analyzed studies included a total number of 1212 patients. For overview see flowchart (**Figure 1**).

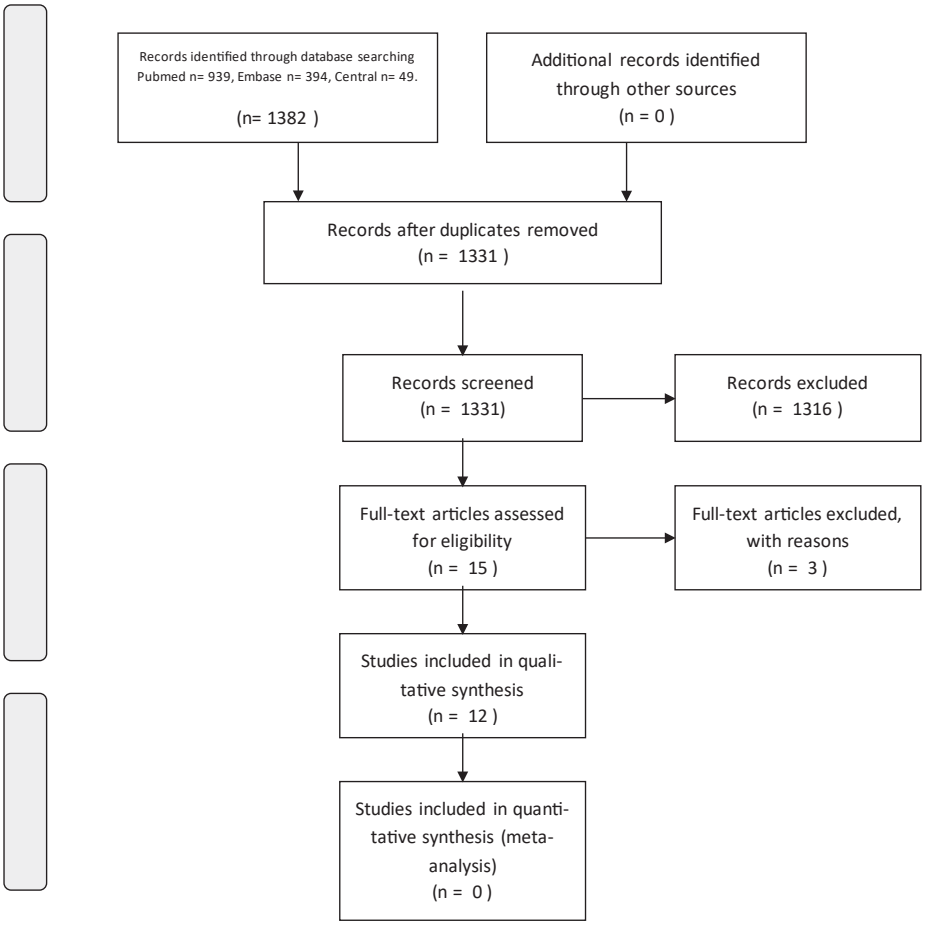

FIGURE 1 Flowchart of systematic review

Risk of Bias (RoB) assessment

The results of the risk of bias assessment are shown in **Table 1**. Of the cross sectional studies classified as low overall risk of bias[21,22], and 5 were classified as moderate risk of biass[16–20], mainly due to inadequate participation[16,17] or moderate outcome reporting [15,16,18,19].

Of the longitudinal studies, 5 were classified as low high quality[14] risk of bias[15,23,27–29] and four were considered as moderate risk of bias[24,25,23,29], mainly due to inadequate participation or high number of drop outs (attrition).

TABLE 1 Results of quality assessment using the adjusted QUIPS-tool

	Participation	Attrition	Prognostic Factor	Outcome	Risk of bias: + = high +/– = moderate - = low
Cross sectional studies					
Piperno [16]	Moderate	Moderate	Low	Moderate	+/–
Brisby [17]	High	Low	Low	Moderate	+/–
Sugimori [18]	High	Low	Moderate	Low	+/–
Cheng [19]	Moderate	Low	Low	Moderate	+/–
Xue [20]	Moderate	Low	Low	Moderate	+/–
Peng [21]	Moderate	Low	Moderate	Low	–
Palada [22]	Low	Low	Low	Low	–
Longitudinal studies					
Schistadt [15]	Low	Moderate	Low	Low	–
Stürmer [23]	Low	Moderate	Low	Low	–
Andrade [24]	High	Low	Low	Moderate	+/–
Andrade [25]	High	Low	Low	Moderate	+/–
Pedersen [26]	Low	High	Low	Moderate	+/–
Wang [27]	Low	Low	Low	Moderate	–
Moen [28]	Low	Moderate	Low	Low	–
Zu [29]	Low	Moderate	Low	Low	–
Chen [30]	Moderate	Moderate	Low	Moderate	+/–

Biomarkers

The following biomarkers were examined, most of them cytokines (12 of 17 studies): interleukin-1β (IL-1β) [21,26], interleukin-2 (IL-2) [21], interleukin 4 (IL-4)[21, 30], interleukin-6 (IL-6)[14,21,25–27], interleukin-8 (IL-8)[17 21,26,27], interleukin-10 (IL-10) [21,27], interleukin-17 (IL-17)[19], interleukin-21 (IL-21) [30]. *Palada et al.* studied a

biomarker panel including TNF, interferon-gamma (INFg), IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 and monocyte chemotactic protein 1 (MCP1) [21]. Three studies measured tumor necrosis factor-α (TNF-α)[25,28,20] and one study looked for phospholipase A2[16]. *Sturmer et al.* and *Sugimori et al.* measured levels of high sensitivity C-reactive protein (hsCRP), a sensitive marker of low grade systemic inflammation[18, 23]. *Peng et al.* looked for expression of the chemokines CX3CL1 and CCL2 [21]. *Moen et al.* measured 92 different pro and anti-inflammatory cytokines the results of which they compiled in an composite inflammation score [28]: 13 were significantly upregulated, including C-X-C motif chemokine 5 (CXCM5; 217% increase), epidermal growth factor (EGF; 142% increase), and monocyte chemotactic protein 4 (MCP-4; 70% increase).

Thirteen studies measured inflammatory activity in serum[15–23, 26–29], four used biopsies of the nucleus pulposus (NP)[20,24,25], annulus fibrosus (AF)[24,25] and ligamentum flavum (LF) [24]. Two studies used CSF for analysis[17,22]. The following techniques were used: ELISA [15, 17, 19, 26, 27, 29], mRNA/ qPCR[20,22,24], proximal extension assay (PEA)[28], Western Blotting [21,30]. The two hsCRP studies used latex agglutination[18,23].

Clinical features in relationship to biomarkers

Tables 2 and 3 summarize the duration of symptoms, age), type of marker and sampling, the clinical parameters and associations between biomarkers and clinical parameters that were found. We distinguished between cross sectional studies (**Table 2**) and longitudinal studies (**Table 3**) studies.

All studies included patients who suffered from sciatica for more than 3 months (average), and therefor had chronic low back pain. All studies reported VAS (Visual analog scale) as assessment tool for pain, except *Sugimori et al.* and *Wang et al.*[18,27]. *Piperno et al.* also used the Dallas Pain Questionnaire[16]. Pain duration at baseline was described precisely in 2 of the cross sectional studies[17, 21] and 4 of the longitudinal studies[15,26,27,29]. Wang et al., determined functioning using the Oswestry Disability Index (ODI) and also used the short form-36 (SF-36) questionnaire[27]. *Sugimori et al.* and *Peng et al.* also used the Japanese Orthopedic Association (JOA) score for overall functioning. Most of the associations between markers and clinical symptoms, were found in the serum studies using ELISA techniques.

TABLE 2 Inflammatory biomarkers in relationship to clinical features (cross sectional studies)

Study	Age (yr)	Duration (months)	Source	Technique	Marker	Clin O	Ass
Piperno [16]	40+−13	20+−26	serum	Degradation	PhosA2	VAS	No
Brisby [17]	N	92 (5–390)[a]	serum & CSF	ELISA	Il-8	VAS	r = −0,48
Sugimori [18]	26.4 (16–39)	N	serum	Latex agl	hsCRP	JOA	r = −0,583
Cheng [19]	44 (30–72)	N	serum	ELISA	Il-17	VAS	r = 0,458
Xue [20]	52 (21–70)	N	serum NP biopsy	mRNA qPCR	Il-21	VAS	r = 0,809
Peng [21]	34.2 (+−5.8)[b]	4.5 (1–22)	serum	Western blot	CX3CL1	VAS	r = 0, 393
			serum	Western blot	CX3CL1	JOA	r = −0,342
			serum	Western blot	CCL2	VAS	r = 0, 360
			serum	Western blot	CCL2	JOA	r = −0,375
Palada [22]	41.13 (15–65)	> 1month	serum	mRNA qPCR	Il-6	VAS	r = 0,380
			CSF	mRNA qPCR	Il-8	VAS	r = 0,395
			serum	mRNA qPCR	MCP1	VAS	r = 0,515

Ass association, *Clin O* clinical outcome, *CSF* cerebrospinal fluid, *ELISA* enzyme linked serum assay, *IL* interleukin, *JOA* Japanese orthopedic association score, *Latex agl* latex agglutination, *NP* nucleus pulposus, *qPCR* quantitative polymerase chain reaction, *VAS* visual analogue scale, *Yr* years

[a]days

[b]VAS>7

For the cross sectional studies a strong positive correlation was found between IL-21 and VAS for pain in one study (r = 0,809[20]. A moderate positive correlation was found for MCP-1 in serum (r = 0,659)[22] and hsCRP in serum (r = 0,538)[18]. The moderate negative correlation between the JOA score and hsCRP. should be explained positively as a high JOA score implies better clinical functioning.

For the longitudinal studies a strong positive correlation was found between Il-21 and VAS for pain in one study (r = 0,834)[30]. A moderate positive correlation was found for TNF-a in both serum (r = 0,629)[27] and biopsy (r = 0.65) [24]. For IL-8 in[2] and Il-6 in annulus fibrosis biopsy [27] low negative correlations were found: the presence of these markers is related to better clinical outcome. Moen et al. calculated an inflammation score (a weighted average of 41 protein scores) that was positive for all high pain patients (VAS >40). Sturmer et al. showed that severe pain (VAS >4) is associated with increased hsCRP levels among patients with sciatica (adjusted OR = 3.4 (95% CI, 1.1 to 10)[23]. Corrections were made for age, sex, smoking and alcohol consumption. The prospective data of *Pedersen et al.* showed that levels IL-6 and IL-8 in serum were related to pain intensity measured on a VAS (IL-6, F(1.0, 118) = 9.7, p **=** 0.002 test of between subjects

TABLE 3 Inflammatory biomarkers in relationship to clinical features (longitudinal studies)

Study	Age (yr)	Duration (weeks)	Source	Technique	Substance	Clin O	Ass
Schistad [15]	41.3 (10)	20.3 (19.9)	serum	ELISA	Il-6	VAS	B = 0,64[a]
Sturmer [23]	44.8 (12.4)	acute[b]	serum	latex agl	hsCRP	VAS >4	aOR = 3,4[c]
Andrade [24]	49	N	NP Biopsy	mRNA qPCR	TNFa	VAS	r = 0,65
			AF Biopsy	mRNA qPCR	TNFa	VAS	r = 0,06
			LF Biopsy	mRNA qPCR	TNFa	VAS	r = 0,29
Andrade [25]	41	13–26	NP Biopsy	mRNA qPCR	IL-6	VAS	r = 0,23
			NP Biopsy	mRNA qPCR	IL-1b	VAS	r = 0,05
			NP Biopsy	mRNA qPCR	IL-6	VAS	r = −0,11
			NP Biopsy	mRNA qPCR	IL-1b	VAS	r = 0,03
Pedersen [26]	39.3 (18–58)	32.3+− 4.5	serum	ELISA	IL-6	VAS	F(1.0, 118) = 9,7
			serum	ELISA	IL-8	VAS	F(1.0, 118,0) = 6,9
Wang [27]	37+−13.3)[d]	48 (+− 29)	serum	ELISA	IL-6	ODI	r = 0,394
			serum	ELISA	TNFa	ODI	r = 0,629
			serum	ELISA	IL-10	ODI	r = 0,415
			serum	ELISA	IL-8	ODI	r = −0,133
Moen [28]	40 (9)	>8	serum	PEA	inflammation score	VAS	positive Linear discriminant analysis
Zu [29]	34.0+−12.3[e]	48 (+− 29)[c]	serum	ELISA	TNFa	ODI+VAS>3	r = 0,2
			serum	ELISA	TNFa	ODI+VAS<3	r = 0,37
			serum	ELISA	IL-4	ODI+VAS>3	r = 0,09
			serum	ELISA	IL-4	ODI+VAS<3	r = 0,08
Chen [30]	51.3+−24.4	N	NP biopsy	Western blot	IL-21	VAS	r = 0.834

AF annulus fibrosus, *aOR* adjusted Odds Ratio, *Ass* association, *Clin O* clinical outcome, *LF* ligamentum flavum, *ELISA* enzyme linked immune assay, *hsCRP* high sensitive c-reactive protein, *Il* interleukin, *latex agl* latex agglutination, *mRNA* messenger RNA, *N* unknown, *NP* nucleus pulposus, *ODI* Oswesty Disability Index, *PEA* proximal extension assay, *TNF* tumour necrosis factor alpha, *Yr* years, *VAS* visual analogue scale

[a]multivariate regression analysis

[b]no definition

[c]adjusted for age, sex, smoking, alcohol, body mass, use of diuretics and analgetic drugs and steroid injections during the previous 24 h

[d]high pain group (VAS >3)

[e]subgroup ruptured AF

effect; IL-8, F(1.0, 118.0) = 6.9, p = 0.01 test of between subjects effect, rmANOVA, covariates age for IL-6; smoking for Il-6 and Il-8; and treatment for IL-8 [26]. In their multivariate analysis Schistadt el al showed that high levels of serum IL-6 correlated with high VAS for leg pain (beta score 0,64) and accounted for 25% of the variance in the VAS for leg pain at 1-year follow-up[15]. *Schistadt et al.* concluded that in addition to elevated Il-6 levels, intense pain, long surgery wait and low education are related to slow recovery[15]. The other studies did not give detailed information about the patients and their history in terms of education, work status, previous back surgery, comorbidity or the medication that was used.

DISCUSSION

The studies under review were heterogeneous with regard to the population, the biomarkers that were studied and the laboratory methods that were used. For that reason pooling of data (meta-analysis) was impossible. The overall Risk of Bias (as assessed by the adapted QUIPS-tool) was moderate 9/12 studies; participation and measurement of the clinical outcome in particular were not optimal. Most frequently the VAS was used for the measurement of pain, but the studies did not accurately describe the location of the pain (back or leg) the reference point (i.e. time-window) or type of pain (for example average pain on activity or during the day). Therefore it is hard to draw firm conclusions, and although the strong positive correlation between IL-21 and pain in two studies [20, 30], and the association between hsCRP levels and severe pain (VAS >40)[23] might be of interest, they should be interpreted with great care.

Strengths and limitations

A strength of this study is the systematic and transparent approach that was followed in all the steps of this systematic review.

Still several biases can be introduced by literature search and selection procedure. First, due to selection bias relevant publications may have been missed. For example in our initial search we missed the relevant publication by *Schistadt et al.*[15]. Second, due to publication bias unpublished studies may have been missed. Third there might be reference bias: screening references may result in an over representation of positive studies, as trials with a negative result are less likely to be referred to.

Another limitation is that we used an adjusted version of the QUIPS-tool to asses ROB. We did not take into account the domains 'study confounding' and 'statistical analysis out'. We did not find relevant information in the literature to decide a-priori which confounders would be the most relevant in this field. Still, where possible, in the result section where we describe which factors were taken into account in the included studies. But unfortunately many studies no detailed information was included about other factors they took into account.

Implications for practice

The results of this review are not overly convincing which may suggest only a minor role for inflammation in sciatica. Of course this is based on limited data, however these results could potentially be interpreted in line with the results from therapeutic studies. There are two interventions in patients with sciatica, targeted at inflammation: 1) use of non steroidal anti inflammatory drugs (NSAIDs); 2) epidural injections with corticosteroids. The effects of both NSAIDs and injections seem to be minor.

A Cochrane review showed very low-quality evidence that the efficacy of NSAIDs for pain reduction is comparable with that of placebo and low-quality evidence that NSAIDs is better than placebo for global improvement[34].

With regard to effectivity of epidural corticosteroid injections a meta-analysis of 23 trials [35] showed a small positive short-term (<3 months) effect for leg pain of epidural corticosteroid injections compared to placebo (mean difference (MD), −6.2 on a 100 points VAS)[95% CI, −9.4 to −3.0]) and disability (MD, −3.1 on a 100 point Oswestry Disability Scale). A second meta-analysis of 30 trials[36] showed an immediate-term (<2 weeks) pain reduction (MD −7.55 on a 100 point VAS[95% CI, −11.4 to −3.74]) and reduction in disability (standardized MD, −0.33[95% CI, −0.56 to −0.09]) of epidural corticosteroid injections compared to placebo.

A potential explanation for a lack of treatment effect of both NSAIDs and epidural corticosteroid injections could be that inflammation plays a minor role in sciatica, or only plays an important role in a small subgroup of patients. Perhaps in the future we can identify patients with sciatica that respond well to both treatments for example acute patients (that were underrepresented in this systematic review) or patients with severe pain.

To summarize: though anti-inflammatory treatment (in the form of NSAIDs or epidural injections with corticosteroids) is the first choice of pain treatment in patients with sciatica, the evidence of inflammation playing a role in sciatica is not overly convincing based on laboratory studies.

Implications for research

The main question to be still answered here is if inflammation plays a role in lumbar radicular syndrome, at what stage and to what extent? From a research perspective, we think that the acute stage of sciatica (< 12 weeks) deserves more attention given that the fact that although most patients recover within this period[37]. During the acute stage serum studies are relatively easy to perform. It is interesting to know what specific cytokines are elevated and if they have a prognostic value e.g. for chronicity. The markers that had high correlations with clinical measures in previous studies (for example Il-21) seem the most interesting candidates for further study. In addition we think that different laboratories should come to a consensus regarding the best method for measuring inflammation in sciatica.

In the nearby future inflammatory biomarkers could possibly predict the clinical course of sciatica and be used to identify subsets of patients that respond best to anti-inflammatory treatment (NSAIDs or epidural injections with corticosteroids) or patients that benefit from surgery.

CONCLUSION

In this systematic review there was considerable heterogeneity in the type of biomarkers and in the clinical measurements in the included studies. Taking into account the overall risk of bias of the included studies there is insufficient evidence to draw firm conclusions regarding the relationship between inflammation and clinical symptoms in patients with sciatica.

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ADDITIONAL FILE 1

The full search strategy for all databases.

PubMed.com, 19-12-2018

No.	Query	Results
#4	Search (#1 AND #2 AND #3)	980
#3	Search "Inflammation"[Mesh] OR inflamm*[tiab] OR proinflamm*[tiab] OR antiinflamm*[tiab]	1027443
#2	Search "Cytokines"[Mesh] OR Cytokine*[tiab] OR Interferon*[tiab] OR IFN-alpha*[tiab] OR Interleukin*[tiab] OR IL-1[tiab] OR IL1[tiab] OR T Helper Factor*[tiab] OR Lymphocyte Activating Factor*[tiab] OR Macrophage Cell Factor*[tiab] OR Epidermal Cell Derived Thymocyte-Activating Factor*[tiab] OR Hematopoietin-1[tiab] OR Catabolin[tiab] OR IL-2[tiab] OR IL2[tiab] OR TCGF[tiab] OR Lymphocyte Mitogenic Factor*[tiab] OR T-Cell Growth Factor*[tiab] OR Thymocyte Stimulating Factor*[tiab] OR Ro-23-6019[tiab] OR Ro236019[tiab] OR Ro-236019[tiab] OR RU 49637[tiab] OR RU49637[tiab] OR IL-3[tiab] OR IL3[tiab] OR Mast-Cell Colony-Stimulating Factor*[tiab] OR Multipotential Colony-Stimulating Factor*[tiab] OR P-Cell Stimulating Factor*[tiab] OR Erythrocyte Burst-Promoting Factor*[tiab] OR Hematopoietin-2[tiab] OR IL-4[tiab] OR IL4[tiab] OR B-Cell Stimulating Factor*[tiab] OR BCGF-1[tiab] OR Binetrakin[tiab] OR BSF-1[tiab] OR Mast Cell Growth Factor-2[tiab] OR MCGF-2[tiab] OR B Cell Stimulatory Factor-1[tiab] OR B-Cell Growth Factor*[tiab] OR B-Cell Proliferating Factor*[tiab] OR B-Cell Stimulatory Factor 1[tiab] OR IL-5[tiab] OR IL5[tiab] OR BCGF-II[tiab] OR Eosinophil Differentiation Factor*[tiab] OR T-Cell Replacing Factor*[tiab] OR T-Cell-Replacing Factor*[tiab] OR B-Cell Growth Factor-II[tiab] OR IL-6[tiab] OR IL6[tiab] OR Differentiation Factor 2, B Cell[tiab] OR IFN-beta 2[tiab] OR MGI-2[tiab] OR Myeloid Differentiation-Inducing Protein*[tiab] OR Plasmacytoma Growth Factor*[tiab] OR B Cell Stimulatory Factor-2[tiab] OR B-Cell Differentiation Factor[tiab] OR B-Cell Stimulatory Factor-2[tiab] OR BSF-2[tiab] OR Hepatocyte-Stimulating Factor*[tiab] OR Hybridoma Growth Factor*[tiab] OR IL-7[tiab] OR IL7[tiab] OR Lymphopoietin*[tiab] OR IL-8[tiab] OR IL8[tiab] OR Monocyte-Derived Neutrophil-Activating Peptide*[tiab] OR Anionic Neutrophil-Activating Peptide[tiab] OR Chemokine CXCL8[tiab] OR CXCL8 Chemokine*[tiab] OR Macrophage-Derived Chemotactic Factor*[tiab] OR Neutrophil Chemotactic Factor*[tiab] OR Neutrophil Activation Factor*[tiab] OR Granulocyte Chemotactic Peptide-Interleukin-8[tiab] OR Monocyte-Derived Neutrophil Chemotactic Factor*[tiab] OR Lymphocyte-Derived Neutrophil-Activating Peptide*[tiab] OR Alveolar Macrophage Chemotactic Factor-I[tiab] OR AMCF-I[tiab] OR IL-9[tiab] OR IL9[tiab] OR T-Cell Growth Factor P40[tiab] OR P40 T-Cell Growth Factor*[tiab] OR IL-10[tiab] OR IL10[tiab] OR CSIF-10[tiab] OR Cytokine Synthesis Inhibitory Factor*[tiab] OR IL-11[tiab] OR IL11[tiab] OR Adipogenesis Inhibitory Factor*[tiab] OR IL-12[tiab] OR IL12[tiab] OR Edodekin Alfa[tiab] OR Natural Killer Cell Stimulatory Factor*[tiab] OR Cytotoxic Lymphocyte Maturation Factor[tiab] OR IL-12p35[tiab] OR IL12p35[tiab] OR IL-12p40[tiab] OR IL12p40[tiab] OR IL-13[tiab] OR IL13[tiab] OR IL-15[tiab] OR IL15[tiab] OR IL-16[tiab] OR IL16[tiab] OR Lymphocyte Chemoattractant Factor*[tiab] OR LCF Factor*[tiab] OR IL-17*[tiab] OR IL17*[tiab] OR CTLA-8[tiab] OR CTLA8[tiab] OR Cytotoxic T lymphocyte-Associated Antigen 8[tiab] OR IL-18[tiab] OR IL18[tiab] OR IFN-gamma-Inducing Factor*[tiab] OR IL-23[tiab] OR IL23[tiab] OR IL-23p19[tiab] OR IL-23 p19[tiab] OR IL23 p19[tiab] OR IL23p19[tiab] OR IL-27[tiab] OR IL27[tiab] OR Monokine*[tiab] OR Tumor Necrosis Factor*[tiab] OR TNF[tiab] OR TNF Receptor Ligand*[tiab] OR TNFalpha[tiab] OR TNF-alpha[tiab] OR Cachectin[tiab] OR TNF Superfamily[tiab] OR TNF[tiab] OR "Biomarkers"[Mesh] OR biomark*[tiab] OR serum mark*[tiab] OR biological mark*[tiab]	1583200
#1	Search "Intervertebral Disc Displacement"[Mesh] OR "Sciatica"[Mesh] OR Sciatic*[tiab] OR slipped dis*[tiab] OR Intervertebral Disc Displacement*[tiab] OR Intervertebral Disk Displacement*[tiab] OR herniated dis*[tiab] OR prolapsed dis*[tiab] OR radicular pain*[tiab] OR disc herniation*[tiab] OR disk herniation*[tiab]	49574

Embase.com, 19-12-2018

PubMed.com, 19-12-2018

No.	Query	Results
#11	#3 AND #6 AND #10	**1435**
#10	#7 OR #8 OR #9	**1903023**
#9	'biological marker'/exp OR biomark*:ab,ti OR 'serum mark*':ab,ti OR 'biological mark*':ab,ti OR bioindicat*:ab,ti	**420964**
#8	'cytokine*':ab,ti OR 'interleukin*':ab,ti OR 'il1*':ab,ti OR 'il 1':ab,ti OR ((leucocyt* NEXT/1 pyrogen):ab,ti) OR ((leukocyt* NEXT/1 pyrogen):ab,ti) OR 'leukocytic endogenous mediator':ab,ti OR 'lymphocyte activating factor':ab,ti OR 'hemopoietin 1':ab,ti OR 'beta interferon inducing 22 k factor':ab,ti OR 'beta inter-feron inducing 22k factor':ab,ti OR 'interferon beta inducing 22k factor':ab,ti OR 'il2*':ab,ti OR 'il 2':ab,ti OR 'bioleukin':ab,ti OR 'lymphocult t hp':ab,ti OR 'lymphocyte mitogenic factor':ab,ti OR 't cell growth factor':ab,ti OR 't cell growth factor 2':ab,ti OR 't lymphocyte growth factor':ab,ti OR 't lymphocyte growth factor 2':ab,ti OR 'il3*':ab,ti OR 'il 3':ab,ti OR (('haematopoietic cell growth' NEXT/1 factor*):ab,ti) OR (('hematopoietic cell growth' NEXT/1 factor*):ab,ti) OR (('haemopoietic cell growth' NEXT/1 factor*):ab,ti) OR (('hemopoietic cell growth' NEXT/1 factor*):ab,ti) OR 'hemopoietin 2':ab,ti OR 'mast cell growth factor':ab,ti OR 'mast cell growth factor 2':ab,ti OR ((multi* NEXT/1 'colony stimulating factor'):ab,ti) OR 'p cell stimulating factor':ab,ti OR 'il4*':ab,ti OR 'il 4':ab,ti OR 'b cell stimulating factor*':ab,ti OR 'b cell stimulatory factor*':ab,ti OR 'b lympho-cyte stimulating factor 1':ab,ti OR 'bsf 1':ab,ti OR 'bsf1':ab,ti OR 'eosinophil differentiation factor':ab,ti OR 'il5*':ab,ti OR 'il 5':ab,ti OR 'b cell growth factor*':ab,ti OR 'killer helper factor':ab,ti OR 't cell replacing fac-tor':ab,ti OR 't lymphocyte replacing factor':ab,ti OR 'il6*':ab,ti OR 'il 6':ab,ti OR '26 k protein':ab,ti OR (('b cell' NEXT/1 stimulat* NEXT/1 'factor 2'):ab,ti) OR 'b lymphocyte stimulating factor 2':ab,ti OR (('beta 2' NEAR/1 interferon):ab,ti) OR (('beta2' NEAR/1 interferon):ab,ti) OR 'bsf 2':ab,ti OR 'bsf2':ab,ti OR 'hepatocyte stimulating factor':ab,ti OR 'liver cell stimulating factor':ab,ti OR 'plasmacytoma growth factor':ab,ti OR 'protein 26k':ab,ti OR 'il7*':ab,ti OR 'il 7':ab,ti OR 'lymphopoietin 1':ab,ti OR 'pre b cell growth factor':ab,ti OR 'pre b lymphocyte growth factor':ab,ti OR 'il8*':ab,ti OR 'il 8':ab,ti OR ((chemokine NEAR/1 cxcl8):ab,ti) OR 'cxc chemokine ligand 8':ab,ti OR 'granulocyte chemotactic peptide':ab,ti OR 'lymphocyte derived neutrophil activating peptide':ab,ti OR 'lynap':ab,ti OR 'monap':ab,ti OR 'monocyte derived neutrophil activating peptide':ab,ti OR 'monocyte derived neutrophil chemotactic factor':ab,ti OR 'neutrophil activating factor':ab,ti OR 'neutrophil activating peptide':ab,ti OR 'neutrophil attracting peptide':ab,ti OR 'polymorphonuclear granulocyte activating factor':ab,ti OR 'il9*':ab,ti OR 'il 9':ab,ti OR 'il10*':ab,ti OR 'il 10':ab,ti OR 'cytokine synthesis inhibitory factor':ab,ti OR 'csif':ab,ti OR 'il12*':ab,ti OR 'il 12':ab,ti OR 'cytotoxic lymphocyte maturation factor':ab,ti OR 'clmf':ab,ti OR 'natural killer cell stimulatory factor':ab,ti OR 'nksf':ab,ti OR 'cytotoxic lymphocyte maturation factor 2':ab,ti OR 'natural killer cell stimulatory factor 2':ab,ti OR 'il13*':ab,ti OR 'il 13':ab,ti OR 'il15*':ab,ti OR 'il 15':ab,ti OR 'il16*':ab,ti OR 'il 16':ab,ti OR 'lymphocyte chemoattractant factor':ab,ti OR 'il17*':ab,ti OR 'il 17':ab,ti OR 'cytotoxic t lymphocyte antigen 8':ab,ti OR 'cytotoxic t lymphocyte associated antigen 8':ab,ti OR 'cytotoxic t lymphocyte associated protein 8':ab,ti OR 'cytotoxic t lymphocyte protein 8':ab,ti OR 'ctla 8':ab,ti OR 'ctla8':ab,ti OR 'il18*':ab,ti OR 'il 18':ab,ti OR 'gamma interferon inducing factor':ab,ti OR 'igif':ab,ti OR 'interferon gamma inducing factor':ab,ti OR 'cutaneous t cell attracting chemokine':ab,ti OR 'cc chemokine ligand 27':ab,ti OR 'ccl27':ab,ti OR 'ctack':ab,ti OR 'scya27':ab,ti OR 'small inducible cytokine a27':ab,ti OR 'eotaxin*':ab,ti OR 'ccl11':ab,ti OR 'fibroblast growth factor*':ab,ti OR 'fibroblast stimulating factor':ab,ti OR 'heparin binding growth factor':ab,ti OR 'granulocyte colony stimulating factor':ab,ti OR 'granulocyte colony-stimulating factor':ab,ti OR 'g csf':ab,ti OR 'granulocyte macrophage colony stimulating factor':ab,ti OR 'granulocyte-macrophage colony-stimulating factor':ab,ti OR 'gm csf':ab,ti OR 'gmcsf':ab,ti OR 'alpha2 interferon':ab,ti OR 'alpha 2 interferon':ab,ti OR 'berofor alpha2':ab,ti OR 'berofor alpha 2':ab,ti OR 'ifn alpha2':ab,ti OR 'ifn alpha 2':ab,ti OR 'interferon alpha ii':ab,ti OR 'interferon alpha2':ab,ti OR 'interferon alpha 2':ab,ti OR 'gamma interferon':ab,ti OR 'human immune interferon':ab,ti OR 'ifn gamma':ab,ti OR 'imunomax gamma':ab,ti OR 'interferon 2':ab,ti OR 'interferon gamma':ab,ti OR 'interferon ii':ab,ti OR 'interferon type ii':ab,ti OR 'interferon-gamma':ab,ti OR 'oh 6000':ab,ti OR 'leukemia inhibitory factor':ab,ti OR (('leukaemia inhibit*' NEXT/1 factor):ab,ti) OR 'cholinergic differentiation factor':ab,ti OR 'macrophage inflammatory protein 1':ab,ti OR 'macrophage inflammatory protein-1':ab,ti OR 'bb 10010':ab,ti OR 'bb10010':ab,ti OR 'cc chemokine ligand 3':ab,ti OR ((ccl3 NEAR/1 chemokine):ab,ti) OR 'ld78':ab,ti OR	**830649**

No.	Query	Results
	'lym-phokine mip 1alpha':ab,ti OR 'mip 1alpha':ab,ti OR ((protein NEAR/1 scya3):ab,ti) OR 'small inducible cytokine a3':ab,ti OR 'cc chemokine ligand 4':ab,ti OR ((ccl4 NEAR/1 chemokine):ab,ti) OR ((scya4 NEAR/1 protein):ab,ti) OR 'small inducible cytokine a4':ab,ti OR 'mip 1beta':ab,ti OR 'platelet derived growth factor':ab,ti OR 'pdgf bb':ab,ti OR 'rantes':ab,ti OR 'cc chemokine ligand 5':ab,ti OR ((chemokine NEAR/1 ccl5):ab,ti) OR 'stem cell factor':ab,ti OR 'c kit ligand':ab,ti OR 'kit ligand':ab,ti OR 'steel factor':ab,ti OR 'stromal cell derived factor 1alpha':ab,ti OR 'sdf 1alpha':ab,ti OR 'stromal cell-derived factor-1alpha':ab,ti OR 'stromal derived factor 1alpha':ab,ti OR 'tumor necrosis factor alpha':ab,ti OR 'mhr 24':ab,ti OR 'tnf alfa':ab,ti OR 'tnf alpha':ab,ti OR 'tumor necrosis factor alfa':ab,ti OR 'tumor necrosis factor-alpha':ab,ti OR 'tumour necrosis factor alfa':ab,ti OR 'tumour necrosis factor alpha':ab,ti OR 'tumour necrosis factor-alpha':ab,ti OR 'alpha lymphotoxin':ab,ti OR 'human tumor necrosis factor beta':ab,ti OR 'human tumour necrosis factor beta':ab,ti OR 'lymphotoxic factor':ab,ti OR 'lymphotoxin alpha':ab,ti OR 'lymphotoxin-alpha':ab,ti OR 'tumor necrosis factor beta':ab,ti OR 'tumour necrosis factor beta':ab,ti OR 'tumor necrosis factor related apoptosis inducing ligand':ab,ti OR ((antigen NEAR/1 cd253):ab,ti) OR (((protein NEAR/1 tnfsf):ab,ti) AND 10:ab,ti) OR ((protein NEAR/1 tnfsf10):ab,ti) OR ((protein NEAR/1 trail):ab,ti) OR 'tnf related apoptosis inducing ligand':ab,ti OR 'tnf-related apoptosis-inducing ligand':ab,ti OR 'tumor necrosis factor ligand superfamily member 10':ab,ti OR 'tumor necrosis factor superfamily member 10':ab,ti OR 'tumour necrosis factor ligand superfamily member 10':ab,ti OR 'tumour necrosis factor related apoptosis inducing ligand':ab,ti OR 'tumour necrosis factor superfamily member 10':ab,ti	
#7	'cytokine'/exp	**1412739**
#6	#4 OR #5	**3718370**
#5	inflamm*:ab,ti OR proinflamm*:ab,ti OR antiinflamm*:ab,ti	**1210995**
#4	'inflammation'/exp	**3249455**
#3	#1 OR #2	**62973**
#2	sciatic*:ab,ti OR ischias:ab,ti OR ischiatic:ab,ti OR 'slipped dis*':ab,ti OR 'intervertebral disc displacement*':ab,ti OR 'intervertebral disk displacement*':ab,ti OR 'prolapsed dis*':ab,ti OR 'radicular pain*':ab,ti OR ((dis* NEAR/2 hernia*):ab,ti) OR ((dis* NEXT/1 prolapse*):ab,ti) OR ((dis* NEXT/1 protrusion*):ab,ti) OR 'hernia disci':ab,ti OR 'hernia nuclei pulposi':ab,ti OR 'herniated intervertebral dis*':ab,ti OR 'herniated nucleus pulpos*':ab,ti OR ((dis* NEXT/1 rupture*):ab,ti) OR 'nucleus pulposus hernia*':ab,ti	**52275**
#1	'intervertebral disk hernia'/exp OR 'sciatica'/exp	**25429**

CENTRAL, 19-12-2018

No.	QuerySearch	Results
#1	MeSH descriptor: [Intervertebral Disc Displacement] explode all trees	786
#2	MeSH descriptor: [Sciatica] explode all trees	275
#3	(Sciatic* or slipped dis* or Intervertebral Disc Displacement* or Intervertebral Disk Displacement* or herniated dis* or prolapsed dis* or radicular pain* or disc herniation* or disk herniation*):ti,ab,kw	3300
#4	{OR #1-#3}	3300
#5	MeSH descriptor: [Inflammation] explode all trees	9267
#6	(inflamm* or proinflamm* or antiinflamm*):ti,ab,kw	62747
#7	{OR #5-#6}	66752
#8	MeSH descriptor: [Biomarkers] explode all trees	18524
#9	MeSH descriptor: [Cytokines] explode all trees	18545
#10	(biomark* or serum NEXT mark* or biological NEXT mark*):ti,ab,kw	30481

No.	QuerySearch	Results
#11	(Cytokine* OR Interferon* OR IFN NEXT alpha* OR Interleukin* OR IL-1 OR IL1 OR "T Helper" NEXT Factor* OR "Lymphocyte Activating" NEXT Factor* OR "Macrophage Cell" NEXT Factor* OR "Epidermal Cell Derived Thymocyte-Activating" NEXT Factor* OR Hematopoietin-1 OR Catabolin OR IL-2 OR IL2 OR TCGF OR "Lymphocyte Mitogenic" NEXT Factor* OR "T-Cell Growth" NEXT Factor* OR "Thymocyte Stimulating" NEXT Factor* OR "Ro-23-6019" OR Ro236019 OR "Ro-236019" OR "RU 49637" OR RU49637 OR "IL-3" OR IL3 OR "Mast-Cell Colony-Stimulating" NEXT Factor* OR "Multipotential Colony-Stimulating" NEXT Factor* OR "P-Cell Stimulating" NEXT Factor* OR "Erythrocyte Burst-Promoting" NEXT Factor* OR Hematopoietin-2 OR "IL-4" OR IL4 OR "B-Cell Stimulating" NEXT Factor* OR "BCGF-1" OR Binetrakin OR "BSF-1" OR "Mast Cell Growth Factor-2" OR "MCGF-2" OR B Cell Stimulatory Factor-1 OR "B-Cell Growth" NEXT Factor* OR "B-Cell Proliferating" NEXT Factor* OR B-Cell Stimulatory Factor 1 OR IL-5 OR IL5 OR BCGF-II OR "Eosinophil Differentiation" NEXT Factor* OR "T-Cell Replacing" NEXT Factor* OR "T-Cell-Replacing" NEXT Factor* OR B-Cell Growth Factor-II OR IL-6 OR IL6 OR Differentiation Factor 2, B Cell OR IFN-beta 2 OR MGI-2 OR "Myeloid Differentiation-Inducing" NEXT Protein* OR "Plasmacytoma Growth" NEXT Factor* OR B Cell Stimulatory Factor-2 OR B-Cell Differentiation Factor OR B-Cell Stimulatory Factor-2 OR BSF-2 OR "Hepatocyte-Stimulating" NEXT Factor* OR "Hybridoma Growth" NEXT Factor* OR IL-7 OR IL7 OR Lymphopoietin* OR IL-8 OR IL8 OR "Monocyte-Derived Neutrophil-Activating" NEXT Peptide* OR Anionic Neutrophil-Activating Peptide OR Chemokine CXCL8 OR "CXCL8" NEXT Chemokine* OR "Macrophage-Derived Chemotactic" NEXT Factor* OR "Neutrophil Chemotactic" NEXT Factor* OR "Neutrophil Activation" NEXT Factor* OR Granulocyte Chemotactic Peptide-Interleukin-8 OR "Monocyte-Derived Neutrophil Chemotactic" NEXT Factor* OR "Lymphocyte-Derived Neutrophil-Activating" NEXT Peptide* OR Alveolar Macrophage Chemotactic Factor-I OR AMCF-I OR IL-9 OR IL9 OR T-Cell Growth Factor P40 OR "P40 T-Cell Growth" NEXT Factor* OR IL-10 OR IL10 OR CSIF-10 OR "Cytokine Synthesis Inhibitory" NEXT Factor* OR IL-11 OR IL11 OR "Adipogenesis Inhibitory" NEXT Factor* OR IL-12 OR IL12 OR Edodekin Alfa OR "Natural Killer Cell Stimulatory" NEXT Factor* OR Cytotoxic Lymphocyte Maturation Factor OR IL-12p35 OR IL12p35 OR IL-12p40 OR IL12p40 OR IL-13 OR IL13 OR IL-15 OR IL15 OR IL-16 OR IL16 OR "Lymphocyte Chemoattractant" NEXT Factor* OR "LCF" NEXT Factor* OR IL-17* OR IL17* OR CTLA-8 OR CTLA8 OR Cytotoxic T lymphocyte-Associated Antigen 8 OR IL-18 OR IL18 OR "IFN-gamma-Inducing" NEXT Factor* OR IL-23 OR IL23 OR IL-23p19 OR IL-23 p19 OR IL23 p19 OR IL23p19 OR IL-27 OR IL27 OR Monokine* OR "Tumor Necrosis" NEXT Factor* OR TNF OR "TNF Receptor" NEXT Ligand* OR TNFalpha OR TNF-alpha OR Cachectin OR TNF Superfamily OR TNF):ti,ab,kw	44204
#12	{OR #8-#11}	76533
#13	#4 AND #7 AND #12 in Trials	41

Web of Science, 19-12-2018

No.	Query	Results
# 6	#5 AND #2 AND #1	1,305
# 5	#4 OR #3	868,558
# 4	TOPIC: ("Hepatocyte-Stimulating Factor*" OR "Hybridoma Growth Factor*" OR IL-7 OR IL7 OR Lymphopoietin* OR IL-8 OR IL8 OR "Monocyte-Derived Neutrophil-Activating Peptide*" OR "Anionic Neutrophil-Activating Peptide" OR "Chemokine CXCL8" OR "CXCL8 Chemokine*" OR "Macrophage-Derived Chemotactic Factor*" OR "Neutrophil Chemotactic Factor*" OR "Neutrophil Activation Factor*" OR "Granulocyte Chemotactic Peptide-Interleukin-8" OR "Monocyte-Derived Neutrophil Chemotactic Factor*" OR "Lymphocyte-Derived Neutrophil-Activating Peptide*" OR "Alveolar Macrophage Chemotactic Factor-I" OR AMCF-I OR IL-9 OR IL9 OR "T-Cell Growth Factor P40" OR "P40 T-Cell Growth Factor*" OR IL-10 OR IL10 OR CSIF-10 OR "Cytokine Synthesis Inhibitory Factor*" OR IL-11 OR IL11 OR "Adipogenesis Inhibitory Factor*" OR IL-12 OR IL12 OR "Edodekin Alfa" OR "Natural Killer Cell Stimulatory Factor*" OR "Cytotoxic Lymphocyte Maturation Factor" OR IL-12p35 OR IL12p35 OR IL-12p40 OR IL12p40 OR IL-13 OR IL13 OR IL-15 OR IL15 OR IL-16 OR IL16 OR "Lymphocyte Chemoattractant Factor*" OR "LCF Factor*" OR IL-17* OR IL17* OR CTLA-8 OR CTLA8 OR "Cytotoxic T lymphocyte-Associated Antigen 8" OR IL-18 OR IL18 OR "IFN-gamma-Inducing Factor*" OR IL-23 OR IL23 OR IL-23p19 OR IL-23 p19 OR "IL23 p19" OR IL23p19 OR IL-27 OR IL27 OR Monokine* OR "Tumor Necrosis Factor*" OR TNF OR "TNF Receptor Ligand*" OR TNFalpha OR TNF-alpha OR Cachectin OR "TNF Superfamily")	375,343
# 3	TOPIC: (Cytokine* OR Interferon* OR "IFN alpha*" OR Interleukin* OR IL-1 OR IL1 OR "T Helper Factor*" OR "Lymphocyte Activating Factor*" OR "Macrophage Cell Factor*" OR "Epidermal Cell Derived Thymocyte-Activating Factor*" OR Hematopoietin-1 OR Catabolin OR IL-2 OR IL2 OR TCGF OR "Lymphocyte Mitogenic Factor*" OR "T-Cell Growth Factor*" OR "Thymocyte Stimulating Factor*" OR Ro-23-6019 OR Ro236019 OR Ro-236019 OR RU-49637 OR RU49637 OR IL-3 OR IL3 OR "Mast-Cell Colony-Stimulating Factor*" OR "Multipotential Colony-Stimulating Factor*" OR "P-Cell Stimulating Factor*" OR "Erythrocyte Burst-Promoting Factor*" OR Hematopoietin-2 OR IL-4 OR IL4 OR "B-Cell Stimulating Factor*" OR BCGF-1 OR Binetrakin OR BSF-1 OR "Mast Cell Growth Factor-2" OR MCGF-2 OR "B Cell Stimulatory Factor-1" OR "B-Cell Growth Factor*" OR "B-Cell Proliferating Factor*" OR "B-Cell Stimulatory Factor 1" OR IL-5 OR IL5 OR BCGF-II OR "Eosinophil Differentiation Factor*" OR "T-Cell Replacing Factor*" OR "T-Cell-Replacing Factor*" OR "B-Cell Growth Factor-II" OR IL-6 OR IL6 OR "Differentiation Factor 2, B Cell" OR "IFN-beta 2" OR MGI-2 OR "Myeloid Differentiation-Inducing Protein*" OR "Plasmacytoma Growth Factor*" OR "B Cell Stimulatory Factor-2" OR "B-Cell Differentiation Factor" OR "B-Cell Stimulatory Factor-2" OR BSF-2)	735,896
# 2	TOPIC: (inflamm* or proinflamm* or antiinflamm*)	964,281
# 1	TOPIC: (Sciatic* or slipped dis* or "Intervertebral Disc Displacement*" or "Intervertebral Disk Displacement*" or "herniated dis*" or "prolapsed dis*" or "radicular pain*" or "disc herniation*" or "disk herniation*")	89,866

Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years

Database	Voor ontdubbelen	Na ontdubbelen
PubMed	980	
Embase.com	1435	
Web of Science	1305	
CENTRAL	41	
Totaal	3761	2076

ADDITIONAL FILE 2

Prisma Checklist for reporting in systematic reviews and meta-analyses.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Add file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6,7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e10000

ADDITIONAL FILE 3

The adjusted Quips tool for bias assessment

Domains of the QUIPS risk of bias assessment.						
Variable	**1. Study Participation**	**2. Study Attrition**	**3. Prognostic Factor Measurement**	**4. Outcome Measurement**	**5. Study Confounding**	**6. Statistical Analysis and Reporting**
Optimal study or characteristics of unbiased study.	The study sample adequately represents the population of interest.	The study data available (i.e., participants not lost to follow-up) adequately represent the study sample.	The PF is measured in a similar way for all participants.	The outcome of interest is measured in a similar way for all participants.	Important potential confounding factors are appropriately accounted for.	The statistical analysis is appropriate, and all primary outcomes are reported.
Prompting items and considerations.	a. Adequate participation in the study by eligible persons.	a. Adequate response rate for study participants.	a. A clear definition or description of the PF is provided	a. A clear definition of the outcome is provided.	a. All important confounders are measured.	a. Sufficient presentation of data to assess the adequacy of the analytic strategy.
	b. Description of the source population or population of interest.	b. Description of attempts to collect information on participants who dropped out.	b. Method of PF measurement is adequately valid and reliable	b. Method of outcome measurement used is adequately valid and reliable.	b. Clear definitions of the important confounders measured are provided.	b. Strategy for model building is appropriate and is based on a conceptual framework or model.
	c. Description of the baseline study sample.	c. Reasons for loss to follow-up are provided.	c. Continuous variables are reported or appropriate cut points are used.	c. The method and setting of outcome measurement is the same for all study participants.	c. Measurement of all important confounders is adequately valid and reliable.	c. The selected statistical model is adequate for the design of the study.
	d. Adequate description of the sampling frame and recruitment.	d. Adequate description of participants lost to follow-up.	d. The method and setting of measurement of PF is the same for all study participants.		d. The method and setting of confounding measurement are the same for all study participants.	d. There is no selective reporting of results.

Domains of the QUIPS risk of bias assessment.						
Variable	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting
	e. Adequate description of the period and place of recruitment.	e. There are no important differences between participants who completed the study and those who did not.	e. Adequate proportion of the study sample has complete data for the PF.		e. Appropriate methods are used if imputation is used for missing confounder data.	
	f. Adequate description of inclusion and exclusion criteria.		f. Appropriate methods of imputation are used for missing PF data.		f. Important potential confounders are accounted for in the study design. g. Important potential confounders are accounted for in the analysis.	

3

THESIS

(Cost-)effectiveness of transforaminal epidural steroid injections

BMC Musculoskelet Disord. 2017 May 25;18(1):215

5

CHAPTER

Treatment of acute lumbosacral radicular syndrome with transforaminal epidural corticosteroids and local anesthetic: design of a randomized controlled trial.

Ter Meulen BC, Maas ET, Vyas A, van der Vegt M, de Priester K, de Boer MR, van Tulder MW, Weinstein HC, Ostelo RWJG.

ABSTRACT

Background

Transforaminal epidural injections with steroids (TESIs) are used increasingly for patients with sciatica. However there is much debate about their safety and effectiveness. It is important to identify patients that benefit most from TESIs and only few trials have yet evaluated the effects in patients with acute sciatica.

Methods

We describe a prospective, randomized controlled trial (RCT), with the aim to evaluate the hypothesis that TESI plus Levobupivacaine (TESI-plus) added to oral pain medication is more effective compared to pain medication alone or compared to transforaminal injection with a local anesthetic of short duration among patients with acute sciatica. We will recruit a total of 264 patients with sciatica (< 8 weeks) caused by a herniated disc, from two clinical sites. Participants are randomly assigned one of three study groups: 1) oral pain medication (control group), 2) oral pain medication and TESI-plus (intervention group 1), 3) oral pain medication and transforaminal epidural injection (TEI) with Levobupivaine and saline solution (intervention group 2). Primary outcomes are functional status (Roland-Morris Disability Questionnaire), pain intensity for both leg and back, (100 mm visual analogous scale (VAS)), and global perceived recovery (GPR, reported on a 7-point Likert scale, dichotomized into 'recovered' and 'not recovered'). The secondary outcomes are health-related quality of life (EQ5D-5L) and patient satisfaction (7-point Likert scale). We will also collect information on healthcare utilization and costs, to perform an economic evaluation. All outcomes are measured at three and six weeks, three and six months after randomization. We defined a minimal clinically relevant difference between groups as a difference between both intervention groups and the control group of 20 points for pain (100-point VAS), 4 points for functional status (24-point RDQ) and a 20% difference on dichotomized GPR (recovered versus not recovered).

Discussion

A clinically relevant outcome in favour of TESI-plus implies that future patients with acute sciatica should be recommended TESI-plus within the first few weeks rather than being treated with pain medication alone in order to relieve pain and improve their functioning. In case of a negative result (no relevant differences in outcome between the three study arms), pain medication will remain the mainstay of treatment in the acute stages of sciatica.

BACKGROUND

Sciatica is characterized by neuropathic pain radiating from the lower back into the leg along following the sciatic nerve[1]. The principal source of the pain is nerve root impingement due to a mechanic compression: about 85% of cases of sciatica are caused by intervertebral disc herniation[2]. Patients may experience tingling or pricking in the dermatomal distribution of a nerve root, but sensory symptoms are usually minor[1]. Paresis is present in less than half of patients, for example foot drop due to weakness of the anterior tibial muscle (in case of L5 radiculopathy). The annual incidence of sciatica in The Netherlands is 9.4 cases per 1000 adults [3]. The economic effect of sciatica is major in terms of costs of hospital care and costs resulting from absenteeism from work and disability compared to any other disease category [4,5].

During the first few weeks of symptoms treatment is focused on pain control by means of medication and mobilization by physical therapy. Disc surgery should only be proposed if symptoms persist after conservative treatment. There is no agreement on how much time (in terms of weeks) conservative therapy should be followed before surgery is advisable [6].

Epidural steroid injections are used increasingly as an alternative to pain medication in patients with sciatica, especially in acute patients with severe pain. In the United Kingdom, the number of epidural injections increased from 47 803 in 2000 to 70 967 in 2010 (increase of 49%) [7]. In a retrospective US cohort from 2000–2014 TESIs against back pain increased 609% with an annual increase of 15% per 100 000 Medicare population [8].

There are three different techniques for epidural injection: caudal, interlaminar and tranforaminal. The original caudal approach was developed around 1900 by Sicard[9], and has largely been replaced by the other two methods. Most pain physicians in The Netherlands prefer a transforaminal approach, that is widely regarded as more effective than the interlaminar technique[10]. However, recent data show equivalence between the two[11, 12]. A wide variety of injections fluids is used, including local anesthetics (for example Procaine or Levobupivacaine) and glucocorticosteroids (including methylprednisolone and triamcinolone). During recent years there has been discussion about the effectiveness and safety of epidural corticosteroids against sciatica. In their 2012 meta-analysis that included 23 trials, *Pinto et al* showed only a small but statistically

significant, short-term (<3 months) effect for leg pain of epidural corticosteroids versus placebo (mean difference (MD), - 6.2 on a 100 point visual analogue scale (VAS) [95% CI, -9.4 to -3.0]) and disability (MD, - 3.1 on a 100 point Oswestry and (converted) Rolland Morris Disability scale [95% CI, -5.0 to - 1.2]) [13]. The pooled long-term effects (>12 months) were smaller and not significant. The level of evidence according to the GRADE approach was regarded as high [14]. Another meta-analysis of 30 trials concluded that epidural corticosteroid injections give greater immediate-term (<2 weeks) reduction in pain (MD -7.55 on a 100 point VAS [95% CI, −11.4 to −3.74]) and reduction in disability (standardized MD, −0.33 [95% CI, −0.56 to −0.09]) compared to placebo. The same analysis also showed a lower short-term (>2 weeks to<3 months) surgery risk for patients treated with epidural corticosteroids (relative risk, 0.62 [95% CI, 0.41 to 0.92] [15].

In 2014, the American Food and Drug Administration (FDA) gave out a safety warning after several neurologic events had been reported in patients undergoing epidural corticosteroids, including some fatal events of spinal cord infarction and stroke [16,17]. However, serious complications of injections below conus-level appear to be rare [16,17]. Complications of epidural corticosteroids against sciatica are usually limited to nausea, headache, dizziness, vasovagal attacks and flushing of the face [20,21].

It is important to select patients that benefit most from epidural corticosteroids while closely monitoring their safety [22,23]. Given the fact that most patients with sciatica recover within three months [24,25], and because biochemical markers of inflammation are elevated especially in patients with a short duration of symptoms [26,27], there seems to be a window of opportunity with regards to the timing to treat patients with epidural corticosteroid injections (directed against inflammation) within the first weeks post onset of sciatica.

AIM

The goal of study is to evaluate the effectiveness of TESI-plus and oral pain medication versus oral pain medication alone in improving pain, physical functioning and recovery among patients with sciatica within eight weeks after onset in outpatient clinics. Our hypothesis is that patients who are randomized to receive TESI-plus (intervention group one), will experience less pain and better functional status compared to patients

randomized to receive pain medication alone (control group). A second hypothesis is that TESI-plus is more effective than transforaminal injection with Levobupivacaine and saline solution (intervention group two). Levobupivacaine is a local anesthetic with a short-lasting effect and is usually injected in a small volume. Its supposed effectiveness is minor. We are interested to see if the type of transforaminal epidural injection matters (using equal volumes).

METHODS

We followed the CONSORT statement when designing and reporting this study, a checklist invented to improve the quality of reports of RCTs[28].

Study design

A multicenter, randomized controlled, prospective, single-blind trial will be performed, along with a full economic evaluation from a societal perspective. The subjects will be enrolled at two Dutch hospitals, the Zaans Medisch Centrum, Zaandam and Onze Lieve Vrouwe Gasthuis, Amsterdam. The two hospitals are located in a populated area of The Netherlands. The subjects will be allocated to one of three groups:

1. (Control) oral medication only;
2. (Intervention group 1) oral medication and TESI-plus;
3. (Intervention group 2): oral medication and TEI with Levobupivacaine and saline solution.

Follow-up will be six months. **Figure 1** shows the study design and patient flow.

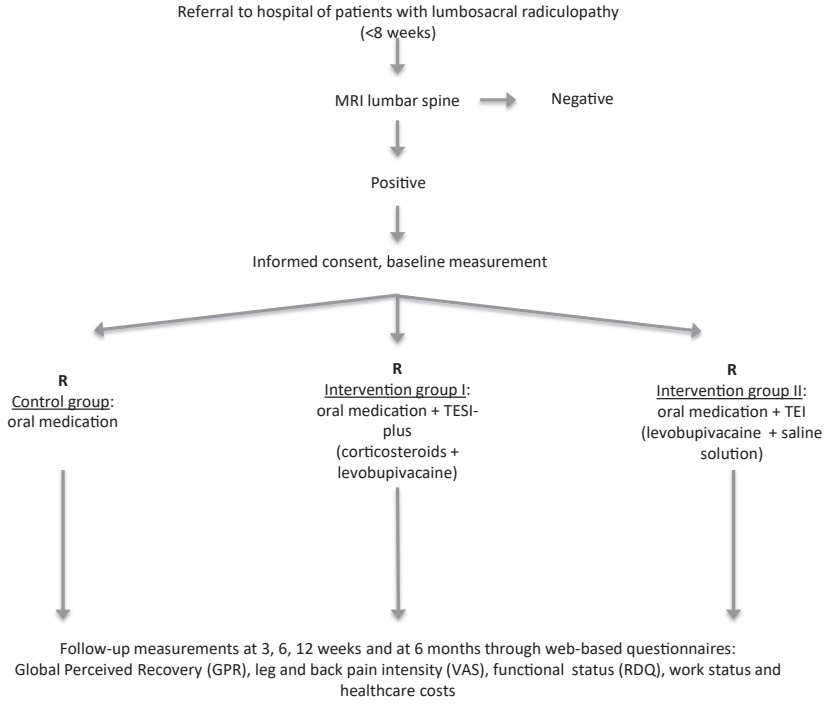

FIGURE 1 Flowchart

This trial will be carried out in accordance with the Declaration of Helsinki. The Boards of Directors of the two hospitals approved the execution of the study in their centers.

Ethical approval

On August 20th 2015, the RCT was evaluated positively by the Medical research Ethics Committees United, Nieuwegein, The Netherlands (registration number NL 45805.100.15) and the protocol was registered at the Dutch Trial Register (number NTR 4457). All patients will give their (written) informed consent before participation in the trial.

Study population

Patients eligible for this study have to have < 8 weeks of sciatic symptoms and will be seen by a neurologist of one of the two study centers upon referral by their general practitioners (GP). Additional inclusion criteria are: a) age between 18 and 75 years; b) a magnetic resonance imaging (MRI) confirmed disc herniation with nerve root impingement causing clinical symptoms; c) pain experienced on average over the last

week rated on a numerical rating scale (NRS) (>4/ 10); d) good understanding of Dutch language; e) internet access in order to complete online questionnaires.

Exclusion criteria are: a) severe weakness of the legs (Medical Research Council ((MRC) score <3); b) spinal surgery < 1 year at the symptomatic lumbar level; c) lumbar spinal stenosis or spondylolisthesis as the cause of radicular pain diagnosed by MRI; d) pregnancy; e) severe comorbidity (e.g. cancer).

Setting

Neurologists at the participating clinics will perform a complete physical and neurological examination. For specific description, see 'baseline measurement'. In case of a clinical suspicion of a herniated disc, MRI of the lumbar spine will be performed. If patients meet the eligibility criteria, they will get oral and written information about the trial. After being informed, the patients will be asked to participate. Upon agreement, the informed consent form will be signed and patients will be randomized by one of the trial nurses. At the start baseline data will be registered. Transforaminal injections will be performed by an experienced anesthesiologist within two working days after randomization. After randomization the clinical and research settings will be separated: all patients will be followed by their own neurologist in the outpatient department and by the research nurse who is responsible for the (web based) questionnaires.

Magnetic Resonance Imaging

Images will be made by a 1.5T MRI scan, gradient strength 33 mT/m, slew rate 125T/m/second (Siemens Magnetom Area , Siemens Medical Solutions, Erlangen, Germany) with a dedicated receive-only spine coil. All participants will be imaged with the same protocol. MR studies will start with a coronal plan scan (GRE;TR/TE=4.20/2.38), followed by a sagittal T1-images (FSE; TR/TE/Etl=660/9,90/3), a sagittal T2-images (FSE;TR/TE/Etl=3530/96/17) and a transverse T2-images (FSE;TR/TE/Etl=5380/91/15). The lumbar spine (T12-S1) will be studied on sagittal images, including imaging of the neural foraminae. Transverse images will be obtained from L3 to S2, with slices angulated parallel to the disci.

Pain medication

Patients in the control and intervention groups use painkillers both over the counter and by prescription. Usually the GPs choose Paracetamol with or without non-steroidal anti-inflammatory drugs (NSAIDs) and, if necessary, opioids following the WHO-pain

ladder[29]. In addition medication against neuropathic pain for example Pregabaline or Gabapentin, is often prescribed. All medication will be registered by online questionnaires. In case of kinesiophobia and/or a substantial inactive lifestyle patients are permitted to go to a physiotherapist. In summary there are no restrictions to pain medication or physiotherapy in all three study groups.

Transforaminal epidural injections

The procedure is similar for both intervention groups. The study participant is brought to a fluoroscopy room and placed in a prone position on the procedure table. Fluoroscopy is used for localization of MRI confirmed disc herniation. Target identification and needle entry into the targeted space is done following internationally accepted procedures[30]. The skin is made sterile using chlorhexidine. The injections are given with 22 gauge 100 mm facet tipped needle (Pajunk RGN™). Right needle position is confirmed with the injection of 0.5-1.5 cc of Joversol 300 mg/ml contrast material (Optiray™ 300, Mallinckrodt). Once an image is obtained demonstrating contrast material spreading into the epidural space medial to a line connecting the ipsilateral lumbar vertebral pedicles, the injection is performed.

The study participants of intervention group one receive 1 ml of 0.5% Levobupivacaine followed by 1 ml of 40 mg/ml Methylprednisolone in an opaque syringe. The study participants of intervention group 2 receive 1 ml 0.5% Levobupivacaine followed by 1 ml NaCl 0.9%. The total volume of the two injections is the same (2 ml).

After the epidural injection the washout of the contrast fluid is demonstrated on an X-ray image. The image will be saved. Finally the needle is removed and the patient is brought to the recovery area.

Baseline measurement & outcomes

We use the core outcome set for clinical trials in low back pain[31].The questionnaires are web-based and will be completed at baseline, three weeks, six weeks, three and six months after randomization.

Baseline measurement

The following potential prognostic factors for recovery at 6 months will be assessed at baseline: age, gender, education, profession, work and marital status, co-existing joint problems, presence of vascular risk factors (diabetes, hypertension) and all primary and secondary outcomes)[32].

Neurological examination, performed by six different neurologists working in the outpatient departments of the participating hospitals, is standardized for all participants. Tests include physical examination of the leg muscles using the Medical Research Council (MRC) scale for muscle strength; sensory examination: tests for perception of light touch, pin prick, and vibration sense of the lower extremities; reflex examination: tests for reflexes in the patellar (L4) and ankle (S1); straight leg raising (or Lasègue's sign): with the patient laying on the back, one leg is lifted upwards by flexing the hip while the knee remains extended. The test is positive if the patient experiences radicular pain when the leg is at an angle between 30 and 70°. A finger-floor distance of more than 25 cm, absence of knee or ankle tendon reflex, leg paresis and a positive straight leg raise test are an indication for a herniated disk with nerve compression on MRI[33]. The added value of a specified neurological examination is limited: most of the information revealed by physical testing will already follow from careful neurological history taking[34].

Primary outcomes

The three primary outcomes are pain, physical functioning and global perceived recovery.

Pain intensity (average previous week) of both back and leg will be rated using a 100 mm VAS: 0 = no pain to 100 = worst imaginable pain[30]. The VAS is known as a valid and reliable measurement among back pain patients[35,36].

GPR will be rated on a 7-point Likert scale that ranges from 'completely recovered' (-3) to 'worse than ever' (+3). The GPR will be dichotomized into success (categories 'completely' and 'much recovered') and non-success (categories 'slightly recovered', 'no change', 'slightly worse', 'much worse' and 'worse than ever'). The GPR is a commonly questionnaire in back pain research[37].

Functional status will be rated using the Dutch version of the Roland-Morris Disability Questionnaire (RDQ) [38]. The RDQ counts 24 items for normal daily activities. Each question has a 'yes' or 'no' option. The RDQ ranges form 0–24 and is a valid and reliable tool that is commonly used back pain studies[38,39].

A minimal clinically important difference is defined as an improvement of 20 points for pain (both leg and back) (100 point VAS), 4 points for functioning (24 point RDQ), and a 20% difference between groups for recovery (recovery vs. non recovery).

Secondary outcomes

The Euroqol-5 dimensions- 5 levels (EQ-5D-5 L) will be used to determine quality of life[40]. The EQ-5D-5 L rates self-care, mobility, pain, psychic functioning (anxiety/depression), and usual activities on a 3-point scale (levels: no problems, moderate problems and severe problems). The EQ-5D-5 L is commonly used in cost-utility analyses and for that reason applied in the economic evaluation as well[39,41].

Patient satisfaction will be assessed using a written 7-point NRS ranging from 'not satisfied at all' to 'completely satisfied'. No gold standard is available for the measurement of patient satisfaction, but in spinal disorders a seven-point global question is recommended[31].

All measurements were registered using web-based questionnaire, which will be sent at baseline, and at three and six weeks, three and six months follow-up.

TABLE 1 Overview of the data collection

Outcome measures		Follow-up			
	Baseline	3 weeks	6 weeks	12 weeks	6 months
Baseline measurements					
Demographic data	X				
Complaint history	X				
Physical examination	X				
MRI lumbar spine	X				
Primary outcomes					
Leg pain intensity (VAS)	X	X	X	X	X
Back pain intensity (VAS)	X	X	X	X	X
Global Perceived Effect (GPE)	X	X	X	X	X
Disability status (RDQ)	X	X	X	X	X
Secondary outcomes					
Work status	X	X	X	X	X
QUALY (EQ-5D)	X	X	X	X	X
Drug use	X	X	X	X	X
Number of surgeries	X	X	X	X	X
Health care costs (journal)	X			X	X

Abbreviations: VAS = Visual Analog Scale; GPE = Global Perceived Effect; RDQ = Roland Disability Scale; EQ-5D = EuroQol

Economic evaluation

The economic evaluation will focus on the comparison of intervention group 1 and the control group.

Intervention costs will be estimated using hospital accounting records. Health care utilization costs (i.e. primary care, secondary care, and the use of prescribed and over-the-counter medication), informal care and unpaid productivity will be collected using self-completed cost questionnaires at three weeks, six weeks, three and six months[42]. Work absenteeism, presenteeism, and productivity losses due to back- or leg pain will be measured by the Productivity and Disease Questionnaire (PRODISC). The PRODISC was validated in samples of patients and employees in The Netherlands[43]. It includes all relevant aspects of the link between health and productivity[44]. Absenteeism from paid work will be estimated by multiplying the total number of sickness absence days during follow-up by their associated costs, using the friction cost approach[45]. Guidelines from the handbook for economic evaluations in the Netherlands will be used[46].

Adverse events and safety issues

All adverse events (AEs) during the study will be recorded on the case record form (CRF), whether or not caused by the study procedure. Registration includes: the event, onset and end date, severity, relation to the study and action taken. AEs considered related to the study will be judged by a medically qualified investigator and followed until resolution (or if the event is regarded stable). All AEs that result in withdrawal from the trial will be followed until there is satisfactory recovery. The investigator will judge whether an AE is severe enough to require the study participant's removal. A study participant may withdraw from the trial if he or she experiences as an intolerable AE. If either side effect will happen, the study participant will get appropriate medical care until symptoms resolve or become stable. There will be an end of study assessment.

Sample Size

Sample sizes were calculated for the three pain, functional status and global perceived effect (for all: power 0.9; two-sided alpha 0.05). A number of 48 patients is needed in each arm to detect a difference of 20 points (VAS for both leg and back pain) between intervention group 1 and the control group between the intervention group 1 and 2. A 20 points difference is considered clinically relevant. A number of 22 patients in each arm is needed to detect a difference of 4 points on the RDQ. A number of 79 patients

in each arm is needed to detect a difference on the dichotomised GPE of 20%. We aim to include a total of 264 patients (n=88 per arm) anticipating a 10% loss to follow up.

Treatment allocation

Randomization will be performed by trial nurses using ALEA® software (NKI-AVL, The Netherlands). Alea® will generate a random schedule of blocks with maximum size of 6. A unique randomization number will be generated for each participant. An independent research nurse will allocate the participants to their group. Patients that belong to one of the intervention groups do not know the type of injection. Coding will not be broken during the trial.

Blinding

This pragmatic trial is partially blinded. The patients do not know the type of injection received, but the anesthesiologist knows the different injection fluids. The neurologists that do the clinical follow-up of the study participants are blinded for the type of injection. The same applies to research nurses and the statistician. All patients will be assigned a unique number to ensure anonymity.

Statistical analysis

Baseline characteristics will be compared of the main outcome measures, potential confounders (including: age, sex, and education) and prognostic factors.

The analysis will be performed according to the intention-to-treat method for all three comparisons (intervention group 1 versus intervention group 2, intervention group 1 versus control group and intervention group 2 versus control group). All continuous variables will be analyzed using a maximum likelihood estimation for linear mixed models under 'missing at random' assumptions. In these analyses we will take into account the levels of patient, time of measurement and hospital, if necessary based on the likelihood ratio test. Regression coefficients and odds ratios with 95% confidence intervals (CI) for all follow up data, adjusted for baseline characteristics will be calculated, with a level of significance of $P<0.05$.

All patients will be analyzed, regardless of the treatment received and violations from the study protocol. Secondly, the per-protocol analysis includes participants with all primary endpoint data available, and for who there have been no major protocol violations. Protocol violations will be reviewed by the research team, blinded to allocation, and

before locking the trial database. Data will be compared between complete and incomplete records to identify possible selective drop-out in the case of missing data.

Economic evaluation

The economic evaluation will be done following an intention-to-treat approach and from a societal perspective.

A multivariate imputation (by chained equations) will be used to impute missing costs and effect data. Bootstrapping with 5000 replications will be used to estimate a 95% CI for differences in total costs between treatment groups.

Cost-effectiveness ratios will be calculated by dividing the difference in mean costs by the mean effect in pain intensity of the two treatment groups. Cost-utility will be expressed in costs per quality adjusted life year (QALY) and based on the EQ5D-5 L. Uncertainties with regard to cost-effectiveness and cost-utility ratios will be estimated using bootstrapping techniques and graphically shown in cost-effectiveness and utility planes. Acceptability curves for cost-effectiveness will also be made. Sensitivity analyses will be carried out for the most important cost drivers in order to assess the robustness.

DISCUSSION

Sciatica is considered to have three pathogenic components: a mechanic component that consists of impingement of the nerve root due to disc herniation; an inflammatory component that can be shown by elevated cytokines in serum and biopsies[26,27]; a neuropathic component caused by neural damage.

We hypothesize that inflammation is predominant during the acute phase of sciatica and wanes after several months in correlation with clinical improvement in most patients. From this idea epidural corticosteroids that are administered locally at the site of the lesion are likely to be effective during the first weeks of an episode of sciatica. We could only find three previous RCTs that have addressed acute treatment of sciatica with epidural corticosteroids before[47–49]. Pooled data (unpublished) did not show significant relief from pain or disability in the corticosteroid group compared to placebo or care as usual. However, due to the low to moderate quality of evidence and the

restricted number of studies included, a firm statement cannot be made based on these results.

A clinically relevant outcome in favor of TESI-plus implies that TESI-plus should be recommended for patients with acute sciatica within the first few weeks rather than being treated conservatively with pain medication alone in order to relieve pain and improve their functioning. In case of a negative result (no clinically relevant differences in outcome) pain medication remains the mainstay of treatment in the acute stages of sciatica.

Regardless of the outcome of our study surgery within the first 2–3 months is reserved for patients with severe pain irresponsive to medication or TESI and patients with neurological deficits (cauda syndrome or weakness).

Recently the safety of TESIs has been debated in the literature[16–22]. Though the complication rate of TESIs of the lumbar spine is known to be low - *Manchikanti et al* doing a thorough review could only identify several cases [18]- all subjects in our study will be closely monitored.The trial started in February 2016. The results will be available at the end of 2017.

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6 CHAPTER

STeroids Against Radiculopathy (STAR) trial: a statistical analysis plan.

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ABSTRACT

Background

Transforaminal epidural injections with steroids (TESIs) are used increasingly for patients with sciatica. However, their safety, effectiveness, and cost-effectiveness are still a matter of debate. This *a priori* statistical analysis plan describes the methodology of the analysis for the STAR-trial that assesses the (cost-)effectiveness of TESI during the acute stage of sciatica (<8 weeks).

Methods

The STAR-trial is a multicenter, randomized controlled, prospective trial (RCT) investigating the (cost-)effectiveness of TESI by making a three group comparison among patients with acute sciatica due to a herniated lumbar disc (<8 weeks): 1) TESI combined with Levobupivacaine added to oral pain medication (Intervention group-1) versus oral pain medication alone (Control group); 2) Intervention group-1 versus transforaminal epidural injection with Levobupivacaine and saline solution added to oral pain medication (Intervention group 2); and 3) Intervention group-2 versus Control group. Co-primary outcomes were physical functioning (Roland Morris Disability Questionnaire), pain intensity (10-point numerical rating scale), and global perceived recovery (7-point Likert scale, dichotomized into 'recovered' and 'not recovered'). For all three comparisons we defined the following minimal clinically relevant between-group differences; two points for pain intensity (range:0-10), four points for physical functioning (range:0-24) and a 20% difference in recovery rate. Secondary outcomes are health-related quality of life (EQ-5D-5L) and patient satisfaction (7-point Likert scale) and surgery rate. We also collected resource use data to perform an economic evaluation. Analyses will be conducted by intention-to-treat with $p<0.05$ (two-tailed) for all three comparisons. Effects will be estimated using mixed models by maximum likelihood. For each comparison, mean differences, or difference in proportions, between groups will be tested per time point and an overall mean difference, or difference in proportions, between groups during the complete duration of follow-up (6 months) will be estimated. In the economic evaluation, Multivariate Imputation by Chained Equations will be used to handle missing data. Cost and effect differences will be estimated using seemingly unrelated regression, and uncertainty will be estimated using bootstrapping techniques.

Discussion

This statistical analysis plan provides detailed information on the intended analysis of the STAR-trial, which aims to deliver evidence about the (cost-)effectiveness of TESI during the acute phase of sciatica (<8 weeks).

UPDATE

Sciatica or lumbar radicular syndrome is a disabling condition characterized by radiating leg pain, with or without low back pain[1]. Sciatica may be accompanied by neurological deficits, such as weakness of the leg muscles or sensory loss. About 85% of sciatica cases are caused by lumbar disc herniation[2]. During the first few weeks after onset, treatment primarily focusses on pain reduction and improvement of physical functioning (https://www.nice.org.uk/guidance/ng59/chapter/Recommendations). Pain medication and physiotherapy are usually initiated by the general practitioner. If patients are referred to a hospital in case of moderate to severe pain or neurological deficits, they are typically treated with epidural corticosteroid injections or surgery. However, the effectiveness, cost-effectiveness and safety [3–6] of epidural corticosteroid injections are still a matter of debate and therefore more high-quality RCTs are needed.

The STAR-trial (STeroids Against Radiculopathy) assesses both the effectiveness and cost-effectiveness of transforaminal epidural injections with steroids (TESIs) in patients with acute sciatica (<8weeks post onset). This is done by making the following three comparisons: (1) TESI combined with levobupivacaine added to oral pain medication (intervention group 1) versus oral pain medication alone (control group), (2) intervention group 1 versus transforaminal epidural injection with levobupivacaine and saline solution added to oral pain medication (intervention group 2), and (3) intervention group 2 versus control group. Our hypothesis is that intervention-1 group will experience less pain and better physical functioning compared to both the control group and intervention group 2 and that intervention group 2 is more effective than the control group as well. Hence, these interventions will be assessed for superiority.

Participant recruitment commenced in January 2016 and was completed in November 2019. Data collection was completed in April 2020. This statistical analysis plan details the planned analyses for the STAR-trial to facilitate transparency of our data analyses and was developed according to appropriate guidelines[7]. The initial statistical analysis plan was approved and signed by the study investigators on April 23th 2020 and was revised on September 1, 2020. All of the statistical analyses will be performed following data integrity checks and locking and will be commenced in October 2020.

STUDY OVERVIEW

Trial design

The STAR-trial is a multicentre, randomized controlled, prospective trial that investigates the effectiveness and cost-effectiveness of TESI by making a three-group comparison among patients with acute sciatica due to a herniated lumbar disc (<8 weeks): (1) TESI combined with levobupivacaine added to oral pain medication (intervention group 1) versus oral pain medication alone (control group), (2) intervention group 1 versus transforaminal epidural injection with levobupivacaine and saline solution added to oral pain medication (intervention group 2), and (3) intervention group 2 versus control group. Follow-up is 6 months. On March 6, 2014, the protocol was registered at the Dutch Trial Register (number NTR 4457). On August 20, 2015, the design of the STAR-trial was approved by the Medical research Ethics Committees United, Nieuwegein, The Netherlands (registration number NL 45805.100.15) and the study protocol has been published elsewhere[8].

Study population

Between January 13, 2016, and September 10, 2019, 141 eligible participants[8], who were seeking care for their back-related leg pain (sciatica), were recruited from two Dutch Neurology outpatient clinics (i.e. the Zaans Medisch Centrum, Zaandam and OLVG, Amsterdam, The Netherlands).

To be eligible for this study had to have <8 weeks of sciatic symptoms and had to be seen by a neurologist in one of the two study centres upon referral by their general practitioners (GP). Additional inclusion criteria were (a) age between 18 and 75 years, (b) a magnetic resonance imaging (MRI) confirmed disc herniation with nerve root impingement causing clinical symptoms, (c) an average pain intensity of >4 on a 10-point numerical rating scale (NRS) during the last week, (d) good understanding of the Dutch language, and (e) Internet access in order to be able to complete online questionnaires [8]. Exclusion criteria were (a) severe weakness of the legs (Medical Research Council [MRC] score <3), (b) spinal surgery during the previous year at the symptomatic lumbar level, (c) lumbar spinal stenosis or spondylolisthesis as the cause of radicular pain diagnosed by MRI, (d) pregnancy, and (e) severe comorbidity (e.g. cancer)[8].

Sample Size

We had initially aimed to include 264 patients (n = 88 per arm)[8]. This sample size was based on the three co-primary outcomes (i.e. pain, physical functioning, and global perceived effect), a 10% loss to follow-up, a power of 0.9, and a two-sided alpha of 0.05. We calculated that 48 patients would be needed per arm to detect a minimal clinical important difference of 20 points (SD = 30) for both leg and back pain on a 10-point NRS between intervention group 1 and control[9]. Moreover, 22 patients were estimated to be required per arm to detect a difference of 4 points (SD = 4) on the RDMQ-24 scale and 79 patients per arm to detect a difference on the dichotomized GPE of 20%. Unfortunately, this sample size was not reached, as the trial was stopped prematurely due to slow participant accrual. Stopping the trial was a decision by the research team only, meaning that there was no data monitoring board involved, and was based on prior evidence that very few trials with less than 50% of the required sample size at 1 to 2 years after launch ultimately attain sufficient accrual[10]. When trial inclusion stopped at September 10, 2019, 46, 50, and 45 patients were randomized to intervention group 1, intervention group 2, and control, respectively. Consequently, the analyses will likely to be slightly underpowered for pain intensity and global perceived effect, but not for physical functioning.

Randomization and treatment allocation

After providing informed consent and completing baseline questionnaires, eligible patients were randomized, stratified for treatment centre, by the study coordinator (BTM) using ALEA® software (NKI-AVL, The Netherlands). Alea® generated a random schedule of blocks with a maximum size of 6. Allocation across groups was at a 1:1:1 ratio.

Study conditions

A detailed description of the study conditions can be found in the design article[8].

In brief, the transforaminal epidural injection procedure was similar for intervention group 1 and intervention group 2. That is, the study participant was brought to a fluoroscopy room and placed in a prone position on the procedure table. Fluoroscopy was used for localization of MRI confirmed disc herniation. Target identification and needle entry into the targeted space was done following internationally accepted procedures [9]. In short, the skin was made sterile using chlorhexidine. The injections were given with 22 gauge 100 mm facet tipped needle (Pajunk RGN™). Right needle position was confirmed with the injection of 0.5–1.5 cc of Joversol 300 mg/ml contrast material (Optiray™ 300,

Mallinckrodt). Once an image was obtained demonstrating contrast material spreading into the epidural space medial to a line connecting the ipsilateral lumbar vertebral pedicles, the injection was performed [8].

Patients in intervention group 1 received 1 ml of 0.5% levobupivacaine followed by 1 ml of 40 mg/ml methylprednisolone in an opaque syringe. Patients in intervention group 2 received 1 ml 0.5% levobupivacaine followed by 1 ml NaCl 0.9%[8].

All treatment groups were allowed to use oral pain medication and were permitted to go to a physiotherapist in case of kinesiophobia and/or an inactive lifestyle. All oral pain medication during the trial was registered by the participants themselves in Survalyzer, an online questionnaire (www.survalyzer.com). All patients participating in the trial underwent MR Imaging of the lumbar spine that was evaluated by a radiologist (see design article for scan protocol) [8].

Protocol deviations

Protocol deviations were defined as Intervention group 1 and Intervention group 2 patients who received no epidural injection, more epidural injections than prescribed by the study protocol, and/or a type of injection fluid other than the one prescribed by the study protocol. For the Control group, protocol deviations were defined as patients who received one or more epidural injections in spite of being randomized to the oral pain medication alone condition. Protocol deviations will be confirmed prior to database lock for the final analysis. All protocol violators will be included in the main analysis and a per-protocol analysis will be performed to assess the impact of protocol deviations if more than 10% of the patients will be found to have deviated from the protocol.

Blinding

This pragmatic trial was partially blinded. Patients in Intervention group-1 and Intervention group-2 did not know which type of injection they received. However, the type of injection fluid was known to the anesthesiologist performing the injections. Neurologists who performing the clinical follow-up of the patients were blinded for the type of injection (intervention group 1 versus intervention group 2). The same applied to research nurses.

Patient characteristics and study outcomes

Patients were asked to complete a web-based questionnaire, containing descriptive questions as well as questions on clinical outcomes and resource use, at baseline, 3 and 6 weeks, and 3 and 6 months after randomization using Survalyzer (www.survalyzer.com). The neurological examination at baseline, length and weight were registered in Openclinica for clinical data (https://www.openclinica.com/). **Table 1** gives a schematic overview of the data collection process.

TABLE 1 Overview of the data collection

Outcome measures	Follow-up				
	Baseline	3 weeks	6 weeks	12 weeks	26 weeks
Baseline measurements					
Demographic data	X				
Prognostic factors	X				
Complaint history	X				
Physical examination	X				
MRI lumbar spine	X				
Primary outcomes					
Leg pain intensity (VAS)	X	X	X	X	X
Back pain intensity (VAS)	X	X	X	X	X
Global Perceived Effect (GPE)		X	X	X	X
Functional status (RDQ)	X	X	X	X	X
Secondary outcomes					
Work status	X	X	X	X	X
Quality of life (EQ-5D-5L)	X	X	X	X	X
Drug use	X	X	X	X	X
Other resource use (cost questionnaire)	X			X	X
Surgery					X

Baseline measurement

At baseline, all primary and secondary outcomes were measured and additional information was collected on:

- Demographics: age, gender, length and weight, education level, work and marital status.
- Episode details: back and leg pain duration.
- Neurological examination : physical examination of the leg muscles using the Medical Research Council (MRC) scale for muscle strength; sensory examination: tests for

perception of light touch, pin prick, and vibration sense of the lower extremities; reflex examination: tests for reflexes in the patellar (L4) and ankle (S1); straight leg raising (or Lasègue's sign) and a finger-floor distance. Straight leg raising was considered positive if the patient experienced radicular pain when the leg is at an angle <60°. A finger-floor distance of more than 25 cm was considered indicative for a herniated disc.

- Magnetic resonance imagining: level and side of disc herniation.

Co-primary outcomes

Our co-primary outcomes included pain intensity (back and leg), physical functioning and global perceived recovery and were assessed at baseline, 3 and 6 weeks, and 3 and 6 months.

Pain intensity was assessed by asking patients about their average pain during the previous week, in both the back and the leg, and was rated using a 10-point NRS: 0 = no pain to 10 = worst imaginable pain[11].

Physical functioning was assessed using the Dutch version of the Roland Morris Disability Questionnaire (RDMQ)[12]. The RDMQ includes 24 items assessing normal daily activities. Each question has a 'yes' or 'no' option and the overall RDMQ-24 scale ranges from 0 to 24, with higher values indicating more physical limitations[13].

Global perceived recovery (GPR) was rated on a 7-point Likert scale, ranging from 'completely recovered' to 'worse than ever'. The GPR was dichotomized into recovered (categories 'completely' and 'much recovered') and (categories 'slightly recovered', 'no change', 'slightly worse', 'much worse' and 'worse than ever')[14].

For the co-primary outcomes, we defined the following minimal clinically relevant between-group differences for all three comparisons: two points for pain intensity (range 0–10), four points for physical functioning (range 0–24) and a 20% difference in recovery rate across groups [9]. In accordance with the guidelines of the 'European Medicines Agency', we will only consider one intervention effective over another, if statistically significant and clinically relevant differences are found between them for all co-primary outcomes (https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf) and therefore we will not adjust our analyses for multiplicity induced by having co-primary outcomes. We will also not

adjust for multiplicity induced by having 3 comparators, because we will conduct various pairwise comparisons (i.e. intervention 1 versus control, intervention 2 versus control, intervention 1 versus control) with a clear hierarchy in anticipated effectiveness (i.e. intervention 1>intervention 2>control), instead of a global test of unordered groups[15].

Secondary outcomes

Secondary outcomes included health-related quality of life, patient satisfaction and surgery rate and were assessed at baseline, 3 and 6 weeks, and 3 and 6 months.

Health-related quality of life was assessed using the Euroqol-5 dimensions-5 levels (EQ-5D-5L) [16]. The EQ-5D-5L asks patients to rate the severity of their health problems (levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems) on five health dimensions (health dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The patients' resulting EQ-5D-5L health states will be converted to utility values ranging from 0 (equal to death) to 1 (equal to full health) using the Dutch tariff[17]. For the economic evaluation, quality-adjusted life years will be estimated by multiplying the time spent in a certain health state by its respective utility value.

Patient satisfaction was assessed using a 7-point Likert scale ranging from 'not satisfied at all' to 'completely satisfied'[18].

Surgery rate was assessed by keeping track of whether or not patients needed surgery in spite of conservative treatment (control group) and a possible epidural injection recorded in the case record form (CRF). Surgery rate was measured as dichotomous outcome, indicating whether patients received a surgery during follow-up (yes = 1/no = 0).

Confounding Factors

Confounding factors were *a priori* selected based on evidence from existing studies in sciatica, and expertise within the study team[19,20]. The factors were age, gender, body mass index (BMI) and severity of back and leg pain at baseline.

Societal costs

Intervention costs will be estimated using a micro-costing approach. That is, detailed information on the number of TESIs performed per patient and the cost per TESI were collected from hospital accounting records. Information regarding the use of all other kinds of resources was collected using online cost questionnaires administered

at 3 weeks, 6 weeks, and 3 and 6 months. See **Additional file** for the questionnaire. For assessing absenteeism and presenteeism, slightly adapted versions of the World Health Organization – Work Performance Questionnaire (WHO-HPQ) and the iMTA Productivity Cost Questionnaire (iPCQ) were used, respectively[21,22]. Healthcare utilization, consisting of the use of primary care, secondary care, prescribed and over-the-counter medication, were valued using Dutch standard prices and unit prices derived from http://www.medicijnkosten.nl. If unavailable, prices according to professional organizations were used. Informal care and unpaid productivity losses were valued using a recommended Dutch shadow price[23]. Absenteeism was valued in accordance with the Friction Cost Approach, with a friction period of 12 weeks, and using gender-specific price weights. Presenteeism was valued using gender-specific price weights as well[24]. All costs were converted to Euros 2020 using consumer price indices.

Adverse events and safety issues

All adverse events (AEs) during the study were recorded on the case record form (CRF), whether or not caused by the study procedure. Registration included: the event, onset and end date, severity, relation to the study and action taken. AEs considered related to the study were judged by a medically qualified investigator and followed until resolution (or if the event was regarded stable). There were no AEs that resulted in withdrawal from the trial.

Registering and handling of data

A trial master file was established in Amsterdam by the coordinating investigator (BTM). The registering of data was done consecutively throughout the study. Data were registered in a case report form (CRF) for each patient. Throughout the study, the registering and handling of data followed the principles of good clinical practice (GCP). The data will be kept in a locked facility for 15 years after the study is finished. After this it will be destroyed. The statistical master file is kept by the department of Data Management, at Amsterdam UMC (location VUMC) Amsterdam, the Netherlands.

STATISTICAL ANALYSIS

All analysis described in this plan are considered *a priori* analyses in that they have been defined in the study protocol and/or this SAP. All *post hoc* analyses will be identified as

such in the article. Analyses will be consistent with the intention-to-treat principle and will be performed using software package SPSS v26 and STATA v16.

Trial profile

The following summaries will be presented in a flow diagram according to the CONSORT statement[25]: the number of patients with acute sciatica that were screened for eligibility at the Neurology outpatient clinics in Amsterdam and Zaanstad and the number of patients that was eventually randomized after providing informed consent, stratified for each treatment group. Additionally, the number and percentages of patients lost to follow-up will be reported per treatment arm, including information about the timing and reason(s) for loss to follow-up. See **Figure 1** for overview.

Data Integrity

Prior to the analyses, the integrity of trial data will be checked by scrutinizing data files for omissions and errors. The source of any inconsistencies will be explored and resolved.

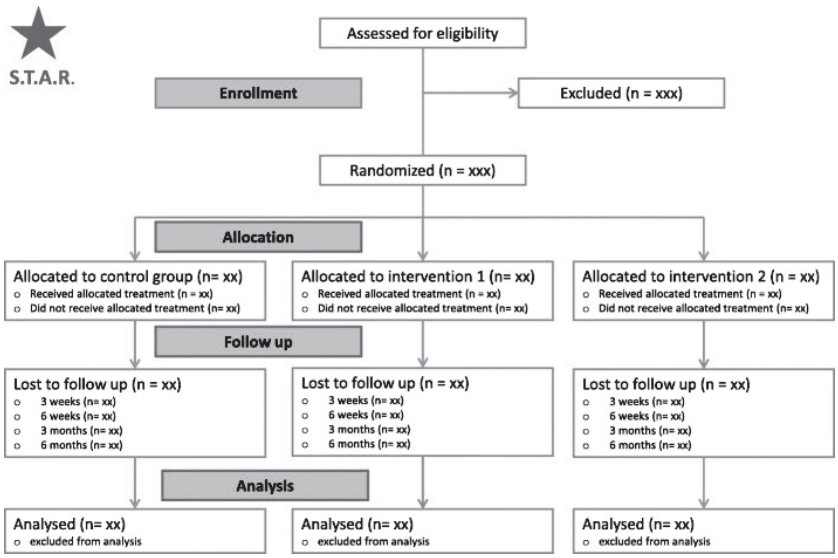

FIGURE 1 STAR-trial: enrollment and randomization

Methods for handling missing data

In the effect analyses, missing data will be handled using mixed models by maximum likelihood estimation[26]. In case more than 10% of patients have missing data, defined as having missing data on one or more variable, sensitivity analyses will be performed using mixed models with multiple imputation. For the economic evaluation, missing data will be multiply imputed, irrespective of the percentage of patients of missing data. This strategy is advised in economic evaluations, because total costs are the sum of numerous cost components, so total costs will already be missing if only one item is missing. Data will be multiply imputed using Multivariate Imputation by Chained Equations (MICE) and the number of imputed datasets will be determined using the loss of efficiency approach[27]. Imputation models will include all available cost and effect measure values as well as variables differing between groups at baseline, those variables related to the "missingness" of data and variables related to the outcomes. Pooled estimates will be calculated using Rubin's rules.

Evaluation of demographics and baseline patient characteristics

Demographic baseline characteristics will be described per treatment group (**Table 2**). Continuous variables will be summarized using standard measures of central tendency and dispersion, as either mean and standard error (data that with a normal distribution) or median and interquartile range (data with a skewed distribution). Dichotomous or categorical variables will be summarized by frequencies and percentages. In accordance with the CONSORT statement, we will not statistically test whether baseline differences across study groups[25,28].

Primary analysis

All statistical tests of the primary and secondary analyses will be 2-sided and both 95% confidence intervals (95% CIs) and p-values will be reported. Moreover, as indicated above, three pairwise comparisons will be conducted per outcome; 1) Intervention-1 versus Control; 2) Intervention-2 versus Control; and 3) Intervention-1 versus control. The assumption of normal distribution will be checked by visual inspection and using a QQ-plot. Non-normally distributed data will be log-transformed. If normality will not be achieved after log-transformation, data will be dichotomized into either having a minimal clinically important improvement or not (e.g. ≥2 points for pain and ≥4 points for physical functioning [yes/no]) Pain intensity (back and leg) and physical functioning will be assessed using linear mixed models by maximum likelihood and global perceived recovery will be assessed using logistic mixed models by maximum likelihood. All models will have a 2-level

TABLE 2 Baseline variables

	Control group (n = xxx)	Intervention group 1 (n = xxx)	Intervention group 2 (n= xxx)
Participants characteristics			
Female	n/N (%)	n/N (%)	n/N (%)
Age (years)	M +- SD	M +- SD	M +- SD
BMI	M +- SD	M +- SD	M +- SD
Vascular risk factors- no. (%)	x (%)	x (%)	x (%)
Joint problems- no. (%)	x (%)	x (%)	x (%)
Education level- no. (%)[a]			
Low	x (%)	x (%)	x (%)
moderate	x (%)	x (%)	x (%)
high	x (%)	x (%)	x (%)
Married or with a partner- no. (%)	x (%)	x (%)	x (%)
Having a paid job- no. (%)	x (%)	x (%)	x (%)
Neurological examination			
Motor deficit – no. (%)	x (%)	x (%)	x (%)
Sensory deficit- no (%)	x (%)	x (%)	x (%)
Pain on straight leg raising- no (%)	x (%)	x (%)	x (%)
Level of herniation (MRI)- no (%)			
L3-4	x (%)	x (%)	x (%)
L4-5	x (%)	x (%)	x (%)
L5-S1	x (%)	x (%)	x (%)
Primary outcomes			
Leg pain intensity score[b]	M +- SD	M +- SD	M +- SD
Back pain intensity score[b]	M +- SD	M +- SD	M +- SD
Functional status[c]	M +- SD	M +- SD	M +- SD
Secondary outcomes			
Quality of life[d]			

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared)

[a] Low indicates preschool, primary school, or lower secondary school; moderate indicates higher secondary school or undergraduate; high indicates tertiary, university, or postgraduate.

[b]Measured by numeric rating scale (score range, 0-10); a higher score indicates more severe pain intensity.

[c]Measured by Roland Disability Questionnaire (score range, 0-24); a higher score indicates worse functioning.

[d]Measured by EQ-5D-5 L (score range, 0-1); a higher score indicates better quality of life.

structure, with time clustered within patients. Linear and logistic mixed models will be fitted using an "independent" covariance matrix for the random effects, which allows for a distinct variance for each random effect within a random-effects equation and assumes that all covariances are 0. Linear mixed models will also use a large-sample approximation of the sampling distribution of the test statistic and will assume that all residuals are independent and identically distributed Gaussian with a common variance (www.stata.com). The necessity of having a random intercept and/or a random slope will be assessed using the likelihood-ratio test. For all co-primary outcomes, the main effect will be the pooled mean difference, or difference in proportions, across groups during the complete duration of follow-up. Additionally, mean differences, or differences in proportions, across groups will be tested per time point using time by treatment interactions. For all co-primary outcomes, adjusted (adjusted for the predefined confounders; see above) and unadjusted analyses will be performed and presented (**Table 3**).

TABLE 3 Primary outcomes according to treatment and timing

Outcome		Intervention group 1 Mean (SD)	Intervention group 2 Mean (SD)	Control group Mean (SD)	Comparison 1 Treatment effect Mean Difference (95%CI)	Comparison 2 Treatment effect Mean Difference (95%CI)	Comparison 3 Treatment effect Mean Difference (95%CI)
Back pain	***Overall effect***				***X (XX – XX)_***	***X (XX – XX)_***	***X (XX – XX)_***
	Baseline	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	3 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	6 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	12 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	26 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
Leg pain	***Overall effect***				***X (XX – XX)_***	***X (XX – XX)_***	***X (XX – XX)_***
	Baseline	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	3 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	6 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	12 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	26 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
Physical functioning	***Overall effect***				***X (XX – XX)_***	***X (XX – XX)_***	***X (XX – XX)_***
	Baseline	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	3 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	6 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	12 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	26 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_

TABLE 3 Primary outcomes according to treatment and timing

		Intervention group N (%)		Control group (%) N (%)	Treatment effect Odds Ratio (95%CI)	Treatment effect Odds Ratio (95%CI)	Treatment effect Odds Ratio (95%CI)
Global Perceived Effect	***Overall effect***				***X (XX – XX)_***	***X (XX – XX)_***	***X (XX – XX)_***
	3 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	6 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	12 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	26 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_

Note: Comparison 1: Intervention group 1 versus control; Comparison 2: Intervention group 2 versus control; Comparison 3: Intervention group 1 versus Intervention group 2

Secondary analysis

Secondary outcomes health-related quality of life and satisfaction will be analysed using the same linear mixed models as the primary analysis. Surgery rate will be assessed using a logistic regression and both an adjusted and an unadjusted analysis will be performed and presented (**Table 4**).

TABLE 4 Secondary outcomes according to treatment and timing

Outcome		Intervention group 1 Mean (SD)	Intervention group 2 Mean (SD)	Control group Mean (SD)	Comparison 1 Treatment effect Mean Difference (95%CI)	Comparison 2 Treatment effect Mean Difference (95%CI)	Comparison 3 Treatment effect Mean Difference (95%CI)
Health-related quality of life	***Overall effect***				***X (XX – XX)_***	***X (XX – XX)_***	***X (XX – XX)_***
	Baseline	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	3 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	6 months	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	12 months	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	26 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
Patient satisfaction	***Overall effect***				***X (XX – XX)_***	***X (XX – XX)_***	***X (XX – XX)_***
	Baseline	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	3 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	6 months	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	12 months	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
	26 weeks	X (XX)	X (XX)	X (XX)	X (XX – XX)_	X (XX – XX)_	X (XX – XX)_
Total number of surgeries performed	26 weeks	X	X	X	X	X	X

Note: Comparison 1: Intervention group 1 versus control; Comparison 2: Intervention group 2 versus control; Comparison 3: Intervention group 1 versus Intervention group 2.

Economic evaluation

The economic evaluation will focus on all three comparisons; i.e. Intervention group-1 versus Control group; Intervention group-1 versus Intervention group-2; and Intervention group-2 versus Control group.

The economic evaluation will be performed for all co-primary outcomes and QALYs. In the main analysis, the societal perspective will be applied, meaning that all costs will be included, irrespective of who pays or benefits from them. Unadjusted as well as adjusted cost differences across groups will be calculated for total and disaggregated costs. 95% CIs around those cost differences will be estimated using Bias Corrected and Accelerated (BCA) bootstrapping, with 5000 replications. Cost and effect differences across groups will be estimated using Seemingly Unrelated Regression (SUR) analyses, in which both are modelled simultaneously so that their possible correlation can be accounted for. Incremental Cost-Effectiveness Ratios (ICERs) will be estimated by dividing the differences in costs by those in effects. The uncertainty surrounding the ICERs will be graphically illustrated by plotting bootstrapped cost-effect pairs on cost-effectiveness planes. Again, these bootstrapped cost-effect pairs will be estimated using the BCA bootstrap, with 5000 replications. An estimate of the joint uncertainty surrounding costs and effects will be provided by constructing cost-effectiveness acceptability curves (CEACs). These CEACs will provide an estimate of the probability of the interventions being cost-effective compared with each other. To assess the robustness of the results, Three sensitivity analyses will be performed. In sensitivity analysis 1 (SA1), the healthcare perspective will be applied, meaning that only costs accruing to the formal Dutch healthcare system will be included in the analyses. In SA2, the Human Capital Approach will be used instead of the Friction Cost Approach for estimating absenteeism costs. In SA3, only data of patients with complete cost and effect measure values at all measurement points will be included.

DISCUSSION

During the last decade, there has been extensive debate about the effectiveness of epidural corticosteroids for treating sciatica. A 2020 meta-analysis, as part of the Dutch multidisciplinary guideline on sciatica (https://richtlijnendatabase.nl/richtlijn/lumbosacraal_radiculair_syndroom/lumbosacraal_radiculair_syndroom_-_startpagina.html) (and based on 6 systematic reviews [4,5,29–32]), showed a small, but statistically

significant, short-term (<3 months) effect for leg pain of epidural corticosteroids versus placebo (mean difference (MD), 0.94 on a 10 point visual analogue scale (VAS) [95% CI, 0.14 to 1.73]). Moreover, for physical functioning, a small not clinically relevant standardized mean difference of 0.32 (95% BI −0.58 to 1.22) was found in favour of epidural steroids. However, the level of evidence of these studies according to the GRADE approach[33] was regarded as low. Therefore, this two-centre, randomized controlled, prospective, single-blind trial (STeroids Against Radiculopathy [STAR]) will provide valuable information about the effectiveness, cost-effectiveness and safety of transforaminal epidural steroids in patients with sciatica shorter than 8 weeks, a subgroup that has hardly been addressed so far[34–36].

Unfortunately, however, we had to stop our trial prematurely, because of slow patient accrual, with only 53.4% of the required sample size being included in 2.5 years. Issues that affected slow patient accrual were the fact that (according to their guidelines) (https://richtlijnen.nhg.org/standaarden/lumbosacraal-radiculair-syndroom) Dutch general practitioners typically wait at least 6 weeks before referring patients with sciatica to a hospital; the fact that there were only 2 participating centres, and the fact that patients who believe in the superiority of epidural steroid injection over conservative treatment experience difficulty with being randomized and prefer active treatment with an epidural steroid injection. This is a well-known problem in back pain research[37,38], but it will likely negatively affect the generalizability of our results to other (Dutch) sciatica patients and will result in the study being slightly underpowered for pain intensity and global perceived effect, but not for physical functioning.

CONCLUSION

The STAR-trial aims to provide evidence about TESIs in the treatment of acute sciatica (<8 weeks). This statistical analysis plan details the study's planned analyses, to aid transparency of results, and may assist the design of studies in the future.

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ADDITIONAL FILE

Kosten-vragenlijsten

Instructie

De volgende vragen zijn bedoeld om in kaart te brengen, met welke hulpverleners u voor uzelf in de **afgelopen 3 maanden** contact heeft gehad. Denk aan de periode tussen nu en drie maanden geleden.

Met het aantal contacten bedoelen wij spreekuren, bezoeken op afspraak, telefonische contacten en huisbezoek. Telefonische contacten met de secretaresse of assistenten van een hulpverlener om een afspraak te maken dienen niet meegeteld te worden.

Als u een antwoord niet precies weet, mag u gerust een schatting geven.

1. Hoeveel afspraken had u in de afgelopen 3 maanden met onderstaande hulpverleners vanwege uw hernia?

Hulpverlener	Aantal afspraken
Huisarts	□ Geen enkele afspraak □ ..... afspraken (Wilt u alle spreekuurbezoek, bezoek op afspraak, huisbezoek en telefonische consulten in de afgelopen 3 maanden bij elkaar optellen.)
Bedrijfsarts	□ Geen enkele afspraak □..... afspraken
Maatschappelijk werker	□ Geen enkele afspraak □ ..... afspraken
Psycholoog/psychotherapeut	□ Geen enkele afspraak □ ..... afspraken
Psychiater	□ Geen enkele afspraak □ ..... afspraken

2. Hoeveel afspraken had u in de afgelopen 3 maanden met onderstaande therapeuten of alternatief geneeskundigen vanwege uw hernia?

Therapeut	Aantal afspraken
Fysiotherapeut	□ Geen enkele afspraak □ ..... afspraken
Cesartherapeut of mensendiecktherapeut	□ Geen enkele afspraak □ ..... afspraken
Ergotherapeut	□ Geen enkele afspraak □ ..... afspraken
Manueel therapeut	□ Geen enkele afspraak □ ..... afspraken
Chiropractor	□ Geen enkele afspraak □ ..... afspraken
Homeopaat	□ Geen enkele afspraak □ ..... afspraken
Acupuncturist	□ Geen enkele afspraak □ ..... afspraken
Andere therapeut of alternatief geneeskundige	□ Geen enkele afspraak → ga verder naar vraag 5 □ Wel afspraken → vul hierna voor iedere therapeut of alternatief geneeskundige apart het aantal afspraken in
Andere therapeut of alternatief geneeskundige, namelijk:	□ ..... afspraken
Andere therapeut of alternatief geneeskundige, namelijk:	□ ..... afspraken
Andere therapeut of alternatief geneeskundige, namelijk:	□ ..... afspraken

3. Hoe vaak bent u in de afgelopen 3 maanden op afspraak geweest bij de polikliniek vanwege uw hernia?

Het gaat om afspraken voor uzelf met een dokter, bijvoorbeeld met de neurochirurg. Bent u meer dan 1 keer ergens behandeld in de afgelopen 3 maanden? Tel dan alle behandelingen bij elkaar op.

Instelling	Aantal keer behandeld
Ziekenhuis,	□ Niet behandeld □ Zo ja, in welk ziekenhuis: .....
Revalidatiecentrum	□ Niet behandeld □ Zo ja, in welk revalidatiecentrum .....
Andere instelling, namelijk:	□ In welke instelling: .....

4. Hoe vaak bent u in de afgelopen 3 maanden voor een dagbehandeling in een instelling geweest vanwege uw hernia?

U bleef dus niet slapen. Bent u meer dan 1 keer ergens voor dagbehandeling geweest in de afgelopen 3 maanden? Tel dan alle behandelingen bij elkaar op.

Instelling	Aantal keer behandeld
Ziekenhuis	□ Niet behandeld □ Zo ja, in welk ziekenhuis: .....
Revalidatiecentrum	□ Niet behandeld □ Zo ja, in welk revalidatiecentrum .....
Andere instelling, namelijk:	□ In welke instelling: .....

5. Hoe vaak bent u in de afgelopen 3 maanden opgenomen vanwege uw hernia?
Bijvoorbeeld omdat u geopereerd was en niet meteen naar huis kon. Moest u meer dan 1 keer ergens worden opgenomen in de afgelopen 3 maanden? Tel dan alle dagen bij elkaar op.

Instelling	Aantal keer opgenomen
Ziekenhuis, Zo ja, op welke afdeling:..... Zo ja, welke ingrepen:.....	□ Niet opgenomen □ Zo ja, In welk ziekenhuis..... ..... keer, ... dagen in totaal
Revalidatiecentrum	□ Niet opgenomen □ Zo ja, In welk revalidatiecentrum..... ..... keer, ... dagen in totaal
Andere instelling, namelijk:	□ Niet opgenomen □ Zo ja, In welke instelling..... .....keer,.....dagen in totaal

6. Hebt u in de afgelopen 3 maanden MEDICIJNEN gebruikt vanwege uw hernia?
(Pakt u zo mogelijk de verpakking van de medicatie erbij. (Medicijnen tijdens ziekenhuisopname **niet** meerekenen, evenmin als de anti conceptie pil.)

□ Nee

□ Ja, namelijk:

Tip: pak het doosje of potje erbij. Daarop staat hoeveel u per keer moest nemen. En hoe vaak op een dag u dat moest doen. ***Heeft u meer of minder gebruikt? Vul dan in hoeveel u echt gebruikt heeft.***

Hoe heet het medicijn?	Hoeveel heeft u per keer genomen? Kijk op het doosje of potje.	Hoe vaak op een dag heeft u dit gedaan? Kijk op het doosje of potje.	Op hoeveel dagen in de afgelopen 6 weken heeft u het medicijn gebruikt?	Zijn de medicijnen op voorgeschreven door de huisarts of andere medisch specialist?	Wat was de toedieningsvorm van het medicijn? (mogelijkheden: tablet, capsule, drank, poeder, injectie, zetpil, crème/zalf)
voorbeeld paracetamol met coffeine	*Voorbeeld* 500 mg	*voorbeeld* 4	*voorbeeld* 3 dagen	*voorbeeld* *Ja/Nee*	*Voorbeeld* *tablet*

7. Hoe vaak kreeg u in de afgelopen 3 maanden hulp van de thuiszorg vanwege uw hernia?

Soort zorg	Hoeveel zorg
Huishoudelijke hulp voorbeeld: stofzuigen, bed opmaken, boodschappen doen	□ Geen huishoudelijke hulp □ ..... weken, gemiddeld ..... uur in de week
Verzorging van uzelf voorbeeld: hulp bij douchen of aankleden	□ Geen verzorging □ ..... weken, gemiddeld ..... uur in de week
Verpleging voorbeeld: verband omdoen, medicijnen geven	□ Geen verpleging □ ..... weken, gemiddeld ..... uur in de week

8. Hoe vaak kreeg u in de afgelopen 3 maanden hulp van familie, buren of vrienden vanwege uw hernia?

Soort zorg	Hoeveel zorg
Hulp van familie, buren of vrienden	□ Geen hulp □ ..... weken, gemiddeld ..... uur in de week

WERK EN VERZUIM

Productivity and Disease Questionnaire (PRODISQ)

1. Heeft u op dit moment betaald werk?

- Ja
- Nee → Ga verder naar vraag 12

2. Voor hoeveel uur per week heeft u een aanstelling volgens uw contract?

…… uren per week

3. Over hoeveel dagen zijn deze uren verdeeld volgens uw contract?

……dagen

4. Werkt u op dit moment het aantal uren volgens uw contract?

Ja

Nee, Ik werk……uren per week

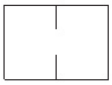
(bijvoorbeeld vanwege gedeeltelijk ziekteverzuim of werk op therapeutische basis)

6. Over hoeveel dagen zijn deze uren op dit moment verdeeld?

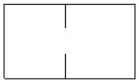
……dagen

7. Verzuimt u op dit moment vanwege uw rugklachten?

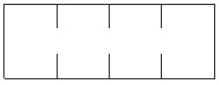
- Ja , sinds wanneer:



dag



maand



Jaar

Ga door naar vraag 12.

- Nee

8. Hoe vaak heeft u de afgelopen 3 maanden verzuimd vanwege uw rugklachten?

…… periodes

9. Hoeveel werkdagen (in totaal) heeft u de afgelopen 3 maanden verzuimd vanwege uw rugklachten?

.....werkdagen

10. Heeft u in de afgelopen 3 maanden onbetaald werk/dagelijkse bezigheden niet kunnen doen vanwege uw rugklachten?

Tel alle uren van de afgelopen drie maanden bij elkaar op.

Soort werk	Tijd niet kunnen doen
Vrijwilligerswerk	□ Niet van toepassing □..... uren in totaal
Huishoudelijk werk	□ Niet van toepassing □..... uren in totaal
Ander onbetaald werk, namelijk:	□ Niet van toepassing □..... uren in totaal

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7

CHAPTER

Effect of transforaminal epidural corticosteroid injections in acute sciatica: a randomized controlled trial.

Ter Meulen BC, Van Dongen JM, Maas E, Van der Vegt M, Haumann J, Weinstein HC, Ostelo RWJG.

ABSTRACT

Objective

Transforaminal epidural steroid injections (TESIs) are widely administered for sciatica. The aim of this trial was to evaluate the effectiveness of TESIs in patients with acute sciatica (<8 weeks).

Methods

This study was conducted in two Dutch hospitals. Participants (n=141) were randomly assigned to: 1) usual care and TESI of 1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine (intervention 1); 2) usual care and transforaminal epidural injection with 1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9% (intervention 2); 3) usual care consisting of oral pain medication with or without physiotherapy (control). Co-primary outcomes were back- and leg pain intensity, physical functioning and recovery measured during 6-month follow-up.

Results

There were no significant mean differences in co-primary outcomes between groups during follow-up, except for leg pain when comparing intervention group 1 with control (-0.96 95%CI:-1.83 to -0.09). For secondary outcomes, some significant between group differences were found for treatment satisfaction and surgery, but only when comparing intervention group 2 to control. Post-hoc analyses showed a significant difference in response (50% improvement of leg pain [yes/no]) between intervention 1 and the control group at 3 months and that both intervention groups used less opioids.

Discussion

Except for a statistically significant effect of TESI on leg pain for patients with acute sciatica compared to usual care, there were no differences in co-primary outcomes. Nonetheless, transforaminal epidural injections seem to be associated with less opioid use, which warrants further exploration.

INTRODUCTION

Sciatica is characterized by pain radiating into the leg following one of the lumbosacral nerve roots[1] and has an estimated prevalence between 1.3 and 43%[2]. This considerable variation in prevalence estimates may be due to differences in definitions, methods of data collection, and perhaps populations studied[2].The most common cause is a herniated disc that will be found in 85%[3].The prognosis is favorable, as 75% of patients are expected to reach acceptable pain levels without surgery within three months[4]. However, a recent study showed that only 55% of sciatica patients had a ≥30% reduction in disability one year after their first medical consultation[5].

As a first line of treatment, patients with sciatica are treated conservatively with analgesics, the advice to maintain daily activities, and possibly physiotherapy[6-8]. According to Dutch General Practitioner (GP)-guidelines[6], patients who do not recover within six weeks are referred to secondary care to explore the potential for transforaminal epidural corticosteroid injections (TESIs) or disc surgery, except patients with severe pain and/or invalidating neurological deficits who are referred immediately.

TESIs are increasingly used in patients with sciatica[9,10]. The current Dutch multidisciplinary protocol on sciatica[11] advises TESIs for patients with severe pain and disability due to sciatica regardless of a time frame. So that means that for both, acute and or chronic, epidural steroid injections are considered as an option, at least for patients with severe complaints. A recent survey in the Netherlands showed that 40% of neurologists and anesthesiologists are of the opinion that TESIs are effective in reducing pain in 40-60% of injected patients[12]. This seems to be in contrast with the current evidence. That is, three recent systematic reviews and meta-analyses found that TESI slightly reduce leg pain and disability compared to a placebo at short-term (4-6 weeks) follow-up in patients with sciatica, but not at long term follow up (>3 months)[13-15]. According to GRADE[16], the quality of that evidence is low to moderate. Moreover, most randomized controlled trials (RCTs) included in the systematic reviews only addressed chronic sciatica (>3 months), and hence the effectiveness of TESIs in acute sciatica remains uncertain (<8 weeks). Therefore, this study aimed to assess the effectiveness of TESI in patients with acute sciatica due to a herniated disc compared to usual care and compared to a transforaminal injection with local anesthetic and saline solution. It could be hypothesized that adequate pain management at an earlier stage might have the potential to prevent patients from becoming chronic.

METHODS

Study design and patients

The STeroids Against Radiculopathy (STAR) trial was conducted in the Zaans Medisch Centrum (Zaandam) and OLVG Hospital (Amsterdam) between January 13th 2016 and March 10th 2020. We compared three arms: 1) usual care and TESI of 1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine (intervention group 1); 2) usual care and a transforaminal epidural injection (TEI) with 1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9% (intervention group 2), and 3) usual care consisting of oral medication with or without physiotherapy (control). We mainly focused on the comparison between group 1 and 3, and group 1 and 2. Written informed consent was obtained from all participants. The trial protocol[17] was published at the start of the trial. The statistical analysis plan (SAP)[18] was published after ending the trial, but before commencement of the data analysis. For reporting, the CONSORT statement was followed.

Eligible patients had<8 weeks of sciatica (new episode) and were seen by a neurologist upon referral by their GPs. Additional inclusion criteria were: a) aged between 18 and 75 years; b) a magnetic resonance imaging (MRI) confirmed disc herniation with nerve root impingement causing clinical symptoms; c) average pain intensity over the last week rated on a numerical rating scale (NRS)(>4/10); d) good understanding of the Dutch language; e) internet access. Exclusion criteria were: a) severe weakness of the legs (Medical Research Council [MRC]) score <3); b) spinal surgery<1 year at the symptomatic level; c) lumbar spinal stenosis or spondylolisthesis as the cause of radicular pain; d) pregnancy; e) severe comorbidity.

Randomization

Randomization, using ALEA® software (NKI-AVL, The Netherlands), generated a random schedule of blocks with a maximum size of six at a 1:1:1 ratio. Patients in the intervention arms were blinded to the type of injection they received. Coding was not broken during the trial.

Interventions

The procedure was similar for both intervention arms (group 1 and 2). Participants were brought to a fluoroscopy room and placed in a prone position on the procedure table. Fluoroscopy was used for the localization of the MRI confirmed disc herniation. Target identification and needle entry was done following international procedures[19]. At first, the skin was prepped using chlorhexidine. Second, the injections were given with 22-gauge 100mm facet tipped needle (Pajunk RGN™). Right needle position was confirmed with the

injection of 0.5-1.5cc of Joversol 300 mg/ml contrast material (Optiray™ 300, Mallinckrodt). Once an image was obtained demonstrating contrast material spreading into the epidural space medial to a line connecting the ipsilateral lumbar vertebral pedicles, the injection was performed at the level of the herniated disc. The injection was not repeated.

The study participants of intervention group 1 received 1 ml of 0.5% Levobupivacaine followed by 1 ml of 40 mg/ml Methylprednisolone in an opaque syringe (TESI). The study participants of intervention group 2 received 1 ml 0.5% Levobupivacaine followed by 1 ml NaCl 0.9%. The total volume of the two injections was the same (2 ml)[16].

After the epidural injection the washout of the contrast fluid was demonstrated on an X-ray image. The image was saved. Finally, the needle was removed and the patient was brought to the recovery area.

Usual care

There were no restrictions to the use of (oral) analgesics in all three groups and if patients used analgesics this was registered using online questionnaires[20]. There were no restrictions regarding physiotherapy. This reflects usual care for patients with acute sciatica in the Netherlands.

Outcomes

Baseline information was collected on demographics (i.e. age, gender, length and weight, education, work, and marital status), back and leg pain duration, neurological examination, and magnetic resonance imagining (level and side of disc herniation)[21]. Co-primary and secondary outcomes were measured at baseline, three and six weeks, as well as three and six months using Survalyzer, a web-based questionnaire[20].

Co-primary outcomes were back and leg pain (average previous week), as measured on a 0-10 Numerical Rating Scale (NRS)[22], physical functioning measured by the Dutch versions of the Roland-Morris Disability Questionnaire (RMDQ)[23,24], and global perceived recovery (GPR). The RDMQ includes 24 items assessing normal daily activities (scored as yes=1/no=0). The overall RDMQ score ranges from 0 to 24, with higher values indicating more physical limitations. The GPR is a 7-point Likert scale[25], ranging from '1=completely recovered' to '7=worse than ever'. The GPR was dichotomized into 'success' ('completely' and 'much recovered') and 'non-success' ('slightly recovered', 'no change', 'slightly worse', 'much worse' and 'worse than ever').

Secondary outcomes included health-related quality of life (EQ-5D-3L)[26], patient satisfaction, and surgery rate. The EQ-5D-3L comprises five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each health dimension has 3 severity levels: no problems, some problems, and extreme problems. The patients' EQ-5D-3L health states were converted to utility values using the Dutch tariff[27]. For satisfaction, a 7-point Likert scale was used, ranging from '1=not satisfied at all' to '7=completely satisfied'[28]. Surgery rate during follow-up was measured as a dichotomous outcome (having received disc surgery during follow-up: yes=1/no=0).

Data on serious adverse events and adverse events were collected[16]. A serious adverse event was defined as any adverse event or reaction, regardless of causality, that resulted in death, was life-threatening, necessitated hospitalization, or was considered to be an important medical event.

Confounding factors were *a priori* selected based on previous studies[29,30]. These factors were age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

Sample size calculation

Sample sizes were calculated for each co-primary outcome based on a power of 0.9 and a two-sided alpha of 0.05. These calculations indicated that 48 patients were needed per arm to detect a clinically relevant between-group MD of two points on the 0-10 NRS for leg and back pain (SD=30). For physical functioning, 22 patients were needed per arm to detect a clinically relevant between-group MD of 4 points (SD=4). For the dichotomized GPR, 79 patients were needed per arm to detect a clinically relevant between-group difference of 20%[31,32]. Anticipating a 10% loss to follow-up, we therefore aimed to include 264 patients (n=88 per arm).

In accordance with the guidelines of the 'European Medicines Agency', we will only consider one intervention effective over another, if statistically significant and clinically relevant differences are found between them for all co-primary outcomes[33,34].

Statistical analysis

Analyses were defined a priori in our SAP[17], were conducted by intention-to-treat, and were performed using SPSS v26 and STATA v16.

All statistical tests of the co-primary and secondary outcomes were 2-sided and both 95% confidence intervals (95%CIs) and p-values were reported. The normality assumption was confirmed by visual inspection and using a QQ-plot. The intervention's effect on pain intensity and physical functioning were assessed using linear mixed models by maximum likelihood. For GPR, logistic mixed models by maximum likelihood were used. All models had a 2-level structure, with time clustered within patients. The necessity of additional random intercepts and/or slopes was assessed using the likelihood-ratio test. This test showed that this was not necessary. For all co-primary outcomes, the overall effect was the pooled MD, or Odds Ratio (OR), between groups during follow-up. Additionally, MDs or ORs between groups were tested per time point using time by treatment interactions. All co-primary outcomes were adjusted for the predefined confounders and their baseline values. Assuming data to be MAR, missing data were handled by maximum likelihood. Secondary outcomes were analysed in accordance with the methods above, i.e. using linear mixed models for continuous outcomes and logistic mixed models for dichotomous outcomes.

Sensitivity and post-hoc analyses

To assess the robustness of our results to the methods used for handling missing data, two sensitivity analyses were performed: 1) a complete-case analysis and 2) an analysis in which missing data were multiply imputed. Additionally, two post-hoc analyses were performed: 1) responder analyses, assessing the interventions' effect on treatment success, defined as either having >30% or >50% improvement in leg pain; and 2) analyses assessing the interventions' effect on opioid use during follow-up (i.e. patient used opioids: yes/no).

RESULTS

Patients

During the study period, 1,564 adults with sciatica (regardless of duration) and MRI-confirmed nerve root were seen in the two participating centres. Of them, 141 patients had acute sciatica (<8 weeks) and were willing to participate. After providing informed consent, 45 patients were randomized to control, 46 to intervention group 1, and 50 to intervention group 2 (**Figure 1**).

Baseline characteristics are presented in **Table 1** and were comparable among groups, except for the proportions of women, participants with a partner, and participants with motor deficits per group.

A positive straight leg raise test was the most frequent finding in 113 (80.1%) participants during neurological examination. Sensory loss was more frequent than weakness (N=96 (68.8%) vs. N=26 (18.4%) examinations). Most patients had a herniated disc at the L4-5 (N=60 (42.6%)) or L5-S1 (N=63 (44.7%)).

In total, 78% of control patients and 70% of patients in intervention group-1 and intervention group-2 completed the trial's six months of follow-up (**Figure 1**). The participants' hospital records showed that there were 4 protocol violators (see **Appendix I**). As this number was below the predefined 10% violation limit, we did not conduct a per-protocol analysis[18]. During the first 3 months of follow-up, 37.5%, 50.0%, and 34.2% of patients visited a physiotherapist in intervention group 1, intervention group 2, and the control group, respectively.

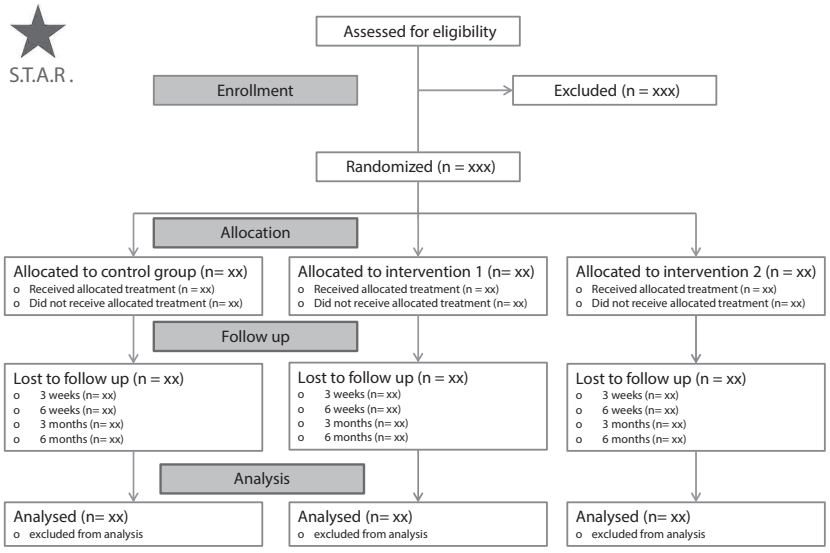

FIGURE 1 STAR-trial: enrollment and randomization

Co-primary outcomes

The adjusted between-group differences during follow-up and per time point can be found in **Table 2** for the co-primary outcomes. The results of the corresponding unadjusted analyses were similar and therefore are not shown.

TABLE 1 Baseline variables

	Control group (n = 45)	Intervention group 1 (n = 46)	Intervention group 2 (n= 50)
Participants characteristics			
Female- no. (%)	19 (42.2)	26 (56.5)	25 (50.0)
Age- years (SD)	49.2 (12.5)	45.7 (12.9)	48.4 (13.8)
BMI (SD)	26.2 (4.5)	26.4 (5.0)	27.3 (5.6)
Vascular risk factors- no. (%)*	11 (24.4)	13(28.2)	16(32.0)
Education level[a]- no. (%)			
low	9 (20.0)	9 (19.6)	13 (26.0)
moderate	24 (53.3)	23 (50.0)	25 (50.0)
high	12(26.7)	14 (30.4)	12 (24.0)
Married or with a partner- no. (%)	35 (77.8)	28 (60.9)	36 (72.0)
Having a paid job- no. (%)	41 (91.1)	43 (93.5)	45 (90.0)
Neurological examination			
Motor deficit – no. (%)	12 (26.6)	6 (13.0)	8 (16.0)
Sensory deficit- no (%)	31 (68.9)	28 (60.9)	37 (74.0)
Pain on straight leg raising- no (%)	37 (82.2)	37 (80.4)	39 (78.0)
Level of herniation (MRI)- no (%)			
L2-3	1 (2.2)	3 (6.5)	3 (6.0)
L3-4	2 (4.4)	6 (13.0)	9 (18.0)
L4-5	19 (42.2)	18 (39.1)	23 (46.0)
L5-S1	23 (51.1)	22 (47.8)	18 (36.0)
Primary outcomes*			
Leg pain intensity score[b] - mean(SD)	7.3 (2.0)	7.8 (1.8)	7.7 (1.9)
Back pain intensity score[b]- mean (SD)	5.3 (3.1)	5.9 (2.7)	5.8 (3.0)
Physical functioning[c]- mean (SD)	17.5 (3.1)	18.2 (4.2)	16.6 (4.6)
Secondary outcomes*			
Health-related quality of life[d]- mean (SD)	0.74 (0.07)	0.71 (0.07)	0.73 (0.07)

*n = 136

a. Low includes preschool, primary school, or lower secondary school; moderate includes higher secondary school or undergraduate; high includes tertiary, university, or postgraduate.

b. Leg pain and back pain intensity were measured by means of the numerical pain rating scale (NRS), whereby patients were asked to measure their average pain over the previous 24 hours on a 0-10 scale, with 0 indicating no pain and 10 indicating the worst imaginable pain.

c. The extent of physical functioning was measured on the Roland Disability Scale of Sciatica (scores ranging from 0 to 23, with higher scores indicating greater physical functioning).

d. Health-related quality of life was assessed using the Euroqol 5- dimensions - 3 levels (EQ-5D-3L) and converted to utility values ranging from 0 (equal to death) to 1 (equal to full health) using the Dutch tariff.

TABLE 2 Co-primary outcomes according to treatment and timing

Outcome		Intervention group 1 Mean (SD)	Intervention group 2 Mean (SD)	Control group Mean (SD)	Comparison 1 (Int. group 1 vs. Control) Treatment effect* Mean Difference (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2) Treatment effect* Mean Difference (95%CI)	p-value	Comparison 3 (Int. group 2 vs. Control) Treatment effect* Mean Difference (95%CI)	p-value
Back pain (0-10)	***Overall effect***				***-0.59 (-1.40 to 0.22)***	***0.153***	***-0.41 (-1.18 to 0.36)***	***0.294***	***-0.22 (-1.08 to 0.65)***	***0.624***
	Baseline	5.89 (2.74)	5.79 (3.01)	5.30 (3.07)						
	3 weeks	4.08 (2.83)	4.26 (3.22)	4.19 (2.96)	-0.71 (-1.94 to 0.51)	0.252	-0.27 (-1.42 to 0.88)	0.641	-0.45 (-1.64 to 0.75)	0.462
	6 weeks	3.65 (2.68)	4.26 (2.93)	4.15 (2.71)	-1.10 (-2.36 to 0.15)	0.085	-0.67 (-1.85 to 0.51)	0.268	-0.43 (-1.66 to 0.79)	0.490
	3 months	3.55 (2.78)	3.76 (3.13)	3.64 (2.82)	-0.74 (-2.05 to 0.57)	0.272	-0.12 (-1.35 to 1.11)	0.849	-0.60 (-1.85 to 0.65)	0.346
	6 months	3.44 (2.97)	3.40 (2.84)	2.97 (2.41)	-0.29 (-1.60 to 1.01)	0.658	-0.07 (-1.30 to 1.17)	0.917	-0.23 (-1.49 to 1.04)	0.726
Leg pain (0-10)	***Overall effect***				***-0.96 (-1.83 to -0.09)***	***0.030***	***-0.64 (-1.44 to 0.16)***	***0.119***	***-0.31 (-1.15 to 0.54)***	***0.473***
	Baseline	7.84 (1.76)	7.65 (1.94)	7.32 (1.97)						
	3 weeks	5.33(2.78)	5.45(2.84)	5.26(2.89)	-0.49 (-1.81 to 0.83)	0.467	-0.28 (-1.50 to 0.95)	0.659	-0.19 (-1.48 to 1.10)	0.770
	6 weeks	4.14 (2.85)	4.82 (2.85)	4.36 (3.11)	-0.77 (-2.12 to 0.59)	0.266	-0.86 (-2.11 to 0.39)	0.178	0.13 (-1.19 to 1.45)	0.845
	3 months	2.74 (2.73)	3.73 (2.90)	3.94 (2.95)	-1.78 (-3.19 to -0.36)	0.014	-1.01 (-2.31 to 0.29)	0.128	-0.69 (-2.04 to 0.66)	0.314
	6 months	2.69 (2.95)	2.91 (3.15)	3.14 (3.03)	-1.08 (-2.49 to 0.32)	0.131	-0.35 (-1.65 to 0.96)	0.600	-0.68 (-2.04 to 0.68)	0.328
Physical functioning (0-24)	***Overall effect***				***-1.61 (-3.81 to 0.58)***	***0.150***	***0.07 (-2.14 to 2.29)***	***0.948***	***-1.65 (-3.90 to 0.59)***	***0.148***
	Baseline	18.18 (4.19)	16.56 (4.55)	17.55 (3.19)						
	3 weeks	11.30 (6.73)	10.48 (5.62)	12.14 (6.48)	-1.58 (-4.53 to 1.36)	0.292	-0.80 (-3.51 to 1.92)	0.564	-0.74 (-3.63 to 2.14)	0.611
	6 weeks	9.08 (7.57)	8.13 (6.78)	10.26 (6.99)	-1.77 (-4.79 to 1.25)	0.251	-0.87 (-3.65 to 1.92)	0.542	-0.88 (-3.84 to 2.07)	0.559
	3 months	8.23 (6.90)	7.76 (7.33)	9.94 (7.23)	-2.38 (-5.53 to 0.77)	0.139	-0.96 (-3.85 to 1.94)	0.517	-1.37 (-4.38 to 1.65)	0.375
	6 months	7.91 (6.75)	6.21 (7.49)	7.03 (7.17)	0.36 (-2.78 to 3.49)	0.823	0.10 (-2.82 to 3.02)	0.947	0.29 (-2.77 to 3.35)	0.853

TABLE 2 Co-primary outcomes according to treatment and timing

		Intervention group 1 N (%)	Intervention group 2 N (%)	Control group N (%)	Comparison 1 (Int. group 1 vs. Control) Treatment effect* Treatment effect Odds Ratio (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2) Treatment effect* Treatment effect Odds Ratio (95%CI)	p-value	Comparison 3 (Int. group 2 vs. Control) Treatment effect* Treatment effect Odds Ratio (95%CI)	p-value
Global Perceived Recovery (non success = ref)	***Overall effect***				***1.79 (0.83 to 3.86)***	***0.136***	***0.93 (0.35 to 2.48)***	***0.886***	***1.60 (0.74 to 3.48)***	***0.233***
	3 weeks	9 (31%)	11 (39%)	7 (24%)	1.95 (0.40 to 9.68)	0.411	0.55 (0.09 to 3.35)	0.516	2.52 (0.56 to 11.30)	0.228
	6 weeks	11 (39%)	16 (55%)	10 (34%)	1.90 (0.41 to 8.67)	0.412	0.41 (0.07 to 2.36)	0.316	3.30 (0.79 to 13.77)	0.102
	3 months	21 (68%)	22 (59%)	22 (56%)	3.19 (0.73 to 13.87)	0.123	2.03 (0.37 to 10.96)	0.412	1.37 (0.38 to 4.90)	0.625
	6 months	22 (69%)	22 (65%)	24 (67%)	1.84 (0.42 to 8.08)	0.419	1.85 (0.33 to 10.33)	0.481	0.94 (0.24 to 3.54)	0.928

*all analyses have been adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

The groups are defined as following: 1) usual care and TESI of 1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine (intervention group 1);2) usual care and a transforaminal epidural injection (TEI) with 1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9% (intervention group 2); 3) usual care consisting of oral pain medication with or without physiotherapy (control).

There were no significant mean differences in co-primary outcomes between groups during follow-up, except for leg pain when comparing intervention group 1 with control, albeit not clinically relevantly so (-0.96 95%CI:-1.83 to -0.09).

Secondary outcomes

For the secondary outcomes (**Table 3**), there were no statistically significant between-group differences when comparing intervention 1 to the control and comparing intervention 1 to intervention 2. When comparing intervention 2 to control there were several statistically significant differences: i.e. the overall MD in treatment satisfaction was -0.62 (95%CI:-1.03 to -0.22), the three months difference was -0.80 (95%CI:-1.42 to -0.19) and the six months difference was -0.87 (95%CI:-1.49 to -0.26). For surgery, the OR was 0.36 (95%CI: 0.13 to 1.00), in favour of patients receiving 1ml 0.5% Levobupivacaine followed by 1ml NaCl 0.9%. Given a 30.3% prevalence of the outcome in the control group, this corresponds to a Relative Risk of 0.46 (95%CI:0.19 to 1.00)[35]. All these differences were not considered clinically relevant.

Adverse effects

There were no adverse effects reported. No participants were withdrawn for the trial out of safety measures.

Sensitivity analyses and post-hoc analyses

Results of the sensitivity analyses were in line with those of the main analysis, meaning that the overall conclusion of the study would not change when using any of their results. (**Appendix II**).

Post-hoc analyses showed that there was a statistically significant difference in response between intervention group 1 and the control group at three months (OR=5.50 95%CI: 1.36 22.2) when response was defined as a 50% improvement in leg pain (**Table 3**). Given a 54.3% prevalence of the outcome in the control group, this corresponds to a Relative Risk of 1.59 (95%CI: 1.14 to 1.77). Moreover, for opioid use, in both intervention groups, statistically significantly less patients used opioids compared to the control group at 3 and 6 months (Table 3). To illustrate, at 6 months, the number of opioid users was 13 (28.3%) in intervention group 1 and 12 (24.0%) in intervention group 2 versus 23 (51.1%) the control group.

TABLE 3 Secondary outcomes and post-hoc analyses according to treatment and timing

Outcome		Intervention group 1 Mean (SD)	Intervention group 2 Mean (SD)	Control group Mean (SD)	Comparison 1 (Int. group 1 vs. Control) Treatment effect* Mean Difference (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. Group 2) Treatment effect* Mean Difference (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect* Mean Difference (95%CI)	p-value
Treatment satisfaction (1-7)	***Overall effect***				***-0.39 (-0.85 to 0.08)***	***0.102***	***0.24 (-0.24 to 0.74)***	***0.330***	***-0.62 (-1.03 to - 0.22)***	***0.003***
	Baseline									
	3 weeks	3.36 (1.39)	3.24 (1.56)	3.54 (0.92)	-0.30 (-0.84 to 0.23)	0.257	0.04 (-0.62 to 0.70)	0.905	-0.37 (-0.93 to 0.19)	0.193
	6 weeks	3.00 (1.58)	2.82 (1.25)	3.16 (1.17)	-0.49 (-1.11 to 0.12)	0.115	0.03 (-0.57 to 0.64)	0.911	-0.45 (-0.98 to 0.09)	0.100
	3 months	3.00 (1.63)	2.65 (1.32)	3.50 (1.21)	-0.52 (-1.24 to 0.20)	0.152	0.18 (-0.51 to 0.87)	0.605	-0.80 (-1.42 to -0.19)	0.012
	6 months	2.91 (1.51)	2.32 (1.12)	3.28 (1.49)	-0.36 (-1.06 to 0.34)	0.307	0.51 (-0.14 to 1.16)	0.125	-0.87 (-1.49 to -0.26)	0.006
Health related quality of life (0-1)	***Overall effect***				***0.05 (-0.05 to 0.14)***	***0.334***	***-0.05 (-0.15 to 0.05)***	***0.307***	***-0.08 (-0.01 to 0.17)***	***0.096***
	Baseline	0.22 (0.36)	0.30 (0.34)	0.28 (0.36)						
	3 weeks	0.42 (0.40)	0.52 (0.28)	0.43 (0.28)	0.05 (-0.11 to 0.21)	0.507	-0.02 (-0.17 to 0.13)	0.770	0.08 (-0.08 to 0.23)	0.331
	6 weeks	0.55 (0.33)	0.61 (0.30)	0.51 (0.32)	0.11 (-0.05 to 0.27)	0.191	0.03 (-0.12 to 0.19)	0.680	0.08 (-0.08 to 0.23)	0.325
	3 months	0.60 (0.37)	0.65 (0.34)	0.61 (0.31)	0.04 (-0.13 to 0.20)	0.671	0.02 (-0.14 to 0.18)	0.779	0.01 (-0.15 to 0.17)	0.884
	6 months	0.67 (0.29)	0.75 (0.28)	0.73 (0.27)	0.00 (-0.17 to 0.17)	0.998	0.00 (-0.17 to 0.16)	0.971	0.00 (-0.16 to 0.16)	0.995

TABLE 3 Secondary outcomes and post-hoc analyses according to treatment and timing

		Intervention group 1 N (%)	Intervention group 2 N (%)	Control group (%) N (%)	Comparison 1 (Int. group 1 vs. Control) Treatment effect* Treatment effect Odds Ratio (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. Group 2) Treatment effect* Treatment effect Odds Ratio (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect* Treatment effect Odds Ratio (95%CI)	p-value
Surgery	Total over 6 months	15 (32.61)	9 (18.75)	15 (33.33)	0.68 (0.25 to 1.80)	0.434	2.08 (0.73 to 5.89)	0.170	0.36 (0.13 to 1.00)	0.049
Responders analysis (30%)	3 months	25 (80.6)	23 (62.2)	24 (68.6)	2.63 (0.70 to 9.82)	0.150	2.95 (0.90 to 9.70)	0.075	0.69 (0.24 to 1.97)	0.489
	6 months	26 (81.3)	25 (71.1)	25 (71.1)	2.63 (0.65 to 10.60)	0.175	2.01 (0.58 to 6.94)	0.268	1.16 (0.37 to 3.62)	0.795
Responders analysis (50%)	3 months	23 (74.2)	22 (59.5)	19 (54.3)	5.50 (1.36 to 22.2)	0.017	2.36 (0.75 to 7.41)	0.142	1.25 (0.45 to 3.45)	0.673
	6 months	23 (71.9)	22 (62.9)	22 (62.9)	1.85 (0.58 to 5.87)	0.296	1.74 (0.57 to 5.33)	0.333	1.10 (0.39 to 3.07)	0.859
Opioid use	3 months	19 (41.3)	18 (36.0)	30 (66.7)	0.33 (0.13 to 0.84)	0.021	1.29 0.55 to 3.03)	0.552	0.25 (0.10 to 0.62)	0.003
	6 months	13 (28.3)	12 (24.0)	23 (51.1)	0.31 (0.11 to 0.86)	0.025	1.18 (0.46 to 3.03)	0.726	0.31 (0.13 to 0.79)	0.013

* all analyses have been adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

The groups are defined as following: 1) usual care and TESI of 1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine (intervention group 1);2) usual care and a transforaminal epidural injection (TEI) with 1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9% (intervention group 2); 3) usual care consisting of oral pain medication with or without physiotherapy (control).

DISCUSSION

This RCT found that when comparing TESI, as administered in intervention group 1 (1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine) to usual care, there was only a small statistically significant, albeit not clinically relevant, effect for improvement in leg pain. For the other co-primary outcomes, no statically significant, nor clinically relevant, differences were found. For the comparison between intervention group 1 and intervention group 2 (1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9%), no statistically significant or clinically relevant differences were found. Consequently, in accordance with the EMA-guidelines, the intervention could not be considered effective[33].

For the comparison between intervention group 2 and control there were several statistically significant between group differences for surgery and treatment satisfaction, but these were considered not clinically relevant. Sensitivity analyses showed that these results are rather robust, so handing missing data differently did not influence the results.

A post-hoc analysis showed that statistically significantly more patients who received TESI experienced a relief in leg pain of more than 50% compared to patients that received usual care alone at 3 months. Moreover, both intervention groups were found to use significantly less opioids than patients who solely received usual care at 3 and 6 months. Further prospective research into the effect of epidural injections (with or without steroids) on the use of pain medication is warranted, particularly in the light of the global 'opioid crisis'[35].

Comparison with the literature

We found only one other RCT that addressed the acute stage of sciatica[36]. This study (n=63), had 2 treatment arms comparing TESI added to usual care to usual care alone. The TESI group scored statistically significant better than the usual care group in terms of physical functioning after half a year and a year, respectively. However, the overall MDs was not considered not be clinically relevant (in line with the results of the STAR-trial). There is one ongoing trial that has a similar comparison as the STAR-trial (i.e. only TESI versus usual care). This RCT that has not finished yet[37].

Strengths and limitations

A major strength is that our study has three treatment arms, while most other studies have two treatment arms. This enabled a head-to-head comparison between two

available treatment options (TESI vs usual care) and to explore the efficacy (the specific effect of steroids) of TESI as we were able to compare it with an injection without steroids. Another strength is the careful selection procedure, as all herniated discs were confirmed by MRI.

Our RCT also had limitations. First, even though the required sample size was reached for the co-primary outcomes pain and physical functioning, the study was underpowered for the co-primary outcome GPR. This was due to the fact that recruitment of patients was hampered by various factors that can be divided into: 1) research factors, such as the fact that (the subjects were only enrolled in 2 hospitals (a larger number of participating hospitals could have helped optimize patient recruitment and was therefore attempted, but this was not successful); 2) patient factors such as the fact that potential candidates sometimes refused to participate, because of their preference for an active treatment with TESI, and 3) physician-related factors such as the fact that (according to their guideline, Dutch GPs have to wait at least six weeks before referring patients with sciatica to hospital[6]. For this trial, GPs agreed to refer earlier, but there was still a relatively small 'window of opportunity' for recruitment. It is highly unlikely, however, that the addition of the required number of patients would result in clinically relevant between-group differences for this outcome as the differences for the first 141 included participants were small. In other words, we think that, despite not reaching the required number of participants for one of the three co-primary outcomes, and also taking into account the pattern in the results of the secondary outcomes, the conclusion that there were no clinically relevant differences for any of the co-primary and secondary outcomes is supported by the data.

Second, another potential source for bias concerns the relatively high percentage of loss to follow–up (i.e. up to 30%). To assess our study's robustness to the method used for handling missing data (i.e. by also performing a complete-case analysis and using multiple imputation), we performed various sensitivity analyses. These analyses showed that the handling of missing data did not affect the results of our trial, and that therefore the results are rather robust. This supports the validity of our results. Third, in contrast to our design paper[17] and SAP[18] the EQ-5D-3L was administered, rather than the EQ-5D-5L. This is a possible limitation, as the EQ-5D-3L was found to have significantly higher floor effects for the health dimension pain/discomfort and ceiling effects for the health dimensions mobility, self-care, pain/discomfort, anxiety/depression, compared with the EQ-5D-5L[38]. However, as the floor and ceiling effects are likely to be equal

in all study groups, we do not expect our use of the EQ-5D-3L to have severely biased our results. A fourth limitation is that we did not assess the successfulness of blinding by asking both physicians and participants to guess whether they had administered or received the injection with steroids and local anesthetic (intervention group 1) versus injection with local anesthetic and saline solution (intervention 2). Since steroids may produce systemic effects (e.g., facial flushing, hyperglycemia), it may have been possible for subjects to unintentionally break blinding. It is difficult to indicate how this might have been reflected in the results. In general, poor blinding is associated with larger effects in the intervention group. But because the reported impact of 'not blinding' in the literature is heterogeneous it is difficult to make firm statements about how the fact that patients might have broken the blinding might have affected the results of our study[39-41].

A fifth limitation is the measurement of the use of pain medication in our study population. When measuring pain it is important to measure the medication that affects pain. However, we only had information on the use of opioids (yes or no), and no indication on the doses. A last potential limitation is that patient groups differed in terms of reported herniation levels. The control group has a significant majority of cases with L4-5 and L5-S1 compared to the interventions group, which both reported greater numbers of L2-L3 and L3-L4 disk pathology. However based on randomization this is probably an accidental finding. In addition considering current evidence from prediction studies[42-44] we do not think that the level of herniation has influenced treatment outcome.

Finally, we would like to acknowledge that determining the cut-off values for clinical relevance is always a challenge. Given the invasive nature of the intervention, and given the fact that the intervention is currently not recommended as a standard for acute sciatica in the Dutch multidisciplinary guideline[11], we would argue that the magnitude of the between-group differences for clinical relevance that were a-priori defined[17] are justified.

CONCLUSION

Except for a statistically significant, albeit not clinically relevant, effect of TESI (with 1 ml of 0.5% Levobupivacaine followed by 1 ml of 40 mg/ml Methylprednisolone) on leg pain for patients with acute sciatica due to herniated disc compared to usual care, there were no statistically significant nor clinically relevant differences in co-primary outcomes. For the secondary outcomes there were some statistically significant differences, for some comparisons, but overall these differences were not considered clinically relevant.

A post-hoc analysis found both injection groups to be associated with less opioid use, which warrants further exploration. The effect of transforaminal injections in patients with back pain or sciatica due to other causes, for example spinal stenosis, was outside the scope of this trial and needs further investigation.

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APPENDIX I

Protocol violations STAR-trial

Study number	Group	Type of violation
3018	Intervention-2	Second injection with steroids (TESI) within 2 weeks because of severe pain. Eventually got surgery
3040	Intervention-2	No intervention because spontaneous recovery
2018	Intervention-2	No intervention because spontaneous recovery
2026	Control	Injection with steroids (TESI) within 2 week because of severe pain. Eventually got surgery

APPENDIX II

Contents:

TABLE A-1 Primary outcomes according to treatment and timing (complete-case analysis, n=94)*

Outcome		Intervention group 1 Mean (SD) N=28	Intervention group 2 Mean (SD) N=33	Control group Mean (SD) N=33	Comparison 1 (Int. group 1 vs. Control) Treatment effect Mean Difference (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2 Treatment effect Mean Difference (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect Mean Difference (95%CI)	p-value
Back pain	***Overall effect***				***-0.54 (-1.41 to 0.33)***	***0.220***	***-0.64 (-1.47 to 0.18)***	***0.127***	***0.11 (-0.81 to 1.04)***	***0.809***
(0-10)	Baseline	5.89 (2.69)	5.42 (3.15)	4.88 (3.05)						
	3 weeks	3.65 (2.66)	4.09 (3.39)	3.54 (2.88)	-0.92 (-2.38 to 0.55)	0.221	-0.92 (-2.31 to 0.48)	0.198	0.00 (-1.40 to 1.40)	1.000
	6 weeks	3.29 (2.54)	3.88 (2.99)	3.52 (2.41)	-1.24 (-2.71 to 0.22)	0.097	-1.06 (-2.46 to 0.33)	0.136	-0.18 (-1.58 to 1.22)	0.799
	3 months	3.46 (2.70)	3.36 (3.03)	3.45 (2.76)	-1.00 (-2.47 to 0.46)	0.180	-0.37 (-1.76 to1.03)	0.605	-0.64 (-2.04 to 0.76)	0.373
	6 months	3.25 (2.95)	3.33 (2.85)	2.82 (2.24)	-0.58 (-2.05 to 0.89)	0.437	-0.55 (-1.95 to 0.84)	0.438	-0.03 (-1.43 to 1.37)	0.966
Leg pain	***Overall effect***				***-1.15 (-2.05 to -0.24)***	***0.013***	***-1.05 (-1.86 to 0.24)***	***0.011***	***-0.03 (-0.91 to 0.86)***	***0.954***
(0-10)	Baseline	7.82 (1.91)	7.48 (2.02)	7.18 (2.16)						
	3 weeks	4.97 (3.00)	5.21 (2.99)	4.82 (2.88)	-0.67 (-2.26 to 0.91)	0.406	-0.76 (-2.26 to 0.74)	0.319	0.09 (-1.43 to 1.61)	0.907
	6 weeks	3.71 (2.84)	4.55 (2.97)	3.76 (2.80)	-0.59 (-2.18 to 0.99)	0.464	-1.17 (-2.67 to 0.33)	0.127	0.58 (-0.95 to 2.10)	0.458
	3 months	2.57(2.66)	3.39 (2.81)	3.82 (2.90)	-1.89 (-3.47 to -0.30)	0.020	-1.16 (-2.66 to 0.34)	0.130	-0.73 (-2.25 to 0.79)	0.349
	6 months	2.32 (2.80)	2.82 (3.16)	2.97 (2.98)	-1.29 (-2.87 to 0.30)	0.111	-0.83 (-2.33 to 0.67)	0.276	-0.45 (-1.98 to 1.07)	0.559
Physical	***Overall effect***				***-2.38 (-4.90 to 0.13)***	***0.063***	***-0.40 (-2.74 to 1.94)***	***0.737***	***-1.58 (-4.13 to 0.97)***	***0.225***
functioning	Baseline	17.68 (4.63)	15.97 (4.61)	17.24 (3.29)						
(0-24)	3 weeks	10.71 (6.60)	10.15 (5.58)	12.12 (6.76)	-1.84 (-5.27 to 1.58)	0.292	-1.15 (-4.24 to 1.95)	0.468	-0.70 (-4.02 to 2.62)	0.681
	6 weeks	8.29 (7.29)	7.55 (6.78)	9.73 (7.16)	-1.88 (-5.31 to 1.55)	0.283	-0.97 (-4.07 to 2.13)	0.540	-0.91 (-4.23 to 2.41)	0.591
	3 months	7.68 (6.67)	7.03 (7.31)	9.82 (6.98)	-2.58 (-6.00 to 0.85)	0.141	-1.06 (-4.16 to 2.03)	0.502	-1.52 (-4.83 to 1.80)	0.371
	6 months	7.11 (6.24)	6.39 (7.52)	6.82 (7.17)	-0.15 (-3.58 to 3.28)	0.933	-1.00 (-4.09 to 2.10)a	0.528	0.85 (-2.47 to 4.17)	0.616

		Intervention group 1 N (%)	Intervention group 2 N (%)	Control group (%) N (%)	Treatment effect Odds Ratio (95%CI)	p-value	Treatment effect Odds Ratio (95%CI)	p-value	Treatment effect Odds Ratio (95%CI)	p-value
Global Perceived Recovery (non success = ref)	***Overall effect***				***2.28 (1.00 to 5.18)***	***0.290***	***1.51 (0.55 to 4.10)***	***0.422***	***1.35 (0.61 to 2.97)***	***0.464***
	3 weeks	9 (32.14)	10 (30.30)	7 (22.21)	2.81 (0.51 to 15.64)	0.236	1.20 (0.18 to 7.92)	0.847	1.90 (0.39 to 9.21)	0.428
	6 weeks	10 (35.71)	14 (42.00)	9 (27.27)	2.47 (0.48 to 12.81)	0.278	0.71 (0.12 to 4.38)	0.716	2.67 (0.59 to 12.18)	0.204
	3 months	20 (71.43)	21 (63.64)	19 (57.58)	4.14 (0.85 to 20.09)	0.078	2.80 (0.48 to 16.28)	0.252	1.38 (0.37 to 5.21)	0.637
	6 months	21 (75.00)	21 (63.64)	23 (69.70)	2.66 (0.52 to 13.60)	0.237	3.80 (0.63 to 22.87)	0.145	0.69 (0.18 to 2.69)	0.594

* All analyses have been adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

TABLE A-2 Secondary outcomes according to treatment and timing (complete-case analysis, n= 94)*

Outcome		Intervention group 1 Mean (SD)	Intervention group 2 Mean (SD)	Control group Mean (SD)	Comparison 1 (Int. group 1 vs. Control) Treatment effect Mean Difference (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2 Treatment effect Mean Difference (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect Mean Difference (95%CI)	p-value
Treatment satisfaction (0-7)	***Overall effect***				***-0.61 (-1.12 to -0.09)***	***0.020***	***-0.08 (-0.58 to 0.42)***	***0.748***	***-0.52 (-0.97 to -0.06)***	***0.025***
	Baseline									
	3 weeks	3.03 (1.45)	3.12 (1.62)	3.42 (0.90)	-0.49 (-1.12 to 0.15)	0.133	-0.22 (-1.01 to 0.55)	0.561	-0.22 (-0.87 to 0.42)	0.489
	6 weeks	2.64 (1.37)	2.79 (1.32)	3.09 (1.18)	-0.73 (-1.37 to -0.08)	0.028	-0.27 (-0.90 to 0.36)	0.392	-0.32 (-0.93 to 0.30)	0.304
	3 months	2.82 (1.61)	2.67 (1.34)	3.48 (1.25)	-0.69 (-1.46 to 0.07)	0.075	-0.03 (-0.74 to 0.68)	0.927	-0.76 (-1.42 to -0.010)	0.025
	6 months	2.68 (1.44)	2.33 (1.14)	3.21 (1.52)	-0.53 (-1.26 to 0.20)	0.153	0.20 (-0.43 to 0.84)	0.518	-0.76 (-1.41 to -0.11)	0.023
Health related quality of life (0-1)	***Overall effect***				***0.060 (-0.035 to 0.156)***	**0.214**	**-0.012 (-0.110 to 0.085)**	**0.805**	**0.061 (-0.036 to 0.158)**	**0.221**
	Baseline	0.258 (0.370)	0.347 (0.323)	0.305 (0.350)						
	3 weeks	0.500 (0.360)	0.536 (0.278)	0.464 (0.276)	0.083 (-0.090 to 0.256)	0.348	0.053 (-0.112 to 0.128)	0.529	0.030 (-0.133 to 0.192)	0.719
	6 weeks	0.594 (0.309)	0.629 (0.309)	0.534 (0.319)	0.107 (-0.066 to 0.280)	0.226	0.053 (-0.112 to 0.218)	0.528	0.054 (-0.109 to 0.216)	0.517
	3 months	0.600 (0.375)	0.658 (0.331)	0.629 (0.301)	0.018 (-0.155 to 0.191)	0.842	0.300 (-0.135 to 0.195)	0.721	-0.012 (-0.175 to 0.150)	0.881
	6 months	0.693 (0.269)	0.748 (0.278)	0.727 (0.271)	0.012 (-0.161 to 0.185)	0.888	0.034 (-0.131 to 0.199)	0.668	-0.021 (-0.184 to 0.141)	0.796
		Intervention group 1 N (%)	Intervention group 2 N (%)	Control group N (%)	Treatment effect Odds Ratio (95%CI)	p-value	Treatment effect Odds Ratio (95%CI)	p-value	Treatment effect Odds Ratio (95%CI)	p-value
Surgery (yes vs no)	over 6 months	7 (25.00)	5 (15.15)	8 (24.24)	***0.46 (0.11 to 1.92)***	***0.289***	***1.77 (0.42 to 7.53)***	***0.438***	***0.41 (0.10 to 1.60)***	***0.198***
Responders analysis (30%)	3 months	23 (82.14)	22 (66.76)	23 (71.88)	2.59 (0.63 to 10.68)	0.188	2.74 (0.75 to 9.98)	0.127	0.73 (0.24 to 2.26)	0.587
	6 months	25 (89.29)	23 (69.70)	23 (71.88)	5.46 (0.98 to 30.32)	0.052	4.90 (1.06 to 22.75)	0.042	1.01 (0.32 to 3.23)	0.986
Responders analysis (50%)	3 months	21 (75.0)	21 (63.64)	18 (56.24)	5.61 (1.30 to 24.15)	0.020	2.11 (0.62 to 7.17)	0.234	1.43 (0.48 to 4.22)	0.518
	6 months	22 (78.57	21 (63.64)	21 (65.63)	2.40 (0.65 to 8.87)	0.188	2.76 (0.78 to 9.79)	0.117	0.97 (0.33 to 2.88)	0.958

* all analyses have been adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

TABLE A-3 Primary outcomes according to treatment and timing (multiple imputation, n= 141)*

Outcome		Intervention group 1 Mean (SE)	Intervention group 2 Mean (SE)	Control group Mean (SE)	Comparison 1 (Int. group 1 vs. Control) Treatment effect Mean Difference (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2) Treatment effect Mean Difference (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect Mean Difference (95%CI)	p-value
Back pain	***Overall effect***				***-0.55 (-1.40 to 0.30)***	***0.204***	***-0.47 (-1.18 to 0.25)***	***0.203***	***0.18 (-1.06 to 0.71)***	***0.691***
(0-10)	Baseline	5.87 (0.41)	5.75 (0.43)	5.33 (0.45)						
	3 weeks	4.15 (0.44)	4.35 (0.47)	4.38 (0.45)	-0.70(-1.98 to 0.58)	0.281	-0.24 (-1.46 to 0.98)	0.694	-0.46(-1.74 to 0.82)	0.480
	6 weeks	3.70 (0.41)	4.42 (0.43)	4.21 (0.47)	-1.03(-2.55 to 0.50)	0.181	-0.80 (-2.02 to 0.42)	0.199	-0.23(-1.76 to 1.30)	0.761
	3 months	3.73 (0.43)	3.82 (0.45)	3.88 (0.43)	-0.72(-1.98 to 0.55)	0.267	-0.21 (-1.48 to 1.05)	0.742	-0.50(-1.75 to 0.75)	0.424
	6 months	3.42 (0.45)	3.42 (0.49)	3.35 (0.40)	-0.49 (-1.78 to 0.80)	0.457	-0.14 (-1.40 to 1.13)	0.829	-0.35(-1.74 to 1.04)	0.615
Leg pain	***Overall effect***				***-0.86 (-1.69 to -0.03)***	***0.042***	***-0.60 (-1.38 to 0.18)***	***0.133***	***-0.30 (1.13 to 0.53)***	***0.476***
(0-10)	Baseline	7.85 (0.26)	7.66 (0.27)	7.32 (0.29)						
	3 weeks	5.37 (0.43)	5.50 (0.41)	5.38 (0.43)	-0.47 (-1.81 to 0.87)	0.495	-0.27 (-1.53 to 1.00)	0.670	-0.20 (-1.47 to 1.07)	0.758
	6 weeks	4.22 (0.42)	4.90 (0.42)	4.40 (0.51)	-0.67 (-2.18 to 0.83)	0.377	-0.84 (-2.06 to 0.39)	0.181	0.16 (-1.28 to 1.61)	0.821
	3 months	3.20 (0.46)	3.80 (0.50)	4.11 (0.45)	-1.52 (-3.00 to -0.08)	0.039	-0.83 (-2.33 to 0.68)	0.272	-0.69 (-2.19 to 0.81)	0.360
	6 months	2.80 (0.54)	2.90 (0.64)	3.47 (0.49)	-1.20 (-2.50 to 0.11)	0.073	-0.32 (-1.61 to 0.98)	0.631	-0.88 (-2.22 to 0.46)	0.197
Physical	***Overall effect***				***-1.26 (-3.38 to 0.87)***	***0.246***	***0.11 (-2.06 to 2.27)***	***0.923***	***1.42 (-3.63 to 0.79)***	***0.206***
functioning	Baseline	18.17 (0.66)	16.58 (0.66)	17.48 (0.49)						
(0-24)	3 weeks	11.37 (0.99)	10.56 (0.88)	12.11 (0.96)	-1.42 (-4.50 to 1.67)	0.367	-0.79 (-3.75 to 2.17)	0.606	-0.63 (-3.54 to 2.29)	0.672
	6 weeks	9.32 (1.23)	8.58 (1.04)	9.86 (1.09)	-1.21 (-4.57 to 2.51)	0.478	-0.81 (-3.79 to 2.16)	0.590	-0.40 (-3.48 to 2.69)	0.801
	3 months	9.38 (1.22)	8.42 (1.09)	10.33 (1.15)	-1.62 (-4.68 to 1.44)	0.299	-0.60 (-3.65 to 2.44)	0.696	-1.02 (-4.01 to 1.97)	0.505
	6 months	8.08 (1.06)	6.86 (1.21)	7.90 (1.19)	-0.36 (-3.41 to 2.70)	0.820	-0.29 (-3.28 to 2.70)	0.849	-0.07 (-3.13 to 3.00)	0.966

TABLE A-3 Primary outcomes according to treatment and timing (multiple imputation, n= 141)*

		Intervention group 1 Prop (SE)	Intervention group 2 Prop (SE)	Control group Prop (SE)	Comparison 1 (Int. group 1 vs. Control) Treatment effect Treatment effect Odds Ratio (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2) Treatment effect Treatment effect Odds Ratio (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect Treatment effect Odds Ratio (95%CI)	p-value
Global Perceived Recovery (1-7)**	***Overall effect***				***2.72 (1.09 to 6.75)***	***0.032***	***2.34 (0.68 to 7.92)***	***0.176***	***1.28 (0.53 to 3.10)***	***0.577***
	3 weeks	0.23 (0.07)	0.30 (0.07)	0.20 (0.06)	2.66 (0.46 to 15.33)	0.271	1.75 (0.23 to 13.33)	0.589	1.52 (0.32 to 7.32)	0.600
	6 weeks	0.41 (0.08)	0.45 (0.08)	0.35 (0.09)	2.94 (0.53 to 16.28)	0.216	1.16 (0.15 to 8.85)	0.883	2.41 (0.52 to 11.36)	0.262
	3 months	0.63 (0.08)	0.57 (0.08)	0.56 (0.08)	5.53 (0.90 to 34.13)	0.065	4.26 (0.48 to 38.09)	0.194	1.57 (0.33 to 7.32)	0.569
	6 months	0.68 (0.08)	0.64 (0.08)	0.61 (0.08)	3.56 (0.49 to 26.05)	0.209	11.13 (1.04 to 119.10)	0.046	0.46 (0.09 to 2.35)	0.352

* All analyses have been adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

** Global Perceived Recovery was dichotomized into success (categories 'completely' and 'much recovered') and non-success (categories 'slightly recovered', 'no change', 'slightly worse', 'much worse' and 'worse than ever').

TABLE A-4 Secondary outcomes according to treatment and timing (multiple imputation, n= 141)*

Outcome		Intervention group 1 Mean (SE)	Intervention group 2 Mean (SE)	Control group Mean (SE)	Comparison 1 (Int. group 1 vs. Control) Treatment effect Mean Difference (95%CI)	p-value	Comparison 2 (Int. group 1 vs. Int. group 2) Treatment effect Mean Difference (95%CI)	p-value	Comparison 3 (Int. group 2 vs. control) Treatment effect Mean Difference (95%CI)	p-value
Treatment satisfaction (1-7)	***Overall effect***				***-0.35 (-0.80 to 0.11)***	***0.139***	***0.14 (-0.32 to 0.59)***	***0.553***	***-0.50 (-0.90 to -0.09)***	***0.017***
	Baseline									
	3 weeks	3.39 (0.21)	3.32 (0.25)	3.56 (0.14)	-0.27 (-0.83 to 0.28)	0.333	-0.03 (-0.62 to 0.55)	0.908	-0.25 (-0.81 to 0.31)	0.373
	6 weeks	3.00 (0.24)	2.89 (0.19)	3.13 (0.19)	-0.23 (-0.79 to 0.32)	0.404	0.01 (-0.56 to 0.59)	0.960	-0.26 (-0.78 to 0.25)	0.318
	3 months	3.05 (0.24)	2.73 (0.21)	3.43 (0.21)	- 0.47 (-1.07 to 0.13)	0.126	0.23 (-0.36 to 0.82)	0.437	-0.72 (-1.31 to -0.13)	0.018
	6 months	2.96 (0.26)	2.52 (0.20)	3.27 (0.24)	-0.40 (-1.10 to 0.29)	0.248	0.33 (-0.34 to 1.00)	0.319	-0.75 (-1.31 to -0.19)	0.009
Health related quality of life (0-1)	***Overall effect***				***0.017 (-0.073 to 0.107)***	***0.710***	***-0.056 (-0.147 to 0.035)***	***0.230***	***0.059 (-0.035 to 0.152)***	***0.215***
	Baseline	0.222 (0.055)	0.301 (0.052)	0.281 (0.053)						
	3 weeks	0.411 (0.063)	0.509 (0.047)	0.423 (0.047)	0.047 (-0.109 to 0.203)	0.553	-0.019 (-0.175 to 0.136)	0.810	0.066 (-0.086 to 0.218)	0.294
	6 weeks	0.540 (0.053)	0.612 (0.046)	0.516 (0.050)	0.083 (-0.084 to 0.250)	0.330	0.006 (-0.162 to 0.175)	0.939	0.076 (-0.78 to 0.230)	0.331
	3 months	0.560 (0.062)	0.633 (0.050)	0.605 (0.053)	0.013 (-0.180 to 0.207)	0.889	0.006 (-0.161 to 0.172)	0.947	0.008 (-0.171 to 0.187)	0.930
	6 months	0.652 (0.050)	0.725 (0.046)	0.723 (0.048)	-0.013 (-0.170 to 0.144)	0.868	0.006 (-0.162 to 0.173)	0.947	-0.019 (-0.199 to 0.161)	0.833
		Intervention group 1 Prop (SE)	Intervention group 2 Prop (SE)	Control group Prop (SE)	Treatment effect Odds Ratio (95%CI)	p-value	Treatment effect Odds Ratio (95%CI)	p-value	Treatment effect Odds Ratio (95%CI)	p-value
Surgery (yes)	Overall effect	0.33 (0.07)	0.19 (0.06)	0.33 (0.07)	0.70 (0.27 to 1.86)	0.479	1.99 (0.70 to 5.64)	0.194	0.39 (0.14 to 1.05)	0.065
Responders analysis	3 months	0.76 (0.07)	0.62 (0.07)	0.66 (0.07)	2.07 (0.67 to 6.33)	0.202	2.09 (0.74 to 5.93)	0.161	0.90 (0.34 to 2.41)	0.835
(30%)	6 months	0.76 (0.07)	0.62 (0.08)	0.66 (0.08)	2.83 (0.77 to 10.38)	0.115	1.77 (0.58 to 5.37)	0.313	1.43 (0.47 to 4.39)	0.522
Responders analysis	3 months	0.67 (0.08)	0.58 (0.09)	0.51 (0.08)	3.29 (0.88 to 12.30)	0.075	1.67 (0.51 to 5.47)	0.388	1.55 (0.55 to 4.34)	0.399
(50%)	6 months	0.67 (0.08)	0.58 (0.09)	0.51 (0.08)	2.08 (0.76 to 5.75)	0.155	1.45 (0.50 to 4.22)	0.488	1.47 (0.52 to 4.10)	0.461

* all analyses have been adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.

Accepted for publication

8 CHAPTER

Cost-effectiveness of transforaminal epidural steroid injections for patients with acute sciatica: a randomized controlled trial.

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ABSTRACT

Background

Transforaminal epidural injections with steroids (TESI) are increasingly being used in patients with acute sciatica (<8 weeks). This study aimed to evaluate the cost-effectiveness of TESI.

Methods

This economic evaluation was conducted along with the STAR trial. Participants were randomized to one of three study arms: Usual Care (UC), that is oral pain medication with or without physiotherapy, n=45); intervention group 1: UC and transforaminal epidural steroid injection (TESI) 1ml of 0.5% Levobupivacaine and 1 ml of 40mg/ml Methylprednisolone and intervention group 2: UC and transforaminal epidural injection (TEI) with 1 ml of 0,5% Levobupivacaine and 1 ml of 0.9% NaCl (n=50). The primary effect measure was health-related quality of life. Secondary outcomes were pain, functioning, and recovery. Costs were measured from a societal perspective, meaning that all costs were included, irrespective of who paid or benefited. Missing data were imputed using multiple imputation, and bootstrapping was used to estimate statistical uncertainty.

Results

None of the between-group differences in effects were statistically significant for any of the outcomes (QALY, back pain, leg pain, functioning, and global perceived effect) at the 26-weeks follow-up. The adjusted mean difference in total societal costs was €1718 (95% confidence interval [CI]: -3020 to 6052) for comparison 1 (intervention group 1 versus usual care), €1640 (95%CI: -3354 to 6106) for comparison 2 (intervention group 1 versus intervention group 2), and €770 (95%CI: -3758 to 5702) for comparison 3 (intervention group 2 versus usual care). Except for the intervention costs, none of the aggregate and disaggregate cost differences were statistically significant. The maximum probability of all interventions being cost-effective compared to the control was low (<0.7) for all effect measures.

Conclusion

These results suggest that adding TESI (or TEI) to usual care is not cost-effective compared to usual care in patients with acute sciatica (<8 weeks) from a societal perspective in a Dutch healthcare setting.

Trial registration:
Dutch National trial register: NTR4457 (March, 6th, 2014)

Keywords:
Sciatica, Lumbar disc herniation, Transforaminal epidural steroid injections, Economic evaluation, Randomized controlled trial

BACKGROUND

Sciatica is characterized by pain radiating to the leg following one of the lumbosacral nerve roots[1]. Other than pain, patients may also experience sensory symptoms and/or weakness of the involved myotome. Approximately 85% of sciatica cases are caused by mechanical compression of the nerve root by a herniated intervertebral disc[2]. The annual incidence of lumbosacral radicular syndrome in the Netherlands has been estimated at 9 per 1000 patient-years[3] and the annual prevalence has been estimated at 17.2 per 1000 patient-years[3]. The prognosis of sciatica is generally described as favourable: within three months, 75% of patients are expected to reach bearable pain levels and can resume their work without surgery[4]. Nonetheless, a UK-based study of patients seeking primary care for back-related leg pain, including lumbosacral radicular syndrome, showed that only 55% of patients with lumbosacral radicular syndrome had more than 30% reduction in disability 1 year after their first visit to primary care[5].

In addition to these patient related problems, sciatica poses a major economic burden. Although there are no recent specific cost data for sciatica, in 2017, the total healthcare cost of lower back pain in general (including sciatica) in the Netherlands was estimated to be 937 million[6]. This equals 1.07% of the total expenditure on health care in the Netherlands. Indirect costs due to absenteeism and lost productivity while being at work (i.e., presenteeism) were not included in this cost estimate; and hence the total societal cost will be even higher. Understanding the cost-effectiveness of different management strategies for sciatica, such as medication, physiotherapy, and transforaminal epidural steroid injections (TESI), is important to prevent high healthcare and socioeconomic costs. This requires formal assessments of the best available evidence on the cost-effectiveness of interventions and, where necessary, undertaking economic studies if there is a lack of good quality evidence[7].

TESI is increasingly used in patients with sciatica[8,9]. In 2021 we described a survey among 80 neurologists (including residents) and 44 anesthesiologists. The results of this survey showed that 40-60% of neurologists think that TESIs are effective in 40% of injected patients and that 23/44(52%) of anesthesiologists think that TESIs are effective in 60-80% of the injected patients[10]. This seems to contradict the current evidence. Four recent systematic reviews and meta-analyses found that TESI only slightly reduced leg pain and disability compared to placebo at short-term follow-up (4-6 weeks) in patients with sciatica, but not at long-term follow-up (>3 months)[11-14]. According to the GRADE[15], the quality of evidence is low to moderate. Recently, our research group finalized the STeroids against Radiculopathy (STAR) trial, a pragmatic two-center, randomized clinical trial (RCT) assessing the clinical effectiveness of TESI against sciatica[16]. Our results do not support TESI as a standard treatment for patients with acute sciatica (<8 weeks). Although it is debated as to whether trial-based economic evaluations should still be performed if positive clinical effects are lacking[17], one should be aware that a lack of statistical differences between therapies does not necessarily mean that they are identical. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Cost Effectiveness Analysis Randomized Clinical Trial (CEA-RCT) task force therefore recommends that researchers perform CEA if positive clinical results are lacking[18]. The aim of this study was to evaluate the cost-effectiveness of TESI in patients with acute sciatica compared to a (1) treatment regimen of medication only (usual care) and (2) to transforaminal epidural injection with local anesthetic and saline solution (TEI), from a societal perspective.

METHODS

Study design

An economic evaluation was conducted alongside the STAR trial[16,17,20], an RCT evaluating the effectiveness of TESI in patients with acute sciatica. The RCT was conducted in two Dutch hospitals, the Zaans Medisch Centrum (Zaandam) and OLVG Teaching Hospital (Amsterdam), between January 13, 2016, and October 24, 2019.

The following three groups were compared:

- Usual Care (UC): Oral pain medication with or without physiotherapy

- Intervention group 1: Usual care and TESI of 1ml of 0.5% Levobupivacaine and 1 ml of 40mg/ml Methylprednisolone
- Intervention group 2: Usual care and transforaminal epidural injection with 1ml of 0.5% Levobupivacaine and 1 ml NaCl 0.9%

We analyzed three pairwise comparisons.

- Comparison 1 (main comparison): Intervention group 1 versus Usual Care
- Comparison 2: Intervention group 1 versus Intervention group 2
- Comparison 3 (for completeness): Intervention group 2 versus Usual Care

The RCT was approved by the Medical research Ethics Committees United, Nieuwegein, The Netherlands (registration number NL45805.100.15). The protocol was registered in the Dutch Trial Register number NTR4457 (6/03/2014). The CONSORT statement was followed for reporting[21].

Participants

Eligible patients had sciatic symptoms <8weeks and were seen by a neurologist at one of the two study centres upon referral by their general practitioners (GPs). Additional inclusion criteria were as follows: a) age between 18 and 75 years; b) magnetic resonance imaging (MRI)-confirmed disc herniation with nerve root impingement causing clinical symptoms; c) pain experienced on average over the last week rated on a numerical rating scale (NRS)(>4/10); d) good understanding of the Dutch language; and e) Internet access to complete online questionnaires[19]. The exclusion criteria were a) severe weakness of the legs (Medical Research Council ((MRC) score <3); b) spinal surgery<1 year at the symptomatic lumbar level; c) lumbar spinal stenosis or spondylolisthesis as the cause of radicular pain diagnosed by MRI; d) pregnancy; and e) severe comorbidity (e.g., cancer) [19].

Randomization and blinding

After informed consent (see **Appendix 1** for consent form) randomization was performed by the study coordinator (BTM) or by one of the two trial nurses using ALEA® software (NKI-AVL, Netherlands). Alea® generated a random schedule of blocks with a maximum size of six. The participants who received a transforaminal injection were blinded to the type of injection.

Intervention

The procedure was similar for both intervention arms). Participants were brought to a fluoroscopy room and placed in a prone position on the procedure table. Fluoroscopy was used to localize MRI-confirmed disc herniation. Target identification and needle entry were performed according to international procedures[21]. First, the skin was prepped using chlorhexidine. Second, injections were administered using a 22-gauge 100 mm facet tipped needle (Pajunk RGN™). The correct needle position was confirmed by the injection of 0.5-1.5cc of Joversol 300 mg/ml contrast material (Optiray™ 300, Mallinckrodt). Once an image was obtained demonstrating contrast material spreading into the epidural space medial to a line connecting the ipsilateral lumbar vertebral pedicles, the injection was performed at the level of the herniated disc. The injections were not repeated.

The study participants in intervention group 1 received 1 ml of 0,5% levobupivacaine, followed by 1 ml of 40 mg/ml methylprednisolone in an opaque syringe. The study participants in intervention group 2 received 1 ml 0,5% levobupivacaine followed by 1 ml of 0.9% NaCl. The total volume of the two injections was the same (2 ml).

After epidural injection, washout of the contrast fluid was observed on an X-ray image. The image was saved. Finally, the needle was removed, and the patient was brought to the recovery area.

Usual Care

Patients in all groups used analgesics registered during the trial using online questionnaires[23]. In the case of kinesiophobia, patients were permitted to visit a physiotherapist. There were no restrictions on the use of analgesics or physiotherapy in any group, and their use was monitored. Pain medication, with or without physiotherapy, was planned at the discretion of the attending physician and according to the patient's personal needs.

Effect measures

The primary effect measure was health-related quality of life. At baseline, 3 and 6 weeks, and 3 and 6 months after the start of the intervention, the patients' health states were assessed using the Euroqol-5 dimensions- 3 levels (EQ-5D-3L)[24]. The EQ-5D-3L comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had three levels: no problems,

problems, and serious problems. The patient indicated her health state by ticking the box next to the most appropriate statement for each of the five dimensions. Each health state was converted into a utility score using the Dutch tariff[25]. Hence, the utility values estimated in this study were indicative of a Dutch person's value or desirability of patients' health states. Values ranged between -0.33 (0 is equivalent to death; negative values are worse than death), and 1 (full health). The EQ-5D-3L is commonly used in cost-utility analyses and, for that reason, applied in this economic evaluation as well[26].

Secondary outcomes were back and leg pain (average previous week) (measured using a 10-cm numerical rating scale [NRS][27]), physical functioning (measured using the Dutch version of the Roland-Morris Disability Questionnaire[28,29]), and global perceived recovery (GPR). The latter was measured on a 7-point Likert scale[30] ranging from 'completely recovered' to 'worse than ever,' which was dichotomized into success (categories 'completely' and 'much recovered') and non-success (categories 'slightly recovered,' 'no change, 'slightly worse', 'much worse' and 'worse than ever').

Costs measures

Resource use was assessed using cost questionnaires administered at three and six months. In line with Dutch guidelines, costs were assessed from a societal perspective, meaning that all costs were included, irrespective of who paid or benefited[31,32]. Intervention costs were estimated using the data acquired from the accounting records of the two participating clinics. Data on other healthcare utilization, informal care, unpaid productivity, and absenteeism due to back pain were collected using 3-monthly self-reported web-based cost questionnaires[20]. Healthcare utilization included primary care (e.g., general practitioner care, physiotherapy, manual therapy, chiropractic care, and exercise therapy), secondary care (e.g., hospitalization, and diagnostic and therapeutic interventions), and the use of prescribed and over-the-counter medications. Healthcare utilization was valued using Dutch standard costs and the prices of professional organizations if standard costs were not available. Medication use was valued using prices derived from http://www.medicijnkosten.nlhttp://www.medicijnkosten.nl. Informal care included care by family, friends, and other volunteers and was valued according to the proxy good method using an estimate of the hourly cost of a housekeeper. Absenteeism was measured using the Productivity and Disease Questionnaire (PRODISQ) [33]. Absenteeism was valued using sex-specific price weights in accordance with the friction cost approach (friction period=12 weeks). Unpaid productivity costs included all hours of volunteer work and domestic and educational activities that participants

were not able to perform owing to their sciatica; these were also valued using the aforementioned proxy method. All costs were converted to 2020 Euros using consumer price indices. Discounting of costs and effects was not necessary because the follow-up period was six months.

Sample Size

Sample sizes were calculated based on a power of 0.9 and a two-sided alpha of 0.05[18,19]. These calculations indicated that 48 patients were needed per arm to detect a clinically relevant between-group MD of two points on the 0-10 NRS for leg and back pain (SD=30). For physical functioning, 22 patients were needed per arm to detect a clinically relevant between-group MD of four points (SD=4). For dichotomized GPR, 79 patients were needed per arm to detect a clinically relevant between-group difference of 20%[34,35]. Anticipating a 10% loss to follow-up, 264 patients were included (n=88 per arm).

In accordance with the guidelines of the 'European Medicines Agency,' we will only consider one intervention effective over another if statistically significant and clinically relevant differences are found between them for all co-primary outcomes[36].

Cost-effectiveness and utility analyses

A cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) were conducted. In the CEA, total costs were related to improvements in back pain, leg pain, functioning, and global perceived effect. In the cost-utility analyses (CUA), total costs were related to the QALYs gained during follow-up. All analyses were performed using intention-to-treat. Baseline characteristics were compared between the intervention and control groups. Missing data for the economic evaluation were handled using multivariate imputation with chained equations. The imputation model included all available cost and effect measure values as well as variables differing between groups at baseline, variables related to the 'missingness' of data, and variables related to the outcomes. Ten complete datasets were created so that the loss of efficiency would be less than 5%[37].

The mean between-group cost differences were calculated for total and disaggregated costs (intervention costs, healthcare costs, informal care costs, absenteeism costs, presenteeism costs, and unpaid productivity costs). To determine the mean incremental difference in the cost and effect between the intervention and control groups, we used seemingly unrelated regression (SUR). SUR runs two regressions to determine incremental

cost and incremental effect differences simultaneously, adjusting for any potential correlation between costs and effects. The regression for determining the incremental cost difference was adjusted for baseline values (if available) and confounding variables (age, sex, body mass index [BMI], severity of back and leg pain at baseline, and work status).

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total costs by the difference in QALYs adjusted for confounders. Uncertainty surrounding the cost differences and ICERs was estimated using bias-corrected and accelerated (BCA) bootstrapping (5000 replications) and graphically presented in cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). The latter indicates the probability of an intervention condition being cost-effective compared with the control condition at different values of willingness to pay (further referred to as the ceiling ratio). In these analyses, SUR analyses and BCA bootstrapping were nested in multiple imputations, meaning that multiple imputations were used to generate 10 complete datasets, after which the SUR and BCA bootstrapping methods were applied to each of the complete datasets. The intermediate results per completed dataset were pooled using Rubin's rules[37].

Economic evaluations were performed using STATA (V16) (Stata Corp., College Station, TX, USA).

Sensitivity analysis

A predetermined sensitivity analysis (SA) was performed to assess the robustness of the results by comparing the friction cost approach with the human capital approach (SA1). Furthermore, complete-case analysis (SA2) and sensitivity analysis using the healthcare perspective (SA3) were performed.

RESULTS

Study Participants

During the study period, 1564 (922 in Amsterdam and 642 in Zaandam) adults with sciatica (regardless of duration) and nerve root compression on MRI were observed. Of these, 141 patients had acute sciatica and were willing to participate in the study.

After providing informed consent, 45 patients were assigned to the control group, 46 to intervention group-1, and 50 to intervention group-2. The baseline characteristics are presented in **Table 1** and were comparable between the groups. Complete data on all measurements was obtained from 35 (of 45) in the control group, 32 (of 46) in intervention-group 1 ('steroids') and 35 (of 50) in intervention-group 2 ('anesthetic only'). Fig. 1 provides an overview.

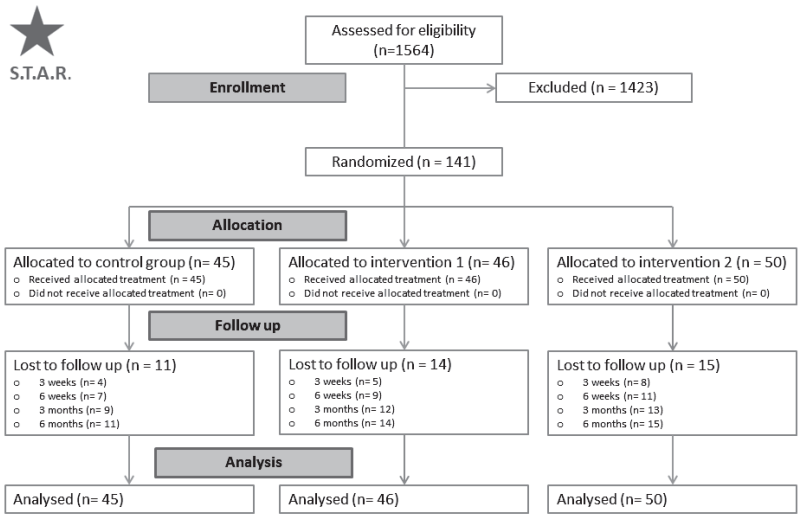

FIGURE 1 STAR-trial: enrolment, randomization and follow-up

Effects

None of the between-group differences in effects were statistically significant, for any of the outcomes (QALY, back pain, leg pain, functioning, and global perceived recovery) at the 26-weeks follow-up.

Costs

The mean cost per patient in the various study groups and the unadjusted mean cost differences between the groups are shown in **Table 2**. For both intervention groups, the cost per participant was estimated to be €486 per participant. The total societal costs were €21724 (SEM 2461) per participant for intervention group 1, €21337 (SEM2087) per participant for intervention group 2, and €21400 (SEM 2165) for the usual care group.

TABLE 1 Baseline variables of included patients

	Control group – Usual care (n = 45)	Intervention group 1 Usual care + TESI (n = 46)	Intervention group 2 Usual care + TEI (n= 50)
Participant's characteristics			
Female- no. (%)	19 (42.2)	26 (56.5)	25 (50.0)
Age- years (SD)	49.2 (12.5)	45.7 (12.9)	48.4 (13.8)
BMI (SD)	26.2 (4.5)	26.4 (5.0)	27.3 (5.6)
Vascular risk factors- no. (%)*	11 (24.4)	13(28.2)	16(32.0)
Education level[a]- no. (%)			
Low	9 (20.0)	9 (19.6)	13 (26.0)
Moderate	24 (53.3)	23 (50.0)	25 (50.0)
high	12(26.7)	14 (30.4)	12 (24.0)
Married or with a partner- no. (%)	35 (77.8)	28 (60.9)	36 (72.0)
Having a paid job- no. (%)	41 (91.1)	43 (93.5)	45 (90.0)
Primary outcomes*			
Leg pain intensity score[b] - mean(SD)	7.3 (2.0)	7.8 (1.8)	7.7 (1.9)
Back pain intensity score[b]- mean (SD)	5.3 (3.1)	5.9 (2.7)	5.8 (3.0)
Physical functioning[c]- mean (SD)	17.5 (3.1)	18.2 (4.2)	16.6 (4.6)
Secondary outcomes*			
Health-related quality of life[d]- mean (SD)	0.74 (0.07)	0.71 (0.07)	0.73 (0.07)

Usual care = Oral medication; TESI = Transforaminal Epidural Steroid Injection; TEI = Transforaminal Epidural Injection

*n = 136

a. Low includes preschool, primary school, or lower secondary school; moderate includes higher secondary school or undergraduate; high includes tertiary, university, or postgraduate.

b. Leg pain and back pain intensity were measured by means of the numerical pain rating scale (NRS), whereby patients were asked to measure their average pain over the previous 24 hours on a 0-10 scale, with 0 indicating no pain and 10 indicating the worst imaginable pain.

c. The extent of physical functioning was measured on the Roland Disability Scale of Sciatica (scores ranging from 0 to 23, with higher scores indicating greater physical functioning).

d. Health-related quality of life was assessed using the Euroqol 5- dimensions - 3 levels (EQ-5D-3L) and converted to utility values ranging from 0 (equal to death) to 1 (equal to full health) using the Dutch tariff.

The adjusted mean difference in total societal costs was €1718 (95% confidence interval [CI], -3020 to 6052) for comparison 1 (intervention group 1 versus usual care), €1640 (95%CI: -3354 to 6106) for comparison 2 (intervention group 1 versus intervention group 2), and €770 (95%CI: -3758 to 5702) for comparison 3 (intervention group 2 versus usual care). Except for intervention costs, none of the aggregate and disaggregate cost difference was statistically significant.

Cost-effectiveness

The results of the cost-effectiveness analyses, including differences in costs, differences in effects, ICERs, and distributions of bootstrapped cost-effect pairs across the four quadrants of the CE plane, can be found in **Table 3** for all comparisons.

At 6 months, the ICER for QALYs was 234,478 for comparison 1 (intervention group 1 versus usual care), indicating that the additional societal cost in intervention group 1 compared to usual care was €234,478 per QALY gained. This ICER shows that the intervention was on average "more costly" and "more effective" than usual care, which was also the case for leg pain and perceived recovery. ICERs for back pain and physical functioning, on the other hand, showed that the intervention was on average "more costly" and "less effective," indicating that it was dominated by usual care.

For comparison 2 (intervention group 1 versus intervention group 2), ICERs for QALYs and physical functioning indicated that intervention 1 was dominated intervention 2 for these outcomes (i.e. on average "more costly" and "less effective"), while ICERs for back and leg pain showed that the intervention 1 was on average "more costly" and "more effective." It should be noted that outcomes for self-perceived recovery are lacking because all participants in both groups indicated recovery after 6 months.

For comparison 3 (intervention group 2 versus usual care), ICERs indicated that the intervention was dominated by usual care for back pain and physical functioning (i.e. on average "more costly" and "less effective"), while it was "more costly" and "more effective" for QALYs, leg pain, and self-perceived recovery.

The CEACs in **Figure 2-6** show that the maximum probability of both interventions being cost-effective compared to usual care was low (<0.7) for all effect measures. A probability of cost-effectiveness of 0.7 means that if the intervention is implemented, it will indeed be cost-effective in 70% of cases, whereas in 30% of cases it will not.

TABLE 2 Mean cost per patient in the various study groups, and unadjusted mean cost differences between groups

Cost category	Intervention group 1 – Usual care + TESI Mean (SEM)	Intervention group 2 – Usual care + TEI Mean (SEM)	Control group – Usual care Mean (SEM)	Comparison 1 (Int. group 1 vs. Control)		Comparison 2 (Int. group 1 vs. Int. group 2)		Comparison 3 (Int. group 2 vs. Control)	
				Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Intervention costs	486 (1)	486 (1)	0 (0)	486 (485 to 487)	486 (485 to 487)	0 (-2 to 1)	0 (-1 to 2)	486 (485 to 487)	486 (485 to 487)
Other healthcare costs	2081 (269)	2394 (722)	2448 (354)	-367 (-1301 to 401)	-690 (-1816 to 165)	-313 (-2719 to 686)	-233 (-2442 to 751)	-54 (-1126 to 2271)	-72 (-1257 to 2636)
Prim. healthcare costs	*1179 (238)*	*1018 (233)*	*1588 (299)*	*-409 (-1162 to 164)*	*-650 (-1622 to 5)*	*161 (-356 to 707)*	*218 (-264 to 745)*	*-570 (-1292 to 9)*	*-635 (-1396 to -3)*
Sec. healthcare costs	*817 (170)*	*1281 (640)*	*761 (170)*	*57 (-373 to 479)*	*-22 (-502 to 423)*	*-463 (-2992 to 312)*	*-440 (-2781 to 317)*	*520 (-258 to 2978)*	*566 (-303 to 3328)*
Medication costs	*86 (15)*	*95 (22)*	*99 (12)*	*-14 (-43 to 27)*	*-19 (-50 to 25)*	*-10 (-69 to 34)*	*-10 (-68 to 30)*	*-4 (-40 to 60)*	*-3 (-41 to 65)*
Informal care costs	1669 (608)	1563 (588)	2031 (610)	-362 (-1785 to 959)	-569 (-1992 to 931)	105 (-1594 to 1302)	61 (-1879 to 1226)	-468 (-1885 to 1229)	-322 (-1635 to 1333)
Absenteeism costs	12959 (2144)	13153 (1646)	12090 (1972)	869 (-3715 to 5099)	2410 (-2116 to 6350)	-194 (-4636 to 4126)	684 (-3176 to 4368)	1063 (-3415 to 5432)	1833 (-2151 to 5498)
Presenteeism costs	3288 (759)	2788 (544)	3374 (613)	-86 (-1649 to 1428)	333 (-1131 to 1806)	499 (-941 to 1866)	858 (-455 to 2053)	-585 (-2080 to 900)	-631 (-2065 to 818)
Unpaid productivity costs	1242 (391)	952 (284)	1458 (289)	-216 (-956 to 574)	-251 (-1058 to 734)	289 (-422 to 1019)	269 (-484 to 1148)	-505 (-1206 to 213)	-524 (-1271 to 184)
Total societal costs	**21724 (2461)**	**21337 (2087)**	**21400 (2165)**	**323 (-4806 to 5117)**	**1718 (-3020 to 6052)**	**387 (-5045 to 5631)**	**1640 (-3354 to 6106)**	**-64 (-5325 to 5441)**	**770 (-3758 to 5702)**

Usual care = Oral medication; TESI = Transforaminal Epidural Steroid Injection; TEI = Transforaminal Epidural Injection

*Comparisons were adjusted for center, gender, level of herniated disc, loss of strength, loss of feel, BMI, age

Total values are depicted in bold font

SEM, standard error of the mean

TABLE 3 Cost-effectiveness analysis results (main analysis)

Outcome	Sample size Outcome		ΔC (95%CI)	ΔE (95%CI)	ICER	Distribution CE-plane (%)			
	Comparison 1 (Int. group 1 (Usual care + TESI) vs. Control (Usual care))								
	Int. Group 1	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	46	45	1839 (-2891 to 6281)	0.008 (-0.41 to 0.57)	234,478	44.5	17.1	8.1	30.3
Back pain (0-10)[2]	46	45	1694 (-3037 to 6177)	0.6 (-0.5 to 1.7)	2,742	11.4	3.7	23.2	61.7
Leg pain (0-10)[3]	46	45	1730 (-2886 to 6247)	-0.4 (-2.2 to 1.4)	-4,409	54.4	16.5	10.2	19.0
Functioning (0-23)[4]	46	45	1746 (-3029 to 6240)	1.5 (-1.7 to 4.7)	1,158	12.0	5.1	21.5	61.4
Global Perceived Effect[5]	46	45	1662 (-2903 to 6156)	0.04 (-0.02 to 0.11)	39,295	71.5	23.5	0.4	4.6
	Comparison 2 (Int. group 1 (Usual care + TESI) vs. Int. group 2 (Usual care + TEI))								
	Int. Group 1	Int. Group 2	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	46	50	1692 (-3245 to 6146)	-0.011 (-0.061 to 0.038)	-150,243	20.5	11.0	15.9	52.6
Back pain (0-10)[2]	46	50	1616 (-3303 to 6113)	-0.01 (-1.3 to 1.3)	-12,3742	37.9	16.1	11.5	34.5
Leg pain (0-10)[3]	46	50	1644 (-3280 to 6062)	-0.1 (-1.5 to 1.3)	-25,791	40.3	15.5	11.7	32.5
Functioning (0-23)[4]	46	50	1644 (-3463 to 6167)	0.99 (-2.15 to 4.12)	1,664	18.6	6.8	20.4	54.2
Global Perceived Effect[56]	46	50	-	-	-	-	-	-	-

TABLE 3 Cost-effectiveness analysis results (main analysis)

Outcome	Sample size Outcome		ΔC (95%CI)	ΔE (95%CI)	ICER	Distribution CE-plane (%)			
	Comparison 3 (Int. group 2 (Usual care + TEI) vs. Control (Usual care)								
	Int. Group 2	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	50	45	735 (-3815 to 5734)	0.012 (-0.040 to 0.064)	59,442	41.9	26.0	12.3	19.9
Back pain (0-10)[2]	50	45	802 (-3895 to 5824)	0.8 (-0.4 to 1.9)	1,033	7.4	4.1	32.5	56.0
Leg pain (0-10)[3]	50	45	770 (-3893 to 5641)	-0.2 (-1.7 to 1.4)	-4,136	42.4	21.3	15.2	21.0
Functioning (0-23)[4]	50	45	772 (-3778 to 5627)	0.4 (-3.3 to 4.0)	2,135	27.0	14.6	22.7	35.7
Global Perceived Effect[5]	50	45	747 (-3863 to 5627)	0.05 (-0.01 to 0.10)	16,564	67.9	32.1	0.0	0.0

Usual care = Oral medication; TESI = Transforaminal Epidural Steroid Injection; TEI = Transforaminal Epidural Injection

C: Costs, E: Effects, ICER: Incremental Cost-Effectiveness Ratio, CE-plane: Cost-Effectiveness plane, NE: Northeast-Quadrant, SE: Southeast-Quadrant, NW; Northwest-Quadrant, ZW; Southwest-Quadrant; Cost differences were adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline.; [1] adjusted for baseline utility values, work status, age, gender; [2] adjusted for baseline values, level of herniated disc; [3] adjusted for baseline values, age, gender, body mass index (BMI), and severity of back and leg pain at baseline. Lasègue's sign; [1] adjusted for baseline values, work status, gender; [5] percentage point (difference in percentage recovered between intervention -and control group) adjusted for work status. [6] No patients were recovered, cannot be estimated

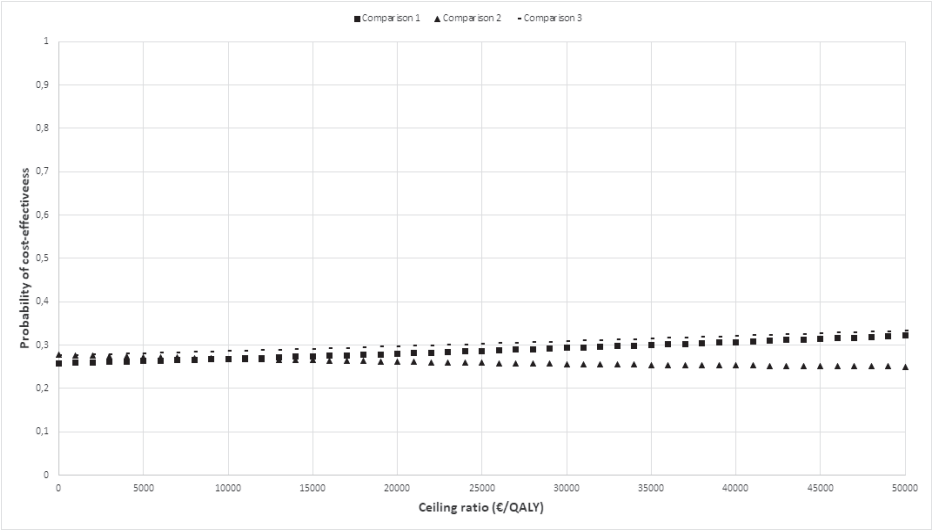

FIGURE 2 Cost-effectiveness acceptability curve indicating the probability of the intervention conditions' being cost-effectiveness compared with control for different ceiling ratios (€) for quality-adjusted life-years

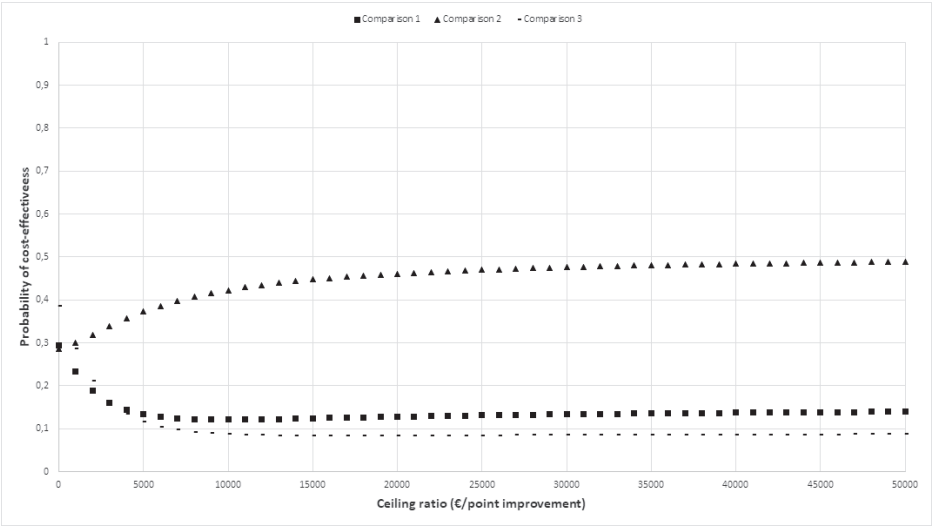

FIGURE 3 Cost-effectiveness acceptability curve indicating the probability of the intervention conditions' being cost-effectiveness compared with control for different ceiling ratios (€) for back-pain

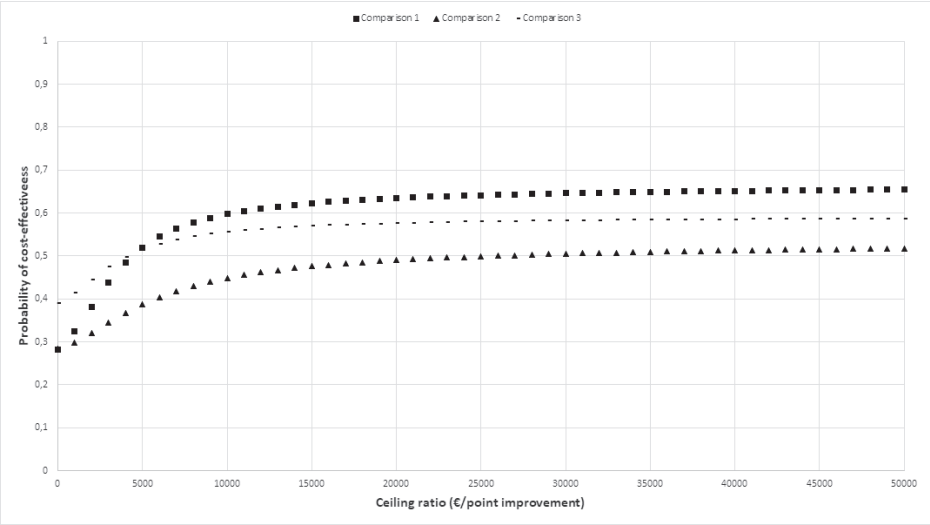

FIGURE 4 Cost-effectiveness acceptability curve indicating the probability of the intervention conditions' being cost-effectiveness compared with control for different ceiling ratios (€) for leg pain

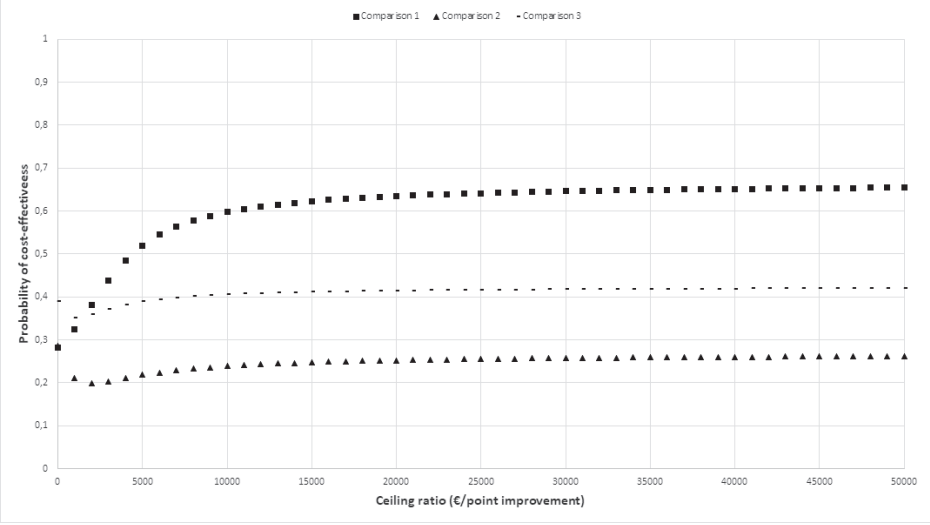

FIGURE 5 Cost-effectiveness acceptability curve indicating the probability of the intervention conditions' being cost-effectiveness compared with control for different ceiling ratios (€) for physical functioning

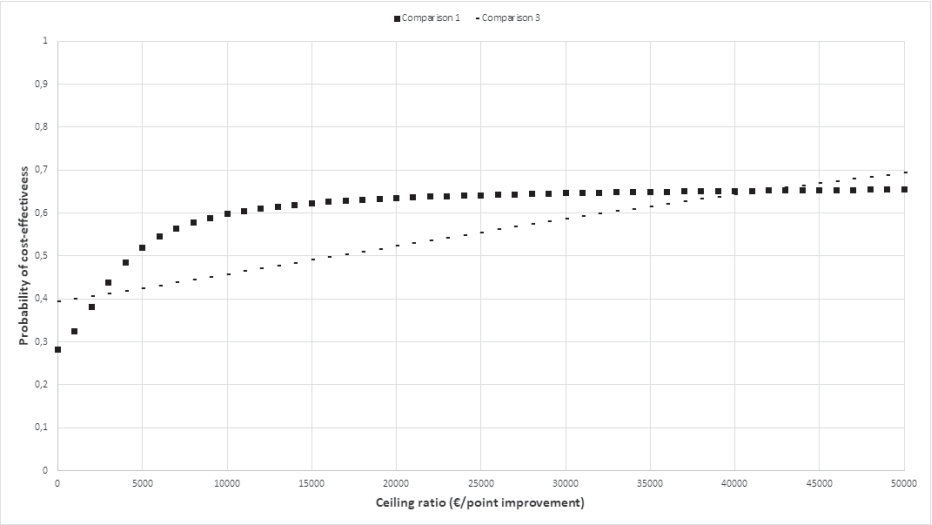

FIGURE 6 Cost-effectiveness acceptability curve indicating the probability of the intervention conditions' being cost-effectiveness compared with control for different ceiling ratios (€) for self-perceived recovery

Sensitivity analyses

In line with the main analysis, between-group differences in total costs and effects were not significant in any of the sensitivity analyses **(Appendix 2).** The complete-case analysis showed a small statistically significant effect on GPR for comparison 1 (0.04 (95%CI 0.02 to 0.07)). However, the overall conclusion of this study does not change when any of the assumptions of the sensitivity analyses are used.

Adverse effects

No adverse events were observed. None of the participants withdrew from the trial out of safety measures.

DISCUSSION

Principal findings

In this study, the cost and cost-effectiveness of adding an invasive treatment, that is, TESI to usual care in the treatment of acute sciatica (< 8 weeks) in the secondary care

setting was assessed. The results suggest that adding TESI to usual care is not cost-effective compared with usual care alone in patients with acute sciatica from a societal perspective in a Dutch healthcare setting. That is, the maximum probability for adding invasive treatment TESI of being cost-effective in comparison to the control was low for all possible outcomes (<0.7) and all comparisons. Comparisons 2 and 3 show comparable results.

Sensitivity analyses confirmed these results, although a small positive effect on GPR was found in the complete-case analysis for comparison 1 (ΔE 0.04 (95%CI 0.02-0.07)). This discrepancy with the main analysis is likely caused by the selective dropout of participants, and as multiple imputation was used in the main analysis to handle missing data, we consider these results to be more valid.

All in all, these results suggest that TESI or TEI in additional to usual care (oral pain medication) is not cost-effective compared with usual care alone from a societal perspective in acute sciatica patients in the Dutch healthcare setting.

Comparison to the literature

Price et al[41] conducted a prospective, double-blind randomized trial in the UK assessing the (cost-)effectiveness of TESI versus a placebo injection of normal saline into the interspinous ligament in 228 participants with sciatica during a 12-month follow-up. The most important outcomes were the number needed to treat to realize a 75% improvement in pain relief and functional status at 3 weeks, which was 11.4 (p= 0.017), and the cost per QALY for one epidural steroid injection which was £25,746 from a provider's perspective and £31,904 from a purchaser's perspective. Given the fact that in this trial there was no clinical benefit of TESI over placebo between 6 and 52 weeks, the authors concluded that TESIs were not cost-effective. However, *Price et al* did not assess the costs of informal care as and productivity losses. In addition *Price et al* assumed that both treatment groups received similar pain medication that did not differ between groups .As a result costs of pain medication were not explicitly measured.

Spijker et al[42] performed a pragmatic, randomized, controlled, single-blinded trial in Dutch general practices (n= 63) and compared one segmental epidural steroid injection containing 80 mg triamcinolone (intervention) to usual care (taking analgesics as needed, and maintaining normal daily activities as much as possible) during 52 weeks. Mean total costs were €4,414 in the intervention group and €5,121 in the control group, a difference

that was mostly due to differences in lost productivity. The point estimate for the ICER was - €730, meaning that a one point decrease on the NRS back pain scale in one patient during the course of one year was associated with a saving of €730 compared with usual care. The cost-effectiveness acceptability curve (CEAC) showed that without additional investments, the probability that epidural corticosteroid injections are cost-effective was more than 80%. *Spijker et al* concluded that the effect on pain and disability of epidural corticosteroid injections in sciatica is small, but significant (contrary to this RCT that found no clinically relevant differences between groups[17]), and at lower costs and recommended that 'policymakers could consider segmental epidural steroid injections as an additional treatment option'. The difference in results between our trial and that of *Spijker et al*[42] could be explained by differences in the way both studies handled missing data (i.e. multiple imputation in our study versus a complete-case analysis in the study of *Spijker et al*) and baseline imbalances (i.e. regression-adjustment in our study versus no adjustment in the economic evaluation of *Spijker et al*) as well as the absence of informal care, unpaid productivity, and presenteeism costs in the study of *Spijker et al*.

Strengths and limitations

The major strength of the STAR trial is its pragmatic design, meaning that its set-up resembled real-life routine practice conditions as much as possible[43]. Thus, the STAR trial enabled us to evaluate TESI against acute sciatica under circumstances directly in line with clinical practice, making the current results generalizable to Dutch clinical practice. The current analyses were also conducted using state of the art methods. That is, multiple imputation was used for handling missing data, regression-based adjustment for handling baseline imbalances, non-parametric bootstrapping for handling the skewed nature of cost data, and seemingly unrelated regression for handling the correlation between costs and effects[44]. This is important, as previous research indicates that using less optimal methods may notably impact results and might even impact on the conclusions of trial-based economic evaluations[45]. Another strength is that not only QALYs, functional status, and pain intensity were used as an outcome measure in the economic evaluation, but also perceived recovery as measured by the GPR. The similarity in results from four different outcome measures gave confidence in the robustness of results. Moreover, varies sensitivity analyses were performed that showed the robustness of results as well. All these attributes support the validity of the findings observed in this study.

This trial also has limitations. One limitation is that we used one particular injection technique, i.e. TESI. Other epidural injection techniques, such as caudal epidural

approach[46] or echography- guided transforaminal approach[47], might further reduce costs and improve the cost-effectiveness of epidural injections. The latter techniques were not chosen because in The Netherlands there is a strong preference for TESI (usual care within the Pain Department). A second limitation is the use of self-reported retrospective cost questionnaires that may have introduced recall bias and/or "social desirability bias. However, as it seems unlikely that recall bias or the degree to which participants gave socially desirable answers systematically differed between groups, it is not expected that self-report biased the results. Another limitation concerns the missing data. To deal with this limitation, missing cost and effect data were multiple imputed. Multiple imputation is currently considered the most appropriate method for imputing cost data, as it accounts for the uncertainty about the missing data by creating several imputed data sets[44]. A fourth limitation was the use of the three-level version of the EQ-5D rather than the 5-level version to measure QALYs[48]. This is a possible limitation, as the EQ-5D-3L was found to have significantly higher floor effects for the health dimension pain/discomfort and ceiling effects for the health dimensions mobility, self-care, pain/discomfort, anxiety/depression, compared with the EQ-5D-5L. However, as the floor and ceiling effects are likely to be equal in all study groups, we do not expect our use of the EQ-5D-3L to have severely biased our results. As a fifth limitation, opioid use was analysed on an aggregate level, and no detailed on the type, number, and dosage of opioids that the patients used was collected. When measuring pain, it is important to measure the medication that affects pain. We recommend future studies to measure this on a detailed level.

CONCLUSION

Although a common treatment among patients with sciatica due to an MRI-confirmed herniated lumbar disc, evidence from our trial-based economic evaluation suggests that TESI in the acute phase (<8 weeks) cannot be considered cost-effective compared to usual care from a societal perspective in a Dutch healthcare setting. Therefore, the current status of this treatment in the Dutch healthcare setting should be reconsidered.

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APPENDIX I

Informed consent form

Epidural corticosteroids in lumbosacral radicular syndrome

I read the test subject information letter. I was able to ask additional questions. My questions were answered enough. I had enough time to decide whether to participate.

I know that participating is completely voluntary. I know I can decide at any time not to participate anyway. I don't have to give a reason for that.

I consent to tell my GP that I am participating in this study (if applicable).

I consent to tell the specialist(s) treating me that I am participating in this study (if applicable).

I know some people can see my data. Those people are listed in the General brochure.

I consent to the use of my data, for the purposes set out in the information letter.

I consent to the retention of my research data for 15 years after the end of this study.

I want to participate in this study.

Subject's name:

Signature: Date : __ / __ / __

I hereby declare that I have fully informed this subject about the said study.

If information becomes known during the study that could affect the subject's consent, I will inform him/her in a timely manner.

Investigator's name (or representative):

Signature: Date: __ / __ / __

Additional information was provided by (if applicable):

Name:

Function:

Signature: Date: __ / __ / __

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* Delete what does not apply.

APPENDIX II

Cost-effectiveness analysis results (Sensitivity analyses)

Outcome	Sample size Outcome		HEALTHCARE PERSPECTIVE ΔC(95%CI)	ΔE(95%CI)	ICER	Distribution CE-plane (%)			
	Comparison 1 (Int. group 1 (Usual care + TESI) vs. Control (Usual care))								
	Int. Group 1	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	46	45	-178 (-1323 to 669)	0.008 (-0.041 to 0.056)	-20,996	18.6	44.2	19.1	18.1
Back pain (0-10)[2]	46	45	-191 (-1350 to 650)	0.6 (-0.5 to 1.7)	-309	6.1	9.4	53.4	31.0
Leg pain (0-10)[3]	46	45	-225 (-2422 to 745)	-0.4 (-2.2 to 1.4)	562	21.1	35.9	23.5	19.5
Functioning (0-23)[4]	46	45	-197 (-1317 to 640)	1.5 (-1.7 to 4.8)	-131	3.5	13.2	51.4	31.9
Global Perceived Effect[5]	46	45	-198 (-1345 to 639)	0.04 (-0.02 to 0.11)	--4,670	40.1	54.7	3.0	2.3
	Comparison 2 (Int. group 1 (Usual care + TESI) vs. Int. group 2 (Usual care + TEI))								
	Int. Group 1	Int. Group 2	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	46	50	-207 (-2315 to 753)	-0.011 (-0.061 to 0.038)	18,258	8.4	23.0	35.5	33.0
Back pain (0-10)[2]	46	50	-195 (-2344 to 746)	-0.03 (-1.2 to 1.1)	6,693	19.1	32.8	24.8	23.4
Leg pain (0-10)[3]	46	50	-225 (-2422 to 745)	-0.1 (-1.5 to 1.3)	2,377	21.1	35.9	23.5	19.5
Functioning (0-23)[4]	46	50	-233 (-2440 to 725)	0.99 (-2.15 to 4.12)	-211	8.3	16.0	43.5	32.2
Global Perceived Effect[56]	46	50	-	-	-	-	-	-	-

	Comparison 3 (Int. group 2 (Usual care + TEI) vs. Control (Usual care)								
	Int. Group 2	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	50	45	385 (-812 to 2985)	0.012 (-0.040 to 0.064)	31,468	40.9	27.5	6.7	24.9
Back pain (0-10)[2]	50	45	464 (-747 to 3218)	0.8 (-0.4 to 1.9)	572	6.8	4.2	27.1	61.9
Leg pain (0-10)[3]	50	45	410 (-784 to 3082)	-0.2 (-1.7 to 1.4)	-2,909	38.7	22.2	10.5	28.6
Functioning (0-23)[4]	50	45	409 (-778 to 3046)	0.4 (-3.3 to 4.0)	1,230	24.1	17.7	15.7	42.5
Global Perceived Effect[5]	50	45	418 (-762 to 3068)	0.05 (-0.01 to 0.10)	9,272	70.9	29.1	0.0	0.0
HUMAN CAPITAL APPROACH									
Outcome	**Sample size Outcome**		**ΔC(95%CI)**	**ΔE(95%CI)**	**ICER**	**Distribution CE-plane (%)**			
	Comparison 1 (Int. group 1 (Usual care + TESI) vs. Control (Usual care))								
	Int. Group 1	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	46	45	1918 (-3142 to 6695)	0.008 (-0.041 to 0.056)	250,146	43.5	18.0	7.7	30.8
Back pain (0-10)[2]	46	45	1714 (-3203 to 6585)	0.6 (-0.5 to 1.7)	2,772	11.4	3.9	24.6	60.1
Leg pain (0-10)[3]	46	45	1762 (-3269 to 6577)	-0.4 (-2.2 to 1.4)	-4,497	53.8	17.0	10.2	19.0
Functioning (0-23)[4]	46	45	1786 (-3222 to 6585)	1.5 (-1.7 to 4.8)	1,178	11.8	5.4	21.9	60.9
Global Perceived Effect[5]	46	45	1675 (-3331 to 6423)	0.04 (-0.02 to 0.11)	39,586	70.5	24.4	0.5	4.7
	Comparison 2 (Int. group 1 (Usual care + TESI) vs. Int. group 2 (Usual care + TEI))								
	Int. Group 1	Int. Group 2	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	46	50	2331 (-2912 to 7032)	-0.012 (-0.061 to 0.038)	-200,983	22.2	8.9	11.4	57.5
Back pain (0-10)[2]	46	50	2236 (-3049 to 7006)	-0.01 (-1.3 to 1.3)	-181,973	38.1	12.6	9.2	40.0
Leg pain (0-10)[3]	46	50	2272 (-3021 to 7077)	-0.1 (-1.5 to 1.3)	-34,677	44.2	11.7	9.8	34.2
Functioning (0-23)[4]	46	50	2271 (-3004 to 7101)	0.99 (-2.15 to 4.12)	2,281	19.9	5.5	15.9	58.8
Global Perceived Effect[56]	46	50	-	-	-	-	-	-	-

	Comparison 3 (Int. group 2 (Usual care + TEI) vs. Control (Usual care)								
	Int. Group 1	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	50	45	332 (-4466 to 5435)	0.012 (-0.040 to 0.064)	26,84412,019	37.0	30.8	13.7	18.4
Back pain (0-10)[2]	50	45	403 (-4471 to 5602)	0.8 (-0.4 to 1.9)	518	6.8	4.9	37.8	50.5
Leg pain (0-10)[3]	50	45	372 (-4423 to 5527)	-0.2 (-1.7 to 1.4)	-2029.	38.0	25.5	17.6	18.9
Functioning (0-23)[4]	50	45	374 (-4491 to 5642)	0.4 (-3.3 to 4.0)	1,045	24.1	17.3	27.0	31.6
Global Perceived Effect[5]	50	45	343 (-4525 to 5532)	0.05 (-0.01 to 0.10)	7,606	61.8	38.2	0.0	0.0
Outcome	**Sample size Outcome**		**ΔC(95%CI)**	**ΔE(95%CI)**	**ICER**	**Distribution CE-plane (%)**			
	COMPLETE-CASE ANALYSIS								
	Comparison 1 (Int. group 1 (Usual care + TESI) vs. Control (Usual care))								
	Int. Group 1	**Control**	**€**	**Points**	**€/point**	**NE**	**SE**	**SW**	**NW**
QALYs (0-1)[1]	21	27	4852 (-1989 to 12523)	-0.001 (-0.057 to 0.053)	-3,456,080	42.6	4.9	3.3	49.2
Back pain (0-10)[2]	21	27	5046 (-2771 to 12863)	0.8 (-0.7 to 2.2)	6,595	35.9	1.4	5.0	57.6
Leg pain (0-10)[3]	21	27	4854 (-3320 to 12118)	-1.7 (-3.5 to 0.1)	-2,889	88.0	6.2	0.3	5.5
Functioning (0-23)[4]	21	27	5011 (-2725 to 12300)	-0.2 (-3.7 to 3.3)	-22,361	49.2	6.03	1.6	42.9
Global Perceived Effect[5]	21	27	4837 (-3273 to 12186)	0.04 (0.02 to 0.07)	130,613	94.4	5.6	0.0	0.0
	Comparison 2 (Int. group 1 (Usual care + TESI) vs. Int. group 2 (Usual care + TEI))								
	Int. Group 1	**Int. Group 2**	**€**	**Points**	**€/point**	**NE**	**SE**	**SW**	**NW**
QALYs (0-1)[1]	21	25	364 (-6199 to 6927)	-0.044 (-0.112 to 0.023)	-8,210	3.9	7.2	37.4	51.4
Back pain (0-10)[2]	21	25	1521 (-4837 to 7880)	0.5 (-1.0 to 1.9)	3,300	38.8	7.9	15.9	37.4
Leg pain (0-10)[3]	21	25	1234 (5168 to 7616)	-0.5 (-2.4 to 1.3)	-2,247	59.4	17.3	8.6	14.7
Functioning (0-23)[4]	21	25	963 (-5645 to 7570)	2.0 (-2.6 to 5.6)	488	7.0	6.5	31.6	54.8
Global Perceived Effect[56]	21	25	-	-	-	-	-	-	-

	Comparison 3 (Int. group 2 (Usual care + TEI) vs. Control (Usual care)								
	Int. Group 2	Control	€	Points	€/point	NE	SE	SW	NW
QALYs (0-1)[1]	25	27	2840 (-3522 to 9446)	0.026 (-0.031 to 0.083)	108,529	64.1	16.2	0.8	18.9
Back pain (0-10)[2]	25	27	2814 (-3573 to 9276)	0.3 (-1.1 to 1.6)	10,426	44.2	5.6	7.4	42.9
Leg pain (0-10)[3]	25	27	3005 (-3423 to 9570)	0.02 (-1.3 to 1.3)	155,638	56.6	7.9	4.5	31.1
Functioning (0-23)[4]	25	27	2721 (-3861 to 9218)	-1.9 (-5.7 to 1.9)	-1450	65.6	16.2	1.2	16.9
Global Perceived Effect[5]	25	27	3031 (-3534 to 9597)	0.04 (-0.04 to 0.11)	81,850	90.5	9.5	0.0	0.0

C: Costs, E: Effects, ICER: Incremental Cost-Effectiveness Ratio, CE-plane: Cost-Effectiveness plane, NE: Northeast-Quadrant, SE: Southeast-Quadrant, NW; Northwest-Quadrant, ZW; Southwest-Quadrant; Cost differences were adjusted for age, gender, body mass index (BMI), and severity of back and leg pain at baseline. [1] adjusted for baseline utility values, work status, age, gender; [2] adjusted for baseline values, level of herniated disc; [3] adjusted for baseline values, age, gender, body mass index (BMI), and severity of back and leg pain at baseline. Lasègue's sign; [1] adjusted for baseline values, work status, gender; [5] percentage point (difference in percentage recovered between intervention -and control group) adjusted for work status. [6] No patients were recovered, cannot be estimated.

9 CHAPTER

General Discussion

INTRODUCTION

Sciatica, or the lumbosacral radicular syndrome, is characterized by pain radiating into the leg following one of the lumbosacral nerve roots[1]. Although both terms are used in this thesis, 'lumbosacral radicular syndrome' is the more exact, preferable one of the two, referring to a specific injured nerve root. The lumbosacral radicular syndrome has an annual incidence of 9.4 per 1000 person-years[2] and a prevalence of between 1.3 and 43% per 1000 person-years[3]. In addition to pain, patients may also suffer from sensory symptoms and/or weakness of the involved myotome[1]. The principal source of the pain is nerve root impingement due to a mechanic compression: i.e. about 65-83% of cases of lumbosacral radicular syndrome are caused by intervertebral disc herniation[4-7]. Besides mechanical compression, there is increasing evidence that inflammation plays a role in the underlying pathophysiology[8]. The economic impact of the lumbosacral radicular syndrome is high compared with other diseases, with relatively high healthcare and productivity-related costs[9,10].

During the first few weeks, patients with lumbosacral radicular syndrome are usually treated by the General Practioner (GP) with a focus on pain control by means of pain medication (e.g. using non-steroidal antiinflammatory drugs (NSAIDs) or opioids) and possibly supplemented by physiotherapy if more intensive activation support is needed[11]. If symptoms persist despite conservative measures or if symptoms are invalidating (severe pain or neurological deficits), patients will be referred to a hospital as 'second line' treatment. Within the hospital setting, the patient will be examined by a neurologist and, if indicated, treated by an anaesthesiologist ('pain specialist') with injections or patients are referred to a spine surgeon for a hernia surgery. For a more detailed description of the clinical picture, diagnosis and treatment of lumbosacral radicular syndrome, the reader is referred to **chapter 1**.

The overall goal of the thesis was to contribute to best clinical practice during the acute stage of lumbosacral radicular syndrome, defined as the first 8 weeks. The main focus is on transforaminal epidural steroid injections (TESIs), which are increasingly used as an alternative to pain medication in patients with lumbosacral radicular syndrome, especially in acute patients with severe pain. This thesis consists of three different research themes. The three themes are briefly described below.

Theme 1 is entitled *'Diagnosis and treatment of acute lumbosacral radicular syndrome'* and contained a historical overview of the use of epidural steroids against lumbosacral radicular syndrome (**chapter 2**) followed by a cross sectional survey among neurologists and anaesthesiologists assessing their views regarding the management of the lumbosacral radicular syndrome (**chapter 3**).

Theme 2 is entitled *'Inflammation'* and contained a systematic review on inflammation as an underlying pathogenic mechanism in lumbosacral radicular syndrome (**chapter 4**).

Theme 3 is entitled *'(Cost-)effectiveness of transforaminal epidural steroid injections'* and contained the design (**chapter 5**), statistical analysis plan (**chapter 6**), effectiveness results (**chapter 7**), and cost-effectiveness results (**chapter 8**) of the 'steroids against radiculopathy' (STAR)-trial. The STAR-trial is a randomized controlled trial evaluating the (cost-)effectiveness of transforaminal epidural steroid injections (TESI) against acute lumbosacral radicular syndrome.

Theme 1: Diagnosis and treatment of acute lumbosacral radicular syndrome

Main results

The historical overview in **chapter 2** showed that epidural injections for back pain and lumbosacral radicular syndrome were first administered in Paris around 1900. This practice gradually gained acceptance and spread to Europe and North America. In the 1950s, corticosteroids were introduced for epidural use. Since the 1970s, clinical trials have been conducted that shown a small, but significant short-term effect in relieving leg pain. Despite ongoing discussions regarding their efficacy and safety, epidural injections continue to be widely used.

We also we conducted an online survey among 124 Dutch neurologists and anaesthesiologists and were particularly interested in their view on TESIs and if, and if so, to what extent, the current guidelines are followed. The results of this survey showed that 40% of neurologists think that TESIs are effective in 40-60% of injected patients and that 52% of anaesthesiologists think that TESIs are effective in 60-80% of the injected patients.

With regard to guideline adherence, several discrepancies between evidence and daily clinical practice were identified and these were classified by an independent panel of clinicians as 'major', 'minor' or 'no discrepancy'. The classification was based on

comparing the answers of the survey with the latest Dutch multidisciplinary guideline[12] and the anaesthesiologists' safety guidelines'[13]. Major discrepancies were identified for 'selective nerve blocks', 'imaging', and 'pulse radio frequency' (PRF). Minor discrepancies were identified for 'medication', and 'physiotherapy'. With regard to TESIs, there was 'no gap' as both neurologists and anaesthesiologists followed the guidelines.

Discussion

When discussing the survey and its implications, it is important to start with its limitations. For example, the number of survey participants was relatively small, i.e. less than 10% of the total number of Dutch neurologists took part. Moreover, most participating clinicians worked in a Teaching or General Hospital, rather than a private practice or the academic setting. Also, relatively few anaesthesiologists who were in in-training participated and there were relatively many men (i.e. 75%). These factors affect the generalizability of the survey's results to the whole population of Dutch neurologists and anaesthesiologists.

The rather positive view of both neurologists and anaesthesiologists on TESIs was remarkable, because the current evidence suggests only a minor effect of TESIs in patients with lumbosacral radicular syndrome, i.e. <1 point improvement on a 0-10 pain scale for the term of 4-6 weeks[14-16]. In light of this finding, it is important to mention that neurologists and anaesthesiologists do follow the multidisciplinary guideline and only order TESIs in case of severe pain refractive to pain medication[12].

The identified discrepancies between evidence and practice will be further discussed below, starting with 1. 'selective nerve root blocks', followed by 2. 'medication', 3. 'physiotherapy' and 4. 'imaging'. PRF was also considered as 'major discrepancy', but is outside the scope of this thesis and will therefore not be discussed.

1. Selective nerve root blocks

Selective nerve root blocks are often ordered to identify the nerve root causing the pain in lumbosacral radicular syndrome patients prior to disc surgery, especially when there is a mismatch between the clinical and radiological level. An example of such a mismatch is a clinical presentation of pain radiating into the L5 dermatome, while a L3-4 disc herniation is seen on the MR imaging. However, although clinicians think selective nerve root blocks are a valuable tool for assessing lumbosacral radicular syndrome, this idea is not supported by current evidence and hence not recommended by the multidisciplinary guideline[12]. That is, based on two (retrospective) studies[17,18], the

guideline[12] concludes that there is a high positive predictive value of selective nerve root blocks combined with a low negative predictive value. This should be interpreted by clinicians as that a positive nerve root block does predict a high probability of a positive outcome of surgery, while a negative block does not necessarily indicate a low probability for a negative outcome of surgery. It is important to mention that the methodological quality of these studies (according to the GRADE classification[19]) was low due to their retrospective design and lack of control (sham) intervention. So overall, there is too much uncertainty and the guideline therefore cautiously recommends against the use of diagnostic blocks.

In accordance with the multidisciplinary guideline, neurologists and anaesthesiologists are advised to be reluctant when it comes to diagnostic blocks. If a diagnostic block is ordered anyway, special attention is needed when interpreting its results, especially in case of a negative block because it does not necessarily predict a negative outcome of surgery.

Prospective trials can be conducted to evaluate the sensitivity, specificity, accuracy, and predictive value of these blocks. The study design of *Yeom et al*[20], a within patient case-control study, is a good example for a future trial. They included patients with a single-level, unilateral lumbosacral radiculopathy confirmed by clinical, radiographic, and MRI findings that were candidates for surgery. Patients with multilevel disc herniation on MRI or incompatible clinical findings were excluded. At 1 or 2 days preoperatively, selective nerve root blocks were done with 1 mL of 2% lidocaine at the presumed pain-generating level and on 1 or 2 adjacent control levels in a random-sequence fashion. A minimum of 6 hours elapsed between blocks. Although the patients were blinded to the levels of the blocks, blinding could not be applied to the physicians administering the injections (single blinded design). A trial nurse, blinded to the injection level, therefore asked the patients to rate the percentage of decrease in their radiating pain compared with their pre-injection state at 30 minutes after each injection. A positive block was predefined as a temporary relief of >70%. Finally, all the patients went on for surgery. The operative findings had to correlate with the images to verify the cause-effect relationship. Based on 105 injections (47 blocks were performed at the symptomatic level, and 58 were performed at the adjacent asymptomatic “control” level) they established a sensitivity of 57%, a specificity of 86%, an accuracy of 73%, a positive predictive value of 77%, and a negative predictive value of 71%.

2. Pain medication

The survey in **chapter 2** showed that a wide range of medication is prescribed, including acetaminophen, NSAIDs, benzodiazepines, opioids and medication against neuropathic pain, i.e. anti-epileptic drugs (e.g. pregabalin and gabapentin) and anti-depressants (e.g. nortriptyline). This broad range of medication is only partly in line with the advice from the guideline.

The multidisciplinary guideline contains a systematic review of all pain-medication used in daily practice[12]. The review showed that: 1. no pain medication is better than placebo in terms of pain and functioning, with the exception of the so called '-oxicams' (Meloxicam and Lornoxicam) that have a small positive effect; 2. no pain medication is superior when compared to others pain medication in terms of pain and functioning. The guideline therefore recommends: 1. to prescribe pain medication according to the 'WHO-pain ladder', a well-known stepped care algorithm that is broadly based on NSAIDs and opioids[21]; 2. that there is no objection against the use of NSAIDs; 3. to refrain from anticonvulsants, antiepileptic drugs and benzodiazepines during the acute stage of the lumbosacral radicular syndrome.

Following this advice, and even though the underlying evidence is weak, only NSAIDs and opioids should be used in painful lumbosacral radicular syndrome. The WHO-pain ladder is 'simply' advised because most physicians are familiar with it. With regard to scientific research it would be interesting to investigate a new medication schedule (instead of the WHO-pain ladder) that addresses both the underlying inflammatory and neuropathic components of lumbosacral radicular syndrome (so called 'mixed pain concept'[22)]. A future prospective randomized controlled trial could therefore compare 'schedule A' (i.e. pain medication is prescribed according to the WHO-pain ladder and no other pain medication is allowed) versus 'schedule B' (i.e. pain medication is prescribed according to the WHO pain ladder plus adjuvant medication against neuropathic pain) in patients with acute lumbosacral radicular syndrome. The suggested minimum follow-up of such a trial would be 3 months, as most patients recover within this timespan with conservative measures (see **Chapter 1**). Suggested primary outcome measurements are physical functioning, pain intensity, health-related quality of life[23] and (based on our own trial) recovery. During the trial, it is recommended to carefully monitor medication use, and the use of opioids, in particular. It is interesting, in the light of the worldwide opioid epidemic if patients who follow 'schedule B' use less of the highly addictive opioids compared with patients who follow 'schedule A'. If we further elaborate on the opioid

crisis, cannabis (low dose THC) might also be a viable substitute for pain treatment because both cannabis and opioids have been reported to offer synergistic analgesic effects when used concomitantly[24]. This can be further investigated in a placebo-controlled trial, i.e. adding cannabis or placebo to the WHO pain ladder (usual care) and make between groups comparison in patients with an acute lumbosacral radicular syndrome.

3. Physiotherapy

Patients with acute lumbosacral radicular syndrome are often referred for non-pharmacologic treatments, including exercise therapy and physiotherapy. The underlying evidence, however, is limited and the guideline therefore recommends an 'active lifestyle' (rather than a specific form of exercise therapy) and to refer patients with lumbosacral radicular syndrome only to a physiotherapist if there is fear of movement (kinesiophobia).

Only few trials examined the effectiveness of referral to physical therapy among acute lumbosacral radicular syndrome for patients (<6-8 weeks). *Hofstee et al*[25] found no differences between physical therapy, bed rest, and advice to continue daily activities for lumbosacral radicular syndrome of less than 1 month's duration. The outcomes were pain intensity or disability over a 6-month follow-up. *Luisterburg et al*[26] compared education from a GP with or without physical therapy among patients suffering from lumbosacral radicular syndrome for less than 6 weeks. After 1 year, patients who were randomly assigned to a GP with physical therapy were more likely to rate themselves as being improved compared with patients who were assigned to a GP without physical therapy, but no differences were seen in back pain intensity and disability. Another interesting study to mention here (published after the guideline came out), is that of *Fritz et al* who compared GP education alone versus GP education combined with 4 weeks of physical therapy in patients who suffered from lumbosacral radicular syndrome for less than 90 days. Their results suggest that the addition of physical therapy improved patients' disability and pain[27].

Given the above, only a subset of patients with lumbosacral radicular syndrome (e.g. those with fear of movement) are ideally referred to physical therapy. Future trials could further refine this recommendation by trying to identify patients who are most likely to benefit from physiotherapy (so called 'stratification-based decision-making'[28-30]). The challenge for clinicians managing lumbosacral radicular syndrome in primary care would then be how to timely distinguish between patients who would only need conservative

management with physiotherapy with or without pain medication and patients who may need early, fast-track referral to secondary care.

4. Imaging

In **chapter 2** we also found that there is a tendency among neurologists to scan more patients with lumbosacral radicular syndrome than strictly necessary according to the guideline recommendations[12]. The guideline namely advises to only perform an MRI in case of 'red flags' (see **chapter 1**), if patients will be injected, or if they are referred to surgery. The main reason for performing an MRI in patients with lumbosacral radicular syndrome is to confirm the presence of a herniated disc and to rule out rare causes, such as a tumour. However, if a conservative trajectory with clinical follow-up is chosen and if there is no clinical suspicion of any underlying cause other than a herniated disc, MRI can wait (until surgery is chosen in case of long persisting symptoms).

For anaesthesiologists this is different. In our survey, we found that there is a tendency among anaesthesiologists to scan less patients than recommended, which is due to their "safety principles"[13]. These "safety principles" advise to only perform an MRI in patients who will be treated invasively (TESI or PRF). In that case, the main goal of the MRI is to ensure that there is nothing other than a herniated disc compressing the nerve root before injecting the patients. This would mean that an MRI is required for every patient that is treated at a Pain Department, whereas this is currently not the case.

If we relate these findings to everyday clinical practice, neurologists should be advised not to order an MRI for every patient with lumbosacral radicular syndrome, whereas anesthesiologists should be advised to order an MRI more frequently (i.e. for every patient that they treat with injections out of safety measures).

With regard to future research, it would be interesting to look for MRI characteristics in patients with lumbosacral radicular syndrome that predict their clinical course ('radiological biomarker') and their response to specific treatments, for example TESIs. As many of the previous studied 'classical' MRI markers for the clinical course of lumbosacral radicular syndrome, such as level and size of disc herniation, presence of an annular tear, and degree of nerve root compression, have been proven invalid[31], it is interesting to look for new markers. A possible 'new' radiological biomarker could be the presence of Modic-changes (MC). MC are vertebral bone marrow changes adjacent to the endplates as noted on MRI and that represent inflammation[32,33]. Patients MC form a

distinct clinical subset with reports of higher intensity of pain, poor clinical and surgical outcomes[34]. It is interesting to specifically look for MCs in relationship to the clinical course of both back pain and lumbosacral radicular syndrome and MCs in relationship to treatment response (**see Theme 2 and 3**).

Theme 2: Inflammation

Main results

A supposedly inflammatory substrate in patients with lumbosacral radicular syndrome could be a potential target for anti-inflammatory therapy, specifically NSAIDs or TESIs (the topic of the STAR-trial discussed under **Theme 3**). For this reason, we tried to summarize the evidence of an underlying inflammatory substrate in patients with lumbosacral radicular syndrome by conducting a systematic review to look for biomarkers that indicate inflammation in lumbosacral radicular syndrome. According to the European Medicine Agency, a 'biomarker' is defined as: *'A biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals.'*[35].

Our literature search revealed the following markers in blood, cerebrospinal fluid and biopsy in patients with a lumbosacral radicular syndrome: interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IL-21, tumour necrosis factor-α (TNF-α), phospholipase A2, high sensitivity C-reactive protein (hsCRP), C-X-C motif chemokine 5 (CXCM5), CX3CL1, CCL2, epidermal growth factor (EGF), and monocyte chemotactic protein 4 (MCP-4). In addition, several positive correlations between biomarkers and clinical symptoms were found in longitudinal studies among patients with lumbosacral radicular syndrome. That is, a strong positive correlation between inflammatory mediators or by-products and pain was found for IL-21 in two studies (r> 0,8). Moderate positive correlations between TNF-a and sciatic pain were found for in both serum (r = 0,629) and biopsy (r = 0.65) Moreover, severe pain was found to be associated with increased hsCRP levels among patients with lumbosacral radicular syndrome (adjusted OR = 3.4 (95% CI, 1.1 to 10). For IL-8 in and Il-6 in annulus fibrosis biopsy, low negative correlations were found. That is, the presence of these markers was found to be related to better clinical outcome. Please note, however, that it is hard to draw firm conclusions from the results of our systemic review due the relatively small sample sizes of the included studies and differences in study design and laboratory assays that were used.

Discussion

Before reflecting on the clinical and research implications of our systematic review, it is interesting to compare our results with those of previous research. *Goupille et al*[36], for example, conducted a narrative review and identified various inflammatory proteins from both human and animal studies. These markers included phospholipase A2, prostaglandin E2, leukotrienes, nitric oxide, immunoglobulins, pro-inflammatory cytokines such as IL-1alpha, IL-1beta, IL-6, and TNF-α . Similar to our study they concluded that '*Although inflammation may partially explain lumbar radiculopathy, involvement of inflammatory mediators in the physiopathology of disk herniation-associated radiculopathy has not been proven*.'[36].

Djuric et al[37] also conducted a systematic review assessing inflammatory activity in patients with lumbosacral radicular syndrome. Their review was based on 14 studies, of which 9 were also included in our systematic review. They found that high levels of TNF-α, TNFR1, IL-6, IL-8, and IFN-γ were all associated high VAS scores for pain. In contrast, high levels of TNFR2 were associated with low VAS scores. Moreover, no associations were found for IL-1a and IL-1β. High levels of both IL-4 and IL-10 were associated with low VAS scores. Moreover, the presence of macrophages (CD68) was associated with low VAS scores. These results differed from those of our systematic review, which might be due to the fact that they dichotomized their outcome into a 'pro-inflammatory response' an 'anti-inflammatory response'. The pro-inflammatory response was characterised by M1 macrophages and pro-inflammatory cytokines, such as TNF-α, TNFR1, IL-6, IL-8, and IFN-γ, and was associated with high VAS scores. The anti-inflammatory response was characterised by M2 macrophages and anti-inflammatory cytokines, such as IL-4 and IL-10, and was associated with lower VAS scores.

Since the publication of the aforementioned reviews, more studies have been published on 'inflammation and lumbosacral radicular syndrome'. Three of them will be briefly described here: *Djuric et al* investigated disc material and MRIs of 119 patients that underwent disc surgery for lumbosacral radicular syndrome and found that inflammation (as seen by Modic changes on MRI and macrophage infiltration in biopsies) was associated with a slow recovery after surgery[38]. *Hider et al* screened 119 patients with lumbosacral radicular syndrome within the primary care setting (a sub-cohort of the ATLAS study) for inflammatory biomarkers and found no significant differences in serum levels of TNFα, IL-6 or any other biomarkers between patients with lumbosacral radicular syndrome due to a herniated disc and those with back pain and referred leg pain ('pseudoradicular

syndrome') without disc herniation as seen on MRI[39]. In a sample of 78 patients with lumbosacral radicular syndrome (due to disc herniation) that were matched to 57 healthy controls, *Jacobsen et al* found that symptoms were positively correlated with circulating levels of three markers that were not part of our review, i.e. HMGB1, PDGFbb, and IL-9[40]. To conclude, many different inflammatory biomarkers have been tested in patients with lumbosacral radicular syndrome, and both positive ('pro-inflammatory') and negative ('anti-inflammatory') correlations between biomarkers and clinical symptoms have been found. As there are also negative trials (that do not show any correlation), the strength and usefulness of these correlations for clinical practice still needs to be established.

Implications for clinical practice

Currently, the knowledge is insufficient to draw firm conclusions on whether inflammation contributes to lumbosacral radicular syndrome. Nonetheless, once an inflammatory substrate underlying lumbosacral radicular syndrome can be identified using biomarkers, this might potentially improve the management for lumbosacral radicular syndrome, because: 1) the biomarker might be used as a prognostic factor for recovery, as one could hypothesize that patients with an 'inflamed disc and root' take more time to recover than patients without; and 2) the inflammatory substrate as indicated by biomarkers, might become a target for anti-inflammatory therapy with NSAIDs, TESIs or anti-TNF inhibitors such as infliximab[41] or adalumimab[42]. In other words, biomarkers could help with better selecting patients for treatment ('precision medicine'), and hence targeting therapeutic interventions at those who will likely benefit most from them, potentially resulting in less expenses and less side effects[43].

Apart from the lack of rigorous and conclusive scientific evidence, there are also practical issues that need to be solved before blood tests for biomarkers can be used in clinical practice. When writing the protocol for a biomarker feasibility study in 2020 (not published) we encountered several of these practical issues. To illustrate, a relatively large volume of blood needs to be taken (10 mL) from the patient, which in turn has to be transported with dry-ice by a commercial courier to an external laboratory with an immunological facility. For this reason, a radiological marker of inflammation ('radiological biomarker', for example Modic changes), rather than a blood biomarker (or one acquired from an invasive procedure such as a biopsy or cerebrospinal fluid punction) seems a far more feasible marker to use in clinical practice, especially because nearly all patients with

lumbosacral radicular syndrome that undergo TESI or surgery will be scanned according to the protocol (see **'Imaging' under Theme 1**).

Implications for research

In order for the biomarker field (in relationship to lumbosacral radicular syndrome) to proceed, there is a strong need for (preferably prospective) studies with larger sample sizes and similar study designs and laboratory assays. Amongst others, consensus should be reached on: 1) the material that is used to investigate specific biomarkers (blood, disc material from surgery, cerebrospinal fluid; 2) the biomarkers of interest; 3) the time points at which biomarkers will be measured, 4) the clinical and radiologic data that will be collected; and 5) how to measure the biomarkers (as a 'panel'). The latter is important, because there are different lab methods to establish inflammatory activity for example *enzyme-linked immunosorbent assay* (ELISA) or polymerase chain reaction (PCR).

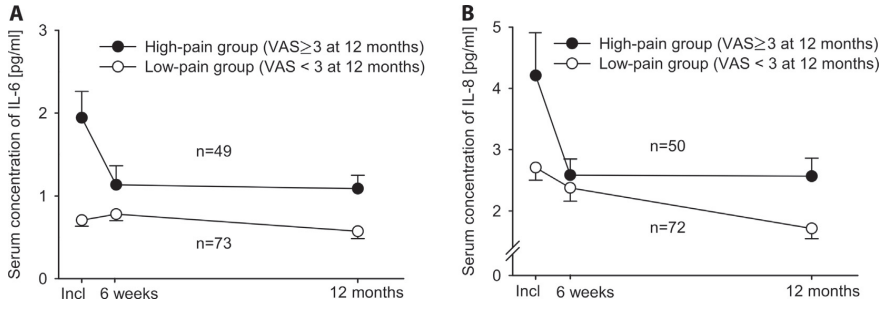

FIGURE 1 Example of a longitudinal biomarker study (interleukin concentrations measured in serum over time and in relationship to pain severity[38].

If there is (at least some) agreement on the preferred laboratory methods for assessing possible inflammation in patients with lumbosacral radicular syndrome, a second step would be to perform longitudinal observational studies among patients with acute and chronic lumbosacral radicular syndrome. A good example of the type of study intended here, is that of *Pedersen et al* who studied the serum concentration of the pro-inflammatory cytokines IL-6 and IL-8 using ELISA in patients with lumbosacral radicular syndrome due to disc herniation measured at inclusion, at 6 weeks and at 12 months follow-up[44]. **See Figure 1**. This kind of study will not only reveal an underlying inflammatory substrate (if present), but can also reveal prognostic information, for example, whether patients with inflammatory activity have an increased risk of chronification. In case of a longitudinal biomarker study, it is important to include

other (non-biomarker) predictors as well, for example pain scores at baseline[45]. The FORECAST-study (factors predicting the transition from acute to persistent pain in people with 'sciatica' is an example of a longitudinal cohort-study combining clinical and biomarker data[46].

Once an inflammatory substrate is established by biomarkers (in a longitudinal study), a third step would be to conduct intervention studies assessing the clinical benefits of anti-inflammatory therapy (see **'research implications'** under **Theme 3**). In such studies, it might also be interesting to assess whether certain subgroups of patients with a lumbosacral radicular syndrome and an inflammatory reaction react better to anti-inflammatory therapy than others, or the patient group as a whole.

Other interesting research areas closely related to biomarkers of inflammation are: 1) MRI studies of inflammation and lumbosacral radicular syndrome ('radiological markers', see also **'imaging' under Theme 1**); and 2) bacteriological studies that look for co-infection with bacteria such as Propriobacterium Acnes (P. Acnes)[47,48]. The latter is important, because a part of the patients with lumbosacral radicular syndrome due to an underlying herniated discs with annular tear turn out to be infected with P. Acnes, as detected in the cultures of disc and muscle samples. Its exact role is unknown, but some hypothesize that the bacteria might be a causative agent, while other research groups propose that P. Acnes in the disc tissue comes from bacterial contamination during surgery[49,50].

Theme 3: Effectiveness and cost-effectiveness of transforaminal epidural steroid injections

Main results

The STAR-trial was a prospective randomized controlled trial (RCT) investigating the (cost-)effectiveness of TESI in patients with acute (<8 weeks) lumbosacral radicular syndrome. This study was conducted in two Dutch hospitals. Participants (n=141) were randomly assigned to: 1) usual care and TESI of 1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine (intervention 1); 2) usual care and transforaminal epidural injection with 1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9% (intervention 2); and 3) usual care consisting of pain medication with or without physiotherapy (control). Co-primary outcomes were back and leg pain intensity, physical functioning, and recovery measured during 6-month follow-up. For the economic evaluation, health-related quality of life was measured as well.

This RCT found that adding TESI to usual care, as administered in intervention group 1, compared to usual care alone, only had a statistically significant, albeit not clinically relevant, effect on leg pain. For the other co-primary outcomes, no statically significant, nor clinically relevant, differences were found. For the comparison between intervention group 1 and intervention group 2, no statistically significant or clinically relevant differences were found either. Consequently, in accordance with the EMA-guidelines, the intervention was not considered effective[51].

A post-hoc analysis showed, however, that statistically significantly more patients who received TESI experienced a relief in leg pain of more than 50% compared to patients that received usual care alone at 3 months. Moreover, both intervention groups were found to use significantly less opioids than patients who solely received usual care at 3 and 6 months.

In the economic analysis, after 6 months, no significant differences in costs between the three treatment groups were found. The adjusted mean difference in total societal costs was €1718 (95%CI:-3020 to 6052) for comparison 1 (intervention-group 1 versus control group), €1640 (95%CI:-3354 to 6106) for comparison 2 (intervention group 1 versus intervention-group 2) and €770 (95%CI: -3758 to 5702) for comparison 3 (intervention group 2 versus control). The maximum probability of the interventions being cost-effective compared with control was low (<0.7) for all effect measures.

Discussion

Several aspects of the trial are discussed here: 1) strengths and limitations; 2) comparison to other studies; 3) clinical implications; and 4) research implications.

1. Strengths and limitations

There were several strengths of the STAR-trial, including the fact that it was a successful collaboration between university and peripheral hospitals, its three-arm design, and the careful selection of patients with lumbosacral radicular syndrome due to a herniated disc on clinical and radiological grounds.

Collaboration can be defined as "*the pooling of knowledge, capacity, resources, and interests and can be used to develop cost effective, evidence based practice to improve health care outcomes*"[52]. The STAR-trial was a successful collaboration between different clinical departments (Neurology, Pain Medicine and Radiology) of two hospitals,

the OLVG Amsterdam and Zaans MC, and two academic departments: the department of Epidemiology and Data Sciences (Vrije Universiteit and the Amsterdam Movement Sciences Research Institute) and the Department of Health Sciences (Faculty of Science, Vrije Universiteit Amsterdam). The academic departments contributed largely to the methodology and statistical analysis of the trial results, while both hospitals were responsible for a proper selection, treatment, and follow-up of patients. A second strength was the three-arm design of the STAR-trial, comparing usual care with two different intervention conditions. This design is in contrast to most other studies investigating TESI that only have two arms, i.e. comparing TESI to usual care or placebo intervention only, see also **'similar research'**. The third arm of our trial not only enabled a head-to-head comparison between two available treatment options (TESI versus oral medication only), but also to explore the (cost-)effectiveness of TESI compared to an injection without the steroids. To our knowledge there are no trials with a similar design. A third strength is the careful selection of the included patients. That is, upon referral by the GP, all potential candidates underwent neurological examination to confirm the clinical diagnosis of a lumbosacral radicular syndrome, followed by radiological confirmation by MR Imaging of an underlying herniated disc causing the lumbosacral radicular syndrome.

There were also several limitations, the most important being the trial's poor inclusion rate and the lack of a proper registration of medication, opioid use in particular. Slow recruitment and failure to reach the planned sample size within the planned timeframe is commonplace in randomized controlled trials. A 2015 analysis of registered trials revealed that 19% of them were terminated early, because they could not recruit enough subjects[53]. A 2013 study even found that over 80% of conducted clinical trials missed their recruitment targets[54] and *Briel et al* found that 76% of discontinued clinical trials were terminated due to poor recruitment[55]. The STAR-trial has also been stopped before the required sample size was reached. That is, based on our sample size calculation (**chapter 5**) we aimed to include 264 patients over a period of 4 years. However, between January 13th 2016 and September 10th 2019, we had only managed to recruit 141 patients, and therefore decided to terminate patient inclusion. The STAR-trial is a typical example of the 'Lasagna effect'[56]. Louis Lasagna (1923-2003) is credited with highlighting a problematic phenomenon in medical research suggesting that "*the number of patients available to join a trial drops by 90% the day the trial begins, while they re-appear as soon as the study is over*" (see **Figure 2**). Hence, the number of participants actually available for recruitment in a study, usually turns out to be much lower than estimated in advance, which might have also be the case in the STAR-trial.

Issues that may have contributed to the relatively slow recruitment for the STAR-trial can be classified into research factors, physician factors, patient factors and are shown in **Table 1** along with possible solutions.

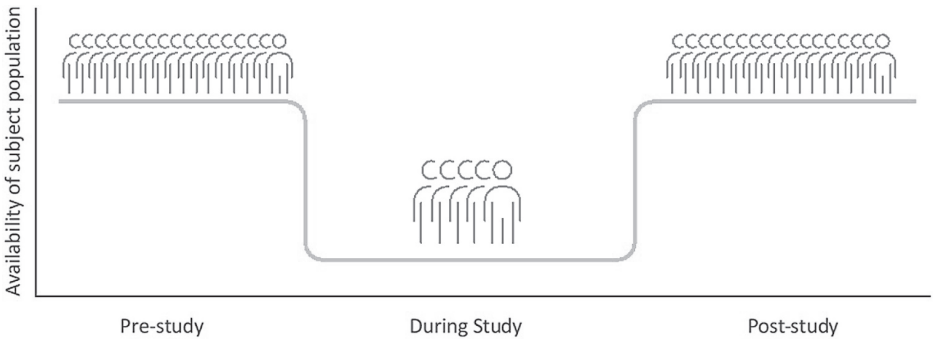

FIGURE 2 The Lasagna-effect[50]

With regard to pain medication, the STAR-trial (similar to other pain trials) allowed the use of auxiliary pain medications, such as rescue and concomitant analgesics in addition to the randomized treatment[57,58]. Changes in auxiliary pain medications after randomization may have affected the interpretation of primary (back and leg pain, functioning and recovery) and secondary outcomes (health related quality of life, satisfaction and number of operations) complicating the assessment of treatment efficacy. For instance, if the intervention in our trial (TESI) is effective, subjects in this group may reduce their concomitant pain medication or use less rescue medication than subjects in the control group. As a result, the difference in pain between the two groups, that is, the treatment effect, will be reduced in comparison to what one would expect to see if these supportive pain medications were not available.

In the STAR-trial, however, we did not register auxiliary pain medication during the STAR-trial properly, nor did we define a strategy to deal with (the effect of pain medication as an intercurrent event) as part of our statistical analysis plan (**chapter 6**)**.** This is a point of improvement for future trials with similar design (see below, under 'research implications').

TABLE 1 Factors affecting low inclusion

Factors by category	Subcategory	Causes	Solution
A. Research factors	Number of centres	Local initiative ('bottom up approach')	Nationwide trial Supraregional trial center ('top down approach')
	Funding	Grant Application failed twice	'Joint venture' Academic centers Local hospitals Other stakeholders (e.g. patients, insurance companies)
B. Patient factors	Patients' preference	The belief that the intervention (TESI) is superior to control (rather than 'equipoise')	Oral information by the recruiting physician Patients' contribution to science should be emphasized
	Health illiteracy	Low socio-economic status Poor education	'Reaching out' Intercultural care consultants Diverse research team
C. Physician factors	Motivation	'Multitasking' (lost focus)	Reward system Keep all clinicians monthly or quarterly informed about the trial progress
	Physician's preference	The belief that the intervention (TESI) is superior to control	Separation of the clinical consultation from randomization

2. Similar research

Spijker-Huiges et al investigated the effect of one epidural steroid injection containing 80mg of triamcinolone in normal saline versus control in 50 patients from primary care. For administering the steroids a lumbar translaminar approach without additional imaging was chosen. Their study was a two-armed RCT with a follow-up period of up to 1 year. The effectiveness and cost-effectiveness results were published separately[60,61]. The effectiveness results showed that the intervention group experienced significantly less symptoms than the control group for the RMDQ-score (p = 0,0173), the NRS back pain score (p = 0,0115) and the NRS score for self-perceived impairment (p = 0,0361) during follow-up. There was also a significant difference in mean patient satisfaction

between the two groups as the intervention group rated their treatment with a 9,0 on a 0 to 10 scale, while the control group rated their treatment with a 7,2 on a 0 to 10 scale (p = 0,006)[60]. In addition, the authors found a statistically significant, but not clinically relevant, difference in favour of the intervention ('steroids') group for the SF-36 questionnaire. The largest differences between group means were found in the domain of physical role limitations: −33.7 (95% CI, −54.8 to −12.7) and −29.1 (95% CI, −50.9 to −7.4) after a follow-up time of half a year and a year, respectively. Their cost-utility analysis showed that with a negligible loss of utility, societal costs could be saved because intervention group participants were more productive than their control group counterparts (i.e. on average €193,354 per quality-adjusted life year lost)[61]. These results are in line with the STAR-trial, i.e. a small significant effect in favour of the steroid injection, albeit not clinically relevant. Although apparently similar, there are several differences between the trial by *Spijker-Huiges et al* and the STAR-trial. That is, the trial by *Spijker-Huiges et al* was conducted in primary care, and not in secondary care, herniated discs were not confirmed by MRI, the injection method was different (translaminar approach instead of transforaminal) and their trial lacked a third study arm.

The currently conducted TEIAS-trial (transforaminal epidural injection versus continued conservative care in acute sciatica) is a prospective randomized controlled trial that compares TESI versus medication in patients with lumbosacral radicular syndrome up to 8 weeks[62]. The design is almost similar to that of the STAR-trial, except for the lack of a third study arm and an MRI confirmation of the herniated disc. The results of the TEIAS trial are still to be expected.

3. Clinical Implications

The STAR-trial was initiated by clinicians departing from the idea that early treatment with TESI would be beneficial to patients with acute lumbosacral radicular syndrome. However, the trial did not confirm that this such an early treatment with TESI was beneficial in terms of the primary outcomes. Based on these results, various recommendations for clinical practice can be made. First, the results of this RCT can be a starting point for reconsidering the rather positive idea that doctors have of TESIs (**see theme 1**). Although it is observed in clinical practice that some patients recover quickly after TESI, this is outweighed by the fact that they only have a small or even no effect in many other patients. Second, based on the STAR-trial, there is no need to change the current treatment protocols for both general practitioners[11] and clinicians working in the hospital setting[12]. This is because the trial showed no clinically relevant benefits of an early delivery of TESI. In

short, (according to the current protocols) patients with lumbosacral radicular syndrome are treated conservatively with pain medication and physiotherapy during the first 6 weeks post-onset. Patients will be referred for second-line treatment (TESI or surgery) only in case of persistent severe pain despite pain medication or if there are neurological deficits, for example weakness or bladder dysfunction (see also **Introduction** of the General Discussion). Third, there has been a discussion on the safety of TESIs, especially in the United States[62,63]. The lack of serious adverse events in the STAR-trial suggests that injections below the L2 spinal level (conus) can be considered as safe. Fourth, it was an interesting outcome that fewer patients who received a TESI used opioids than those receiving usual care. Though the registration of the pain medication used in this trial had its limitations, these data are promising for the future. Maybe TESIs are a good alternative to the potentially addictive opioids that have a lot of side effects (especially in the light of the 'opioid crisis'), but this warrants further exploration.

4. Research Implications

The fact that many clinicians have a positive opinion regarding TESIs is possibly based on their clinical experience rather than on scientific evidence (see **Theme 1**). Still, this may suggest there are specific patients with lumbosacral radicular syndrome who respond well to TESI. If we further elaborate on **Theme 2** of this General Discussion, it would be interesting to explore if patients with signs of inflammation (as shown by a panel of laboratory markers or radiological biomarkers such as Modic changes) are good responders to TESI, given the fact that it is an anti-inflammatory treatment. A first step could be a retrospective analysis of the MRI data of the STAR-trial for presence of Modic changes in relationship to clinical and surgical outcomes. In a future prospective trial, participants could be dichotomized between an 'inflammatory' and 'non-inflammatory' group based on radiological and biomarker characteristics; for each group different interventions (TESI and transforaminal injection with local anaesthetic and saline solution) could be compared in a way similar to the STAR-trial. It is interesting to see if the 'inflammatory' group does better on TESI in terms of pain, functional status and recovery, compared to the other (sub)groups). If such a new prospective trial ('STAR 2.0') is carried out, the factors responsible for the low inclusion rate and high number of drop-outs in the current trial need to be addressed. Specific issues on the level of the patient, the doctor and the research setting and how to possibly solve them are summarized in **Table 1** (page 213).

Besides searching for the best responders to TESI, it also worth investigating if patients with lumbosacral radicular syndrome treated with TESI use less severe pain killers (opioids) than patients that are not injected. This was found in our trial, but needs further elaboration, i.e. in a new trial the use of medication should be closely monitored (in terms of both quantities and frequencies) during the trial with a comparison between the control and intervention groups afterwards. Better monitoring of participants and their drug use asks for close supervision that can only be reached by investments in computer software and research assistants.

Conclusion

The major conclusion of this PhD-thesis is that although clinicians have a positive idea of TESIs in patients with an acute lumbosacral radicular syndrome, this could not be confirmed by the STAR-trial. Except for a statistically significant, albeit not clinically relevant, effect of TESI on leg pain for patients with acute lumbosacral radicular syndrome due to herniated disc compared to usual care, there were no statistically significant nor clinically relevant differences in all other co-primary outcomes. In addition the results of the trial suggest that adding TESI (or TEI) to usual care is not cost-effective compared with usual care. The clinical consequence of these findings is that the current treatment protocols of lumbosacral radicular syndrome for both GPs and clinicians working in the secondary care setting seems to be appropriate, and hence do not need to be revised.

A post-hoc analysis of the STAR-trial found both injection groups to be associated with less opioid use, which warrants further exploration. Also, in terms of further research, it might be interesting to investigate if patients with an underlying inflammatory substrate are possible responders to TESI.

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APPENDICES

ENGLISH SUMMARY

Background

Chapter 1 gives an introduction about the clinical aspects of lumbosacral radicular syndrome ('sciatica'), including its diagnosis and treatment, the motivation for this thesis, and the research questions to be answered. That is, lumbosacral radicular syndrome or sciatica is a common neurological problem characterized by pain radiating into the leg, following one of the lumbosacral nerve roots. The yearly incidence of sciatica in the Netherlands has been estimated at 9 per 1000 person years and the yearly prevalence at 36 per 1000 person years[1]. The most common underlying cause of the lumbosacral radicular syndrome is a herniated lumbar disc. There are several treatment options for the lumbosacral radicular syndrome, including medication, physiotherapy, transforaminal epidural steroid injections (TESIs) and disc surgery. This thesis, that was aimed to contribute to best clinical practice during the acute stage of the lumbosacral radicular syndrome, was subdivided into three themes, all of which will be further summarized below:

Theme 1: Diagnosis and treatment of acute lumbosacral radicular syndrome

In this theme, two research questions were answered:

> *What is the historical evolution of epidural corticosteroid injections from ancient times to present?*

Chapter 3 contains an historical overview. The first injections against back pain and sciatica were given around 1900 in Paris by Jean Sicard (1872-1929) and Fernand Cathelin (1873-1945), who worked independently. They both injected small volumes of cocaine into the sacral hiatus. After a slow start, the epidural treatment of back pain and lumbosacral radicular syndrome gradually spread to other parts of Europe and Northern America, including the Netherlands.

How do neurologists and anesthesiologists diagnose and treat patients with acute sciatica in daily practice?

In **Chapter 4** we described a survey among 80 neurologists (including residents) and 44 anesthesiologists. The results of this survey showed that 40% of neurologists think that TESIs are effective in 40-60% of injected patients and that 52% of anesthesiologists think that TESIs are effective in 60-80% of the injected patients. We also found that neurologists treat patients with lumbosacral radicular syndrome initially with pain medication and physiotherapy, followed by epidural steroid injections and referral for surgery. Anesthesiologists treat patients with lumbosacral radicular syndrome with one or more steroid injections or may perform a selective nerve root block. Imaging, selective nerve root blocks, medication, physiotherapy, and pulse radiofrequency are topics for further research (based on disconcordance with the current multidisciplinary guideline[2]).

Theme 2: Inflammation

This theme contained a systematic review that answers the following two questions:

What inflammatory biomarkers have been identified in patients with the lumbosacral radicular syndrome in the literature so far, and is there an association between the level of inflammatory activity and clinical symptoms?

Chapter 5 is a systematic review of the literature until December 19th 2018. We found 16 articles that fulfilled the criteria for inclusion and included a total of 1212 patients. The following markers were identified: interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IL-21, tumor necrosis factor-α (TNF-α), phospholipase A2, high sensitivity C-reactive protein (hsCRP), C-X-C motif chemokine 5 (CXCM5), CX3CL1, CCL2, epidermal growth factor (EGF), and monocyte chemotactic protein 4 (MCP-4). Several positive correlations were found in longitudinal studies: a strong positive correlation between inflammatory mediators or byproducts and pain (measured by a visual analogue scale, VAS) was found for IL-21

in two studies (r > 0,8), and moderate positive correlations for TNF-a in both serum (r = 0,629) and biopsy (r = 0.65); severe pain (VAS > 4) is associated with increased hsCRP levels among patients with sciatica (adjusted OR = 3.4 (95% CI, 1.1 to 10). Based on the results of the systematic review, we concluded that there was considerable heterogeneity in the type of biomarkers and in the clinical measurements in the included studies and that, taking into account the overall risk of bias, there is insufficient evidence to draw firm conclusions regarding the relationship between inflammation and clinical symptoms in patients with sciatica.

Theme 3 (Cost-)effectiveness of transforaminal epidural steroid injections in patients with acute lumbosacral radicular syndrome

This theme described the design (**chapter 5**), statistical analysis plan (**chapter 6**)**,** and results of the STAR-trial (**chapter 7 and 8**), which aimed to answer the following two research questions:

> *What is the effectiveness of transforaminal epidural steroid injections (TESIs) plus local anesthetic and oral pain medication versus oral pain medication alone in improving pain, physical functioning and recovery among patients with the lumbosacral radicular syndrome within eight weeks after onset in outpatient clinics?*

A total of 141 patients with acute lumbosacral radicular syndrome (due to a herniated disc) was included. Participants were randomly assigned to: 1) usual care and TESI of 1ml of 40mg/ml Methylprednisolone plus 1ml of 0.5% Levobupivacaine (intervention 1); 2) usual care and transforaminal epidural injection with 1 ml of 0.5% Levobupivacaine and 1ml NaCl 0.9% (intervention 2); or 3) usual care, consisting of oral pain medication with or without physiotherapy (control). Co-primary outcomes were back and leg pain intensity, physical functioning, and recovery measured during 6-month follow-up. Secondary outcomes included health-related quality of life, patient satisfaction, and surgery rate.

There were no significant mean differences in co-primary outcomes between groups during follow-up, except (a not clinically relevant difference) for leg pain when comparing intervention group 1 with control (-0.96 95%CI:-1.83 to -0.09). For secondary outcomes,

some significant between group differences were found for treatment satisfaction and surgery, but only when comparing intervention group 2 to control. There were no serious side effects. Based on these results, we do not recommend TESI as a standard treatment for patients with acute lumbosacral radicular syndrome. Nonetheless, TESIs seem to be associated with less opioid use, which warrants further exploration.

What is the cost-effectiveness of TESI plus local anesthetic and oral pain medication versus oral pain medication alone in improving pain, physical functioning and recovery among patients with the lumbosacral radicular syndrome within eight weeks after onset in outpatient clinics?

After 6 months, no significant differences in costs between the three treatment groups were found. The adjusted mean difference in total societal costs was €1718 (95%CI:-3020 to 6052) for comparison 1 (intervention-group 1 versus control group), €1640 (95%CI:-3354 to 6106) for comparison 2 (intervention group 1 versus intervention-group 2) and €770 (95%CI: -3758 to 5702) for comparison 3 (intervention group 2 versus control). The maximum probability of the interventions being cost-effective compared with control was low (<0.7) for all effect measures.

These results suggest that adding TESI (or TEI) to usual care is not cost-effective compared with usual care in patients with acute sciatica from a societal perspective in a Dutch healthcare setting.

Discussion

In **Chapter 9,** the main findings of this thesis are summarized, followed by a discussion of the strengths and weaknesses for each theme as well as the clinical and research implications of the current thesis.

The **overall conclusion** of this PhD-thesis is that although clinicians have a positive view of TESIs in patients with an acute lumbosacral radicular syndrome, this could not be confirmed by the STAR-trial. Except for a statistically significant, albeit not clinically relevant, effect of TESI (1 ml of 0.5% Levobupivacaine followed by 1 ml of 40 mg/ml Methylprednisolone) on leg pain, there were no statistically significant, nor clinically

relevant differences in co-primary outcomes, nor was it cost-effective. The clinical consequence of this finding is that the current treatment protocols of lumbosacral radicular syndrome for both GPs and clinicians working in the secondary care setting seem appropriate, and hence do not need to be revised. It is noteworthy, however, that a post-hoc analysis of the STAR-trial found both injection groups to be associated with less opioid use, which warrants further exploration (a prospective trial with better registration of pain medication use). It might also be interesting to investigate if patients with an underlying inflammatory substrate (based on laboratory or radiological biomarkers) are possible responders to TESI.

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2. https://richtlijnendatabase.nl/richtlijn/lumbosacraal_radiculair_syndroom_lrs/startpagina_-_lrs.html

NEDERLANDSE SAMENVATTING

De van oorsprong Vlaamse Simon Stevin (1548-1620) was een man met vele kwaliteiten. Een paar voorbeelden: hij introduceerde het decimale stelsel voor breuken en gaf de vestingbouw een wiskundige grondslag; hij leverde vele bijdragen aan de wis- en natuurkunde, termen die hij zelf bedacht heeft. Los van deze inhoudelijke bijdragen is misschien wel zijn belangrijkste nalatenschap die van de taal van de wetenschappen in Nederland. Simon Stevin publiceerde zijn geschriften voor het eerst in het Nederlands en niet langer in het Latijn, wat tot dan toe op universiteiten als die van Leiden (gesticht in 1575) gebruikelijk was. Op die manier kon Stevin zijn lezerspubliek beter bereiken. Bovendien was het gebruik van het Nederlands ook de trotse uiting van onafhankelijkheid van de Spanjaarden ten tijde van de Tachtigjarige Oorlog (1568-1648). Tegenwoordig zien we een omgekeerde ontwikkeling en wordt het Nederlands als taal van de wetenschap steeds meer vervangen door het Engels als mondiale wetenschapstaal, oftewel het 'latijn van nu'. Ook dit proefschrift ontsnapt niet aan deze ontwikkeling en is in het Engels geschreven. Bij wijze van concessie (en eerbetoon aan Stevin) bevat het echter een Nederlandse samenvatting, met als belangrijkste drijfveer 'voeling houden met je lezerspubliek':

Het lumbosacraal radiculair syndroom was vroeger ook wel bekend als 'ischias' en wordt gekenmerkt door uitstralende pijn in het been in het beloop van een aangedane zenuwwortel. De jaarlijkse incidentie van het lumbosacraal radiculair syndroom wordt in Nederland geschat op 9 per 1000 persoonsjaren en de prevalentie wordt geschat op 36 per 1000 persoonsjaren[1]. De meest gebruikelijke oorzaak van het lumbosacraal radiculair syndroom is een uitpuilende tussenwervelschijf ('hernia nuclei pulposi' of HNP). Er zijn een aantal behandel opties voor het lumbosacraal radiculair syndroom, waaronder pijnmedicatie, fysiotherapie, (transforaminale) epidurale corticosteroïd injectie of een operatie van de tussenwervelschijf ('discotomie'). Dit proefschrift, welke tot doel heeft bij te dragen aan 'best clinical practice' van het lumbosacraal radiculair syndroom, is opgedeeld in drie thema's. Hieronder zullen alle drie de thema's worden samengevat.

Thema 1 Diagnostiek en behandeling van het acuut lumbosacraal radiculair syndroom

In dit thema worden de volgende twee onderzoeksvragen beantwoord:

Wat is de historische ontwikkeling van epidurale corticosteroïd injecties van vroeger tot nu?

De Utrechtse oud-hoogleraar neurologie Jan van Gijn schreef ooit: *'Wie het verleden vergeet, is het gedoemd het te herhalen'*[2]. Deze prikkelende zin, onderdeel van een historische beschouwing over het lumbosacraal radiculair syndroom was reden om in **hoofdstuk 2** nader in te gaan op de historische context van epidurale corticosteroïd injecties tegen rugpijn met uitstraling. De eerste injecties werden in 1900 gezet door de Parijse artsen Jean Sicard (1872-1929) en Fernand Cathelin (1873-1945), die onafhankelijk van elkaar werkten en beiden claimden de eerste te zijn (rivaliteit!). Deze pioniers injecteerden een kleine hoeveelheid cocaïne in het heilig been (sacrale hiatus) met goed effect op de pijn wat circa twee weken aanhield. In de daarop volgende decennia breidde het gebruik van epidurale corticosteroïd injecties tegen het lumbosacraal radiculair syndroom zich langzaam uit naar andere landen, waaronder Nederland. Tegenwoordig zijn epidurale corticosteroidsteroid injecties een alledaagse behandeling, die veilig geacht wordt.

Hoe diagnosticeren neurologen en anesthesiologen patiënten met een lumbosacraal radiculair syndroom?

Deze vraag wordt beantwoord in **hoofdstuk 3** dat een enquête of 'survey' bevat onder 80 neurologen (deels in opleiding) en 44 anesthesiologen. Deze werden benaderd via e-mail en kregen vervolgens een online vragenlijst toegestuurd, welke bestond uit zowel algemene vragen over diagnostiek en behandeling van lage rughernia 's als casuïstiek.

De resultaten van deze enquête lieten zien dat 40% van de neurologen van mening is dat (transforaminale) epidurale steroïd injecties (TESIs) effectief zijn bij 40-60% van de geïnjecteerde patiënten en dat 52% van de anesthesiologen denkt dat TESIs effectief zijn bij 60-80% van de geïnjecteerde patiënten. Tevens bleek dat de meesten zich goed aan de nationale richtlijn 'lumbosacraal radiculair syndroom' houden[3]. Dit houdt in dat patiënten initieel met pijnmedicatie en fysiotherapie behandeld worden. Mocht die aanpak niet effectief zijn, dan volgt een verwijzing naar de tweede lijn (ziekenhuis) voor een eventuele TESI of herniachirurgie.

Uit de enquête kwamen tevens een aantal kennishiaten naar voren namelijk: het voorschrijven van pijnmedicatie bij het lumbosacraal radiculair syndroom, het gebruik van fysiotherapie en het toepassen van zogenaamde 'diagnostische blokkades'. Het laatste type injectie moet onderscheiden worden van TESI, omdat deze injecties erop gericht zijn een zenuwwortel kortdurend te verdoven om op die manier na te gaan of deze zenuwwortel aan de klachten van de patiënt te relateren is. Deze kennishiaten zijn interessante onderwerpen voor toekomstig wetenschappelijk onderzoek.

Thema 2 Inflammatie

Dit thema bevat een systematische review waarin twee onderzoeksvragen beantwoord worden:

> *Welke inflammatoire biomarkers zijn er tot nu toe geïdentificeerd bij patiënten met het lumbosacraal radiculair syndroom en welke correlaties zijn er in longitudinale studies gevonden tussen de aanwezigheid van biomarkers en klinische symptomen?*

De bovenstaande vragen zijn in **hoofdstuk 4** beantwoord middels een literatuurstudie (systematic review) van alle artikelen op het gebied van ontstekingseiwitten bij patiënten met een lumbosacraal radiculair syndroom (tot oktober 2018). De achterliggende gedachte om deze studie uit te voeren is dat TESIs een ontstekingsremmende, anti-inflammatoire werking hebben. Dit veronderstelt dat er bij patiënten met lumbosacraal radiculair syndroom sprake is van ontsteking.

Er werden in totaal 16 relevante artikelen gevonden, waarin in totaal 1212 patiënten beschreven zijn. In deze studies werden de volgende biomarkers gevonden: interleukine (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IL-21, tumor necrosis factor-α (TNF-α), phospholipase A2, high sensitivity C-reactive protein (hsCRP), C-X-C motive chemokine 5 (CXCM5), CX3CL1, CCL2, epidermal growth factor (EGF), en monocyte chemotactic protein 4 (MCP-4).

Er werd een sterke positieve correlatie (r>0.8) gevonden tussen de aanwezigheid van IL-21 en pijn en een matig positieve correlatie tussen TNF-α en pijn, zowel in serum (r= 0.629) als in biopten uit de aangedane tussenwervelschijf (r= 0.65). Hevige pijn was geassocieerd met verhoogde hsCRP spiegels in patiënten met een lumbosacraal radiculair syndroom. De conclusie van dit hoofdstuk was dat er behoorlijke heterogeniteit was, zowel in biomarkers als klinische uitkomstmaten, en dat het onmogelijk was sterke conclusies te trekken over de relatie tussen de aanwezigheid van een eventuele ontsteking en klinische uitkomstmaten zoals pijn en functioneren bij patiënten met een lumbosacraal radiculair syndroom.

Thema 3 (Kosten)effectiviteit van transforaminale epidurale steroïd injecties bij patiënten met een acuut lumbosacraal radiculair syndroom

Dit thema gaat over de STAR-trial. De volgende twee onderzoeksvragen komen aan bod:

Wat is de effectiviteit van transforaminale epidurale steroïd injecties bij patiënten met een kort bestaand lumbosacraal radiculair syndroom (< 8weken) als gevolg van een rughernia?

Deze vraag wordt beantwoord in **hoofdstuk 7** aan de hand van een gerandomiseerde, gecontroleerde trial (RCT), de STAR-trial. Het design en het statistisch analyse plan van deze studie zijn beschreven in respectievelijk **hoofdstuk 5** en **hoofdstuk 6**.

De STAR-trial liep tussen 13 januari 2016 en 20 maart 2020 in twee Nederlandse ziekenhuizen, het Zaans Medisch Centrum in Zaanstad en het OLVG in Amsterdam. Uiteindelijk werden 141 patiënten geïncludeerd met een acuut lumbosacraal radiculair syndroom veroorzaakt door een rughernia zoals vastgesteld middels een MRI-scan. De

deelnemers werden willekeurig verdeeld (‘gerandomiseerd’) over drie behandelgroepen: 1) interventiegroep 1 bestaande uit deelnemers die naast de gebruikelijke behandeling of ‘usual care’ een transforaminale epidurale steroïd injectie (TESI) kreeg die naast steroïden (1 ml van 40mg/ml Methylprednisolon) ook 1ml 0.5% Levobupivacaine bevatte, een lokaal anestheticum; 2) interventiegroep 2 bestaande uit deelnemers die naast ‘usual care’ een transforaminale epidurale injectie (TEI) kregen die 1 ml 0.5% Levobupivacaine bevatte naast 1ml NaCl 0.9%; 3) de controlegroep die ‘usual care’ van de huisarts kreeg, namelijk pijnmedicatie en fysiotherapie.

Gedurende 6 maanden werden de uitkomsten gemeten op verschillende schalen die de deelnemers zelf invulden binnen een online-portal. Dat deden ze bij aanvang van de studie (‘baseline’), en na 3 en 6 weken en na 3 en 6 maanden. De primaire uitkomstmaten waren: rug- en beenpijn (gemeten op een 10 punten visueel analoge schaal (VAS)), functioneren (gemeten op een 24 punten Roland-Morris Disability Scale) en herstel (gemeten op 7 punten Global Perceived Recovery). De secundaire uitkomstmaten waren kwaliteit van leven (gemeten op de EQ-5D-3L) en tevredenheid (gemeten op een 7 punten Likertschaal). Ook werd gekeken naar het gebruik van pijnstillers en het aantal operaties.

De klinische effecten in termen van de primaire uitkomsten waren vergelijkbaar in de drie studiegroepen; er werd enkel een statistisch significant verschil wat betreft beenpijn bij de vergelijking van interventie groep 1 met de controle groep (-0.96 95%CI:-1.83 tot -0.09) gevonden, maar dit verschil was niet klinisch relevant. Dit laatste houdt in dat de deelnemers aan de studie het voordeel van TESI nauwelijks bemerkt zullen hebben. Een ‘post hoc’ analyse liet daarnaast zien dat de deelnemers uit beide interventiegroepen significant minder vaak opioïden gebruikt dan de deelnemers uit de controle groep. Daarnaast zijn er geen ernstige bijwerkingen gerapporteerd in beide interventiegroepen. Op basis van deze studieresultaten wordt TESI niet als een standaard behandeling aanbevolen bij patiënten met een acuut lumbosacraal radiculair syndroom. Het feit dat de geïnjecteerde patiënten gemiddeld minder opioïden gebruiken is echter wel interessant voor de alledaagse praktijk (dit in het licht van de ‘opioïden-crisis’) en vraagt om vervolgonderzoek.

Wat is de kosteneffectiviteit van transforaminale epidurale steroïd injecties ten opzichte van gebruikelijke zorg bij patiënten met een kort bestaand lumbosacraal radiculair syndroom (< 8weken) als gevolg van een rughernia?

Deze vraag werd beantwoord in **hoofdstuk 8**. Na 6 maanden waren er geen significante verschillen in kosten tussen de drie behandelgroepen. De 'adjusted mean difference' voor maatschappelijke kosten was €1718 (95%CI:-3020 tot 6052) voor vergelijking 1 (interventie-groep 1 versus controle groep), €1640 (95%CI:-3354 tot 6106) voor vergelijking 2 (interventie groep 1 versus interventie-groep 2) en €770 (95%CI: -3758 tot 5702) voor vergelijking 3 (interventie groep 2 versus controle groep). De maximale waarschijnlijkheid dat de interventies kosteneffectief waren ten opzichte van de controle groep was laag (<0.7) voor alle effectmaten.

Deze resultaten suggereren dat het toevoegen van een TESI (of TEI met lokaal anestheticum) aan de gebruikelijke zorg niet kosteneffectief is bij patiënten met een acuut lumbosacraal radiculair syndroom binnen de Nederlandse gezondheidszorg.

Discussie

In **Hoofdstuk 9** zijn de belangrijkste bevindingen van de (deel)onderzoeken besproken, gevolgd door een sterkte/zwakte analyse per thema. Ook zijn in dit hoofdstuk de klinische en wetenschappelijke relevantie van het huidige onderzoek besproken.

Tot slot zijn er een aantal **algemene conclusies** te verbinden aan dit ruim 11 jaar durende onderzoeksproject. De STAR-trial is ooit bedacht vanuit het positieve beeld dat veel artsen hebben ten aanzien van de effectiviteit van TESI. Dit kwam ook naar voren in de survey. Dit positieve beeld moet echter bijgesteld worden op basis van de STAR-trial waarin geen klinisch relevant voordeel van TESI (1 ml 0.5% Levobupivacaine en 1 ml 40 mg/ml Methylprednisolon) ten opzichte van de gebruikelijke zorg ('usual care') naar voren kwam in de acute fase van het lumbosacraal radiculair syndroom veroorzaakt door een rughernia. Dat geldt ook voor de kosteneffectiviteit van TESI.

De klinische relevantie van de STAR-trial is dat de huidige behandelprotocollen met betrekking tot het lumbosacraal radiculair syndroom niet hoeven worden aangepast.

Het is wel belangrijk te melden dat een post-hoc analyse van de trial een afname in het gebruik van opioïden liet zien in de groepen die geïnjecteerd werden (interventie groepen). Dit vraagt om meer prospectief onderzoek naar het lumbosacraal radiculair syndroom met een betere registratie van pijnmedicatiegebruik. Ook is het interessant om te onderzoeken of patiënten met een acuut lumbosacraal radiculair syndroom en een onderliggend ontstekingsinfiltraat (zoals vastgesteld kan worden door laboratorium of MRI-onderzoek) beter reageren op behandeling met TESI in vergelijking met patiënten zonder ontstekingsinfiltraat.

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Het realiseren van dit proefschrift was niet mogelijk zonder een aantal 'reuzen'* die ik op deze pagina's graag wil bedanken. In de rangorde van het bedanken staan de hoogleraren die het traject begeleid hebben vaak bovenaan. Dat is 'best gek eigenlijk'. Immers, je thuis is de basis, waar alles iedere dag begint en eindigt. En daarom begin ik hier met mijn thuisfront te bedanken.

Lieve Asmaé, mijn eerste en grootste dank gaat uit naar jou. Je hebt me kort na ons trouwen in 2012 gestimuleerd om de weg van de wetenschap in te slaan, naast mijn baan als neuroloog in OLVG (het voregere SLAZ) en ZaansMC. Het begrip 'neuroloog' moet overigens breed opgevat worden: naast het dokteren, waren er nog zoveel meer taken te volbrengen, zoals de Commissie Ethiek, de COVID-palliatieve unit (OLVG Oost) en verschillende initiatieven op vlak van 'diversiteit en inclusie'.

Promoveren bleek een lange en steile weg waar veel *sabr* voor nodig was. Lees: eindeloze bureaucratische procedures om de STAR-trial in de lucht te krijgen, het missen van subsidies, het almaar niet vullen van de trial wat op voorhand 'appeltje-eitje' leek en meermaals afgewezen artikelen. Feit is dat ik zonder jouw nimmer aflatende liefde en steun de finish van dit proefschrift zeker niet gehaald had.

Een concreet voorbeeld van die onvoorwaardelijke liefde en steun, is het op en neer rijden naar bakker De Groot in Den Bosch om als verrassing verse chocoladebollen voor de vakgroep op beide lokaties te halen. Dit ter ere van mijn 10-jarig neuroloog zijn.

Ook inhoudelijk ben ik je dankbaar voor de vele gesprekken die wij regelmatig hebben over 'diversiteit en inclusie' binnen de gezondheidszorg (niet zelden in de weekenden en tot in de kleine uurtjes). Dit heeft ook betrekking op wetenschappelijk onderzoek: worden alle patiënten uit de spreekkamer wel voldoende gerepresenteerd in trials? Hier is duidelijk nog een slag te maken. Het feit dat één van de uitgevers onlangs vroeg een *diversity statement* op te nemen in een wetenschappelijk artikel is een eerste, kleine stap. Ik heb in ieder geval in de General Discussion van dit proefschrift willen pleiten voor de aanstelling van een interculturele zorgconsulent om *alle* patiënten bij wetenschappelijk

* Isaac Newton: 'If I have seen a little further it's because I stand on the shoulders of giants'

onderzoek te betrekken. Dit als onderdeel van jouw *legacy* binnen het OLVG, waar je kort voor mij in 2009 startte.

Uiteraard is er nog veel meer om je voor te bedanken buiten dit proefschrift om. Als iemand *kintsugi* verstaat, de Japanse kunst om scherven te lijmen met goudverf, dan ben jij het. Volgens *kintsugi* worden de voorwerpen die gelijmd worden mooier dan ze voorheen waren. Uit die nieuwe heelheid ontstaat iets wat zeer waardevol is en het leven voller en rijker maakt.

Nu is het de plaats om academici en collega's te bedanken

Prof. dr. Ostelo. **Beste Raymond,** ons eerste contact dateert uit 2013. Ik kwam naar Maurits van Tulder en jou in het W&N gebouw om te sparren over wetenschappelijk onderzoek naar wortelblokkades. Het idee achter de samenwerking tussen het 'Lucas' en de Vrije Universiteit was een win-winsituatie: in de ziekenhuizen worden veel patiënten (lees: potentiële onderzoekskandidaten) gezien en de universiteit bezit de methodologische kennis en expertise om wetenschappelijk onderzoek op te zetten. Van die kennis en expertise heb ik de afgelopen jaren ruimschoots gebruik mogen maken. Naast deze praktische steun wil ik je vooral bedanken voor je morele steun, namelijk de aanmoediging om vooral door te zetten, niet *tot aan* maar *tot in* de aula van de Boelelaan. Ik heb je leren kennen als een scherp analyticus met een enorm oog voor detail. Dat laatste blijkt bijvoorbeeld uit het compleet uitgeprinte proefschrift op A4-formaat dat ik kort voor de eindstreep van je ontving en waarin je met rode pen pagina-voor-pagina geannoteerd had. *Het oog van de meester maak het paard vet*.

Prof. dr. Weinstein. **Beste Henry**, onze eerste gesprekken over wetenschappelijk onderzoek gaan terug tot de zomer van 2009 toen we samen met **Theo van Woerkom**, één van mijn voormalige opleiders uit het Hagaziekenhuis, afspraken bij *Vis aan de Schelde*. Ons idee was om onderzoek naar somatisch onverklaarde klachten (SOLK) te gaan doen. Dat was toen in de mode - ik verwijs o.a. naar de onderzoeken van **Jon Stone** uit Edinburgh en **Rien Vermeulen** in het AMC- echter bleek het een lastig te operationaliseren onderzoek. Immers, hoe includeer je patiënten in een trial als er geen duidelijke definitie voor hun ziektebeeld is? En wat zijn je uitkomstmaten?

Het idee werd dan ook verlaten en vervolgens werd gekozen om onderzoek naar wortelblokkades bij het acuut lumbosacraal radiculair syndroom te doen. Wortelblokkades

worden in veel ziekenhuizen veelvuldig toegepast, zonder een goede wetenschappelijke basis. Vooral de acute fase van het ziektebeeld bleek nog nauwelijks bestudeerd en daar lag een gouden kans voor wetenschappelijk onderzoek. Inmiddels zijn we ruim 10 jaar verder, heb jij je pensionering bereikt, en hebben we de trial opgeschreven als hoofdonderwerp van dit proefschrift.

Ik wil je bedanken dat je jarenlang '*mijn zaag scherp hield*' en me liet focussen op het eindresultaat, namelijk promoveren. Naast dat je mijn promotie begeleid hebt, waren we natuurlijk ook een goed team als opleider en plaatsvervangend opleider. Ik wens je nog vele vitale jaren toe na verlaten van het vertrouwde OLVG.

Dr. Van Dongen. **Beste Hanneke**, graag wil ik je als copromotor en 'rechterhand' van Raymond bedanken voor het feit dat je altijd zo laagdrempelig beschikbaar was bij vragen, me enorm geholpen hebt bij alle lastige analyses in SPSS en kritisch naar alle stukken gekeken hebt.

Dr. Maas. **Beste Esther**, jou wil ik graag als 'tweede rechterhand' van Raymond bedanken voor je steun bij uitwerken van de kosten-effectiviteitsanalyse (KEA) van de STAR-trial (hoofdstuk 8), je kritische blik en aanvullingen op hoofdstuk 1, en hulp bij het opmaken van het definitieve manuscript. Jouw eigen promotieonderzoek, de MINT-trial, was bovendien een belangrijke inspiratie voor me.

Drs. Van der Vegt. **Beste Rien**, helaas werken we beiden niet meer in hetzelfde ziekenhuis. Ik mis onze *Varadero's* en de talloze tips die je me gaf over motoren. De STAR-trial werd destijds uitgebroed op de pijnpoli van het Zaans MC. Samen met wijlen **Emiel Spoelder**, anesthesioloog, sta jij aan de basis van dit onderzoek. Ik wil je bedanken voor je hulp bij het includeren van patiënten in de trial en het verrichten van talloze wortelblokkades in trialverband. Ook dank ik je voor je aanvullingen op vrijwel alle gepubliceerde artikelen binnen deze onderzoekslijn. Bovendien is het een eer dat je mijn **paranimf** wil zijn bij de verdediging van dit proefschrift.

Dr. Haumann. **Beste Johan**, je was jarenlang mijn aanspreekpunt voor de STAR-trial binnen de vakgroep anesthesiologie van het OLVG. Ik wil je bedanken voor het mede mogelijk maken van de trial, de vele wortelblokkades die je verricht hebt en je aanvullingen op de artikelen die we samen geschreven hebben. Je was altijd de eerste om een felicitatie-mailtje te sturen als na lang zwoegen een artikel geaccepteerd was.

Mw. Waal en hr. Smits. **Beste Monique en Menno.** Jullie wil ik als trialverpleegkundigen bedanken voor het helpen verzamelen van alle onderzoeksdata en het nabellen van vele studiedeelnemers met de vraag of zij hun online vragenlijsten toch echt wilden invullen.

De afgelopen jaren meldden zich een aantal medisch studenten voor een onderzoeksstage in het OLVG en waren zo ook betrokken bij de STAR-trial. Ik wil in het bijzonder **Caroliene Overwegh, Maarten Jüngen** en **Amrita Vyas** bedanken. Mede dankzij hun hulp zijn respectievelijk de hoofdstukken 3, 4 en 5 van dit proefschrift tot stand gekomen.

Ik bedank de leden van de beoordelingscommissie **dr. Sidney Rubinstein, prof. dr. Judith Bosmans, prof. dr. Bart Koes, prof. dr. Geert Jan Groeneveld**, **prof. dr. Frank Huygen** en **dr. Dolf Boerman** voor de tijd en energie die jullie gestoken hebben in het lezen en beoordelen van het proefschrift. Ik kijk al uit naar de publieke verdediging.

Ik bedank de neurologen en arts-assistenten van het OLVG en Zaans MC voor hun morele steun bij dit onderzoeksproject en in praktische zin voor hun hulp bij het includeren van de studiekandidaten. Als *primus inter pares* wil ik mijn kamergenoot **Ernest Wouda** noemen, die altijd bereid was om mee te denken over 'ruggen' en die bovendien veel kennis heeft kunnen overdragen aan een nieuwe generatie neurologen, mijzelf incluis. Ik noem hier begrippen als *Kennmuskeln* en *Trendelenburg gang* die hiermee aan de vergetelheid onttrokken zijn. Beste Ernest, ook voor jou geldt dat het een eer is dat je mijn **paranimf** wil zijn bij de publieke verdediging van dit proefschrift.

Ik bedank de leden van de vakgroepen anesthesiologie van het OLVG en Zaans MC voor hun jarenlange steun en het 'prikken' van talloze patiënten met een lumbosacraal radiculair syndroom, ook buiten studieverband om.

Ik bedank de leden van de werkgroep pijn van de Nederlandse Vereniging voor Neurologie die zich sterk maken voor 'pijn' als aandachtsgebied binnen de neurologie. Daar vallen ook radiculaire syndromen onder. Het blijft 'best gek eigenlijk' (zie ook alinea 1) dat misschien wel het meest voorkomende symptoom binnen de neurologie nauwelijks de aandacht krijgt die het onzes inziens ('wij van de pijn') verdient op basis van volume en impact.

Daarnaast wil ik het bestuur van patiëntenvereniging NVVR De Wervelkolom bedanken, in het bijzonder de heer **Leen Voogt**. Trials kunnen niet alleen zonder patiënten als

'participanten in onderzoek', maar ook om mee te denken over de opzet van een wetenschappelijke studie en bij uitwerken van subsidieaanvragen. Ik heb de NVVR de afgelopen jaren als een goede, constructieve sparring partner ervaren.

Verder wil ik een aantal collega's bedanken voor hun bijdragen aan publicaties als onderdeel van dit proefschrift, of simpelweg omdat ze de trial een warm hart toedroegen en er vaak naar informeerden: **Maurits van Tulder, Michiel de Boer, Jan Willem Kallewaard, Michel Terheggen, Koo de Priester** en **Henk Koning.**

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LIST OF PUBLICATIONS

1. Publications of this thesis

1. Ter Meulen BC, Van Dongen JM, Maas E, Van der Vegt MH, Haumann J, Weinstein HC, Ostelo R. Effect of Transforaminal Epidural Corticosteroid Injections in Acute Sciatica A Randomized Controlled Trial. Clin J Pain. 2023 Dec 1;39(12):654-662
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2. Accepted for publication included in this thesis

7. Ter Meulen BC, Maas E, Van der Vegt M, Haumann J, Weinstein HC, Ostelo R, Van Dongen J. Cost-Effectiveness of Transforaminal Epidural Steroid Injections for Patients with Sciatica: a randomized controlled trial. BMC, *accepted.*

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8. Ter Meulen BC, van Dongen JM, Maas E, van der Vegt MH, Haumann J, Weinstein HC, Ostelo R. Author's Reply to the Letter of Van Boxem, Van Gaag, Van Zundert and Kallewaard, Entitled 'Response to Ter Meulen et al. Effect of Transforaminal Epidural Corticosteroid Injections in Acute Sciatica'. Clin J Pain. 2023 Dec 21.
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4. Other publications

4.1 articles

12. Klein Heerenbrink S, Coenen P, Coppieters MW, Van Dongen JM, Vleggeert-Lankamp C, Rooker S, Ter Meulen BC, Bosboom JLW, Bouma GJ, Lutke Schipholt IJ, Sleijser-Koehorst MLS, de Vries R, Ostelo RWJ, Scholten-Peeters GGM. Cost-)effectiveness of personalised multimodal physiotherapy compared to surgery in patients with cervical radiculopathy: a systematic review. Journal of Evaluation in Clinical Practice. *Submitted*.
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4.2 Chapters in books

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4.3 Book

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ABOUT THE AUTHOR

Bastiaan ('Bas') Coen ter Meulen was born on the 15th of June 1976 in Berkel-Enschot, the Netherlands. It was a sunny Tuesday afternoon. In 1994 he graduated from secondary school at the Sint-Odulphuslyceum in Tilburg (gymnasium-beta). Between 1994-2002 Bastiaan studied medicine at the Katholieke Universiteit Leuven, Radboud Universiteit Nijmegen, Northwestern University Chicago and Mount Sinai School of Medicine in New York City.

After finishing his studies he started his residency in Neurology at the Erasmus Medical Center in Rotterdam (under supervision of prof. dr. P. Sillevis Smitt). The latter part of the residency program was completed in the Haga Teaching Hospital in The Hague (under supervision of dr. S. de Bruijn).

Since 2009 Bastiaan works as a neurologist in the OLVG Teaching Hospital in Amsterdam (OLVG). Between 2009-2020 he also worked as a neurologist in the Zaans Medical Center in Zaandam (ZMC). Over the past years he subspecialized into the diagnosis and treatment of headache and chronic pain ('*the most frequent but least addressed symptom in neurology*'). Out of this interest he is a member of the 'Workgroup on Pain' of the Dutch Neurological Society and member of the advisory board of the patient organization for people with back pain ('De Wervelkolom'). He was co-author of the national multidisciplinary guideline on the lumbosacral radicular syndrome in 2020.

Besides working as a clinician there were several other roles to fulfill over the past years, such as teaching and management. In 2020, amidst the pandemic, Bastiaan worked at the COVID palliative ward of the OLVG. As vice-chairman of the Neurology Residency program he worked on a more inclusive residency program. There are two other important interests worth mentioning here: medical ethics and research.

Out of his interest in ethics Bastiaan has been active as a facilitator of moral case deliberation and co-authored the 'Leerboek Medische Ethiek' in 2020 together with his uncle prof. dr. R. ter Meulen. He was member and chairman (2017-2019) of the Ethics Committee in both the OLVG and ZMC. He is a member of the Dutch network for ethics support (NEON) and the Leyden Islam Academy (medical ethics). He has often lectured on 'Islam and organ donation' and 'Islam and palliative care'.

The research underlying this thesis was started in 2012/2013 under supervision of prof. dr. R. Ostelo and prof. dr. H. Weinstein and has been a collaboration between the Departments of Neurology and Anesthesiology of the OLVG and ZMC, and research departments of the Vrije Universiteit, Amsterdam. Over the years, the research leading up to this thesis has been a long and winding road, but finally we made it: '*hora est*'.

Bastiaan lives in Gooise Meren together with Asmaé, Koko, Billy and Sophie.