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Transforminal Epidural Injection in Acute Sciatica

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Transforaminal Epidural Injection in Acute Sciatica (TEIAS)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
DSMB	Data Safety Monitoring Board
GP	General Practitioner
GRP	Good Research Practice
IC	Informed Consent
METC	Medical Research Ethics Committee (MREC); in Dutch: Medisch-Ethische Toetsing Commissie (METC)
LRS	Lumbosacral radicular syndrome
LUMC	Leiden University Medical Center
NRS	Numerical Rating Scale
(S)AE	(Serious) Adverse Event
Sciatica	Condition of radicular pain in the leg
SIPS	Spine Intervention Prognostic Study Group
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
TEI	Transforaminal Epidural Injection
TEIAS	Transforaminal Epidural Injection in Acute Sciatica
VAS	Visual Analogue Scale
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: To study (cost) effectiveness of the transforaminal epidural injection with analgesic and anti-inflammatory medication (TEI) in order to relieve the symptoms and to evaluate the intervention as a predictor tool for symptoms of sciatica in the long term.

Objective: To evaluate the percentage of patients that experience satisfactory (long term) decrease in leg pain in the TEI group in comparison to the conservative care group.

Study design: Randomised controlled trial

Study population: Patients that suffer 3-8 weeks from sciatica (Numeric Rating Scale ≥ 6 , on a 10 point scale)

Intervention: transforaminal epidural injection with analgesic and anti-inflammatory medication

Main study parameters/endpoints: the percentage of patients that experience satisfactory decrease (NRS lower than 4) in leg pain after 2, 10 and 21 weeks after randomization in both treatment arms

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: the participants fill in questionnaires at baseline, at 1, 2, 4, 10 and 21 weeks after randomization. Participants will also fill in cost-diaries during this period. TEI as an intervention tool is considered usual care for sciatica patients, though the timing of the injection is not clearly defined. The extent of risk from TEI is comparable to usual care.

1. INTRODUCTION AND RATIONALE

Sciatica is a condition of radicular pain in the leg and is usually caused by herniation of a lumbar intervertebral disc. The herniated disc compresses a lumbar nerve root that continues its route into the sciatic nerve. About 13% to 40% of all people will suffer from sciatica at least once during their lifetime [1]. Sciatica can have severe socio-economic effects; patients are immobilised by the pain they experience and therefore cannot go to work or participate in social events.

Most cases resolve spontaneously with conservative therapy using only standard analgesics and/or physiotherapy. In a large RCT it was demonstrated that outcome of conservative and surgical therapy was comparable after 26 weeks [2]. 40% of patients randomized to the conservative care group crossed over and was treated surgically, with a mean delay of 15 weeks. With this knowledge the guidelines for surgical treatment of sciatica were adjusted and it is nowadays usual care to offer surgery only after at least 8 weeks of conservative care and preferably after 14-16 weeks of conservative care. This decision is made together with the patient in a process of Shared Decision making [3,4].

Although this treatment regimen has been demonstrated to be efficacious and cost effective, the burden for a patient during these weeks of conservative care is usually high. We seek to find a type of conservative care to reduce the discomfort due to the pain and to enable the patient to remain physically active. Not only will this add to the quality of life of the patient, but it will also prevent the patient from taking a sick-leave.

Rationale for this study

We would like to explore the effectivity of the transforaminal epidural injection (TEI) with analgesic and anti-inflammatory medication to relieve the symptoms. Theoretically, such an injection would have a painkilling effect within the first two weeks after injection, and this effect may last for months, but we know that some patients do not experience this beneficial effect [5]. Some patients report initial pain reduction but report a re-arousal of pain after several hours, days or weeks [6].

There has been extensive research on TEI, but these studies generally include patients with chronic sciatica or a mixed population of patients with acute and chronic symptoms. We performed a systematic review on TEI specifically in the acute phase and it occurred that we could find only one article on the efficacy of epidural injections administered to patients with acute sciatica (<8 weeks of symptoms) [6]. This study, conducted by Spijker et al., randomized 63 patients with a duration of symptoms of at least 2 weeks and a maximum of 4 weeks. Patients were divided over an intervention group (receiving TEI with triamcinolone) and a control group (usual care with non-iv medication). It was demonstrated that

functionality and pain relief in the back were more beneficial in the group that received an injection, but that differences were (too) small. However, the analysis of the effect was averaged over all patients in the treatment group. It is known that there is a group of non-responders after TEI, averaging 33% of patients [5]. If the outcome values of all patients are averaged, no effect will be retrieved, while there could be a clear effect for the responders. In the study of Joswig [5] recruiting 63 patients with radicular pain in the leg, 66% of patients responded well to TEI within hours after the injection and in the first 14 days after injection the VAS leg pain remained around 30 mm on a 100 mm scale. In the non-responders the VAS pain was on average 55 mm and persisted on that level for at least 14 days.

Not only was in Spijker's study no distinction made between responders and non-responders, the injection was lacking a painkilling component, like xylocaine. Moreover, the baseline values for VAS leg pain, VAS back pain and Roland Disability score were lower (better) in the control group, and the group of patients evaluated was relatively small. It appears that there is only little literature on TEI in the acute phase of sciatica and therefore additional research is obligatory.

Furthermore, it is not yet understood why some patients experience more pain than other patients. From literature it is known that pain score does not correlate with the size of the herniated lumbar disk, but there are indications that degree of infection is related [7]. It has been demonstrated that at the site of the herniated disc several inflammatory cytokines can be found leading to prostaglandin synthesis and macrophage recruitment [8-9]. For this reason, disc material will be retrieved from patients undergoing lumbar surgery during this study and histological analysis will be performed.

2. OBJECTIVES

Primary study objective:

To study effectivity of the epidural injection with analgesic and anti-inflammatory medication to relieve the symptoms within two weeks follow up.

It will be evaluated what the average leg pain score is in both treatment arms at two weeks follow up. It will be evaluated how long the effect lasts.

The leg pain and functionality at 4 weeks after randomization will also be evaluated to get informed on the responsiveness on TEI in a somewhat later stage.

Secondary study objectives:

To evaluate the outcome of TEI in the first two weeks after randomization as a predictor of NRS leg pain at 14-16 and ca 26 weeks after onset of leg pain.

Ideally, responsiveness to TEI can predict the clinical condition at 14-16 weeks after onset of sciatica. The hypothesis is that being non-responsive to TEI within two weeks, predicts an unsatisfactory condition after 14-16 weeks of suffering. This is the category of patients that in contemporary care in the Netherlands will be offered a surgical intervention. If our hypothesis is correct, in the future, this population of patients can be offered a surgical intervention at an earlier time point.

The ca 26-week time point is chosen since in the Sciatica trial [2], both the conservative and the surgical group demonstrated comparable outcome data.

Patients in this study are included while suffering from severe leg pain for 3-8 weeks.

Presumably most patients will enter the study with 4-6 weeks of leg pain. This means that on average 10 weeks after randomization, the 14-16 week leg pain time point is reached. This means that 21 weeks after randomization the ca 26-week leg pain time point is reached.

The response in NRS leg pain, ODI and patient satisfaction at 1 week after injection and at 2 weeks after injection will be correlated to the value of these parameters at 10 and 21 weeks after randomisation.

To evaluate the cost-effectivity of analgesic/anti-inflammatory epidural injections to relieve symptoms of early sciatica.

A substantial portion of the patients in this study will eventually have an MRI of the lumbar spine. These MRIs will be evaluated according to our standard MRI evaluation protocol, that has been proven to generate additional successful conclusions and subsequent publications in the past [10-15]. Protruding disc, disc and vertebral end plate changes (MODIC) will be correlated to clinical data.

A portion of the patients in this study will eventually be operated. Disc material from these patients will be evaluated for the presence (and type) of macrophages and these data will be correlated to MRI and clinical data. These additional outcome measures can be combined with the research lines on etiology of sciatica that are executed in the Neurosurgery Department of the LUMC [16].

3. STUDY DESIGN

This is a prospective, open-label, randomized controlled trial on patients suffering from acute sciatica (3-8 weeks pain in the leg with a NRS ≥ 6) (see inclusion and exclusion criteria) in which consecutive patients who meet the inclusion criteria are invited to participate in the trial. The trial will take place at the Spaarne Gasthuis Hospital (SG) in Hoofddorp and Haarlem, the Netherlands in cooperation with researchers from Leiden University Medical Center (LUMC), Leiden, the Netherlands. Patient recruitment will occur at GP practices (GP collective Haarlemmermeer and Kennemerland, 185 GP's). The GP will diagnose the patient and, if the patient is diagnosed with sciatica, refer to the study investigator.

Eligible patients that are willing to participate are randomized to treatment with transforaminal epidural injections (treatment group) or standard conservative care (control group).

Randomization will take place using block randomization in a 1:1 allocation ratio. Patients from the treatment group will be treated with TEI, oral pain medication and, if deemed necessary by the GP, physiotherapy. The control group will only receive oral pain medication and if deemed necessary additional physiotherapy. For this study, the control group will not include placebo injections since we want to compare treatment with injections to treatment without injections. The focus will not be on the type of medication that is contained in the injection. Furthermore, a control group without injections will demonstrate what percentage of patients will experience spontaneous relief of symptoms (only using medication and/or physiotherapy) as it is known that in a significant part of the patients sciatica resolves without any intervention.

At baseline, clinical and demographic data are gathered for patients in both groups. Patients from the treatment group will receive TEI within 4 days after randomization. Patients from this group can receive multiple injections but an injection is only repeated after a certain interval time according to usual anaesthesiological guidelines. For all injections, details on timing, frequency and prevailing complications will be gathered.

NRS leg pain that decreases below the value of 4 (on a 10 point scale) within two weeks after TEI is documented as successful effect of TEI. NRS leg pain that remains higher than a value of 4 at a time interval of two weeks after TEI makes a patient eligible for surgery if the patient requests for surgery. If surgery is requested by the patient (either in the control or intervention group), general guidelines for timing of surgery will be conducted, meaning that the patient is encouraged to postpone surgery till 14-16 weeks after onset of pain. This decision is made using Shared Decision Making and it is possible that the patient is operated before the 14-16 week time point. The patients who are randomized cannot be operated in the first two weeks after randomization, unless sudden loss of strength or a cauda equina syndrome is reported. We expect that during these two weeks TEI will have its effect. Four

weeks after randomization the outcome parameters are measured again to be informed on the late effect of TEI. Patients will be followed up for a total duration of 21 weeks starting from the moment of randomization. Questionnaires will be filled in at baseline, 1, 2, 4, 10 and 21 weeks follow-up. A schematic overview of the study procedures is outlined in figure 1. Note that this figure does not hold into account that it is possible for patients randomized to the treatment group to receive additional injections if necessary.

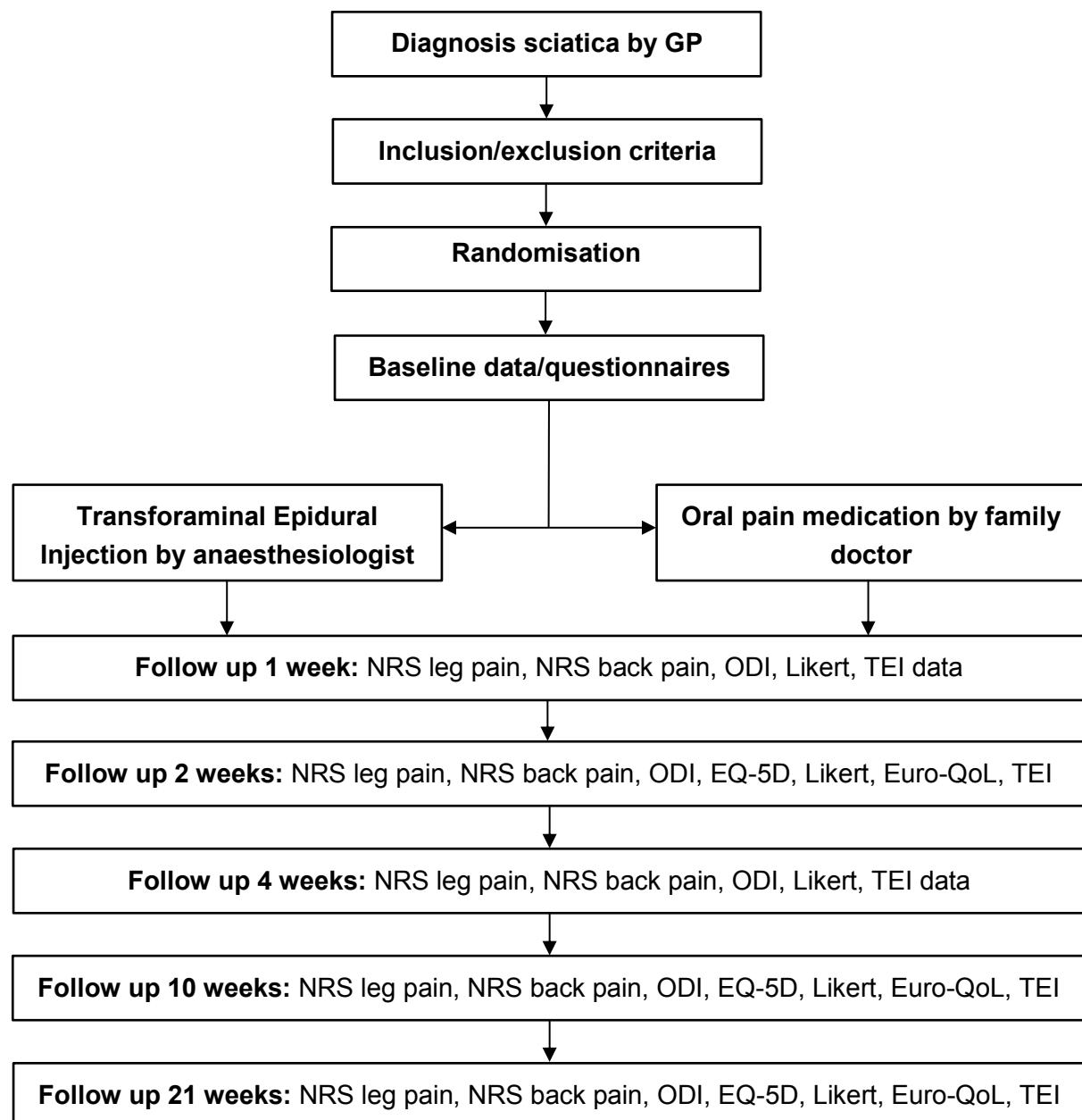


Fig.1 Flow diagram of study procedures

4. STUDY POPULATION

4.1 Population (base)

Patients suffering from sciatica that visit the general practitioner (GP collective Haarlemmermeer (60 GP) and Kennemerland (125 GP) referring to the Spaarne Gasthuis location Haarlem and location Hoofddorp (adherence 750.000 patients) are evaluated to be candidates for this study. If the general practitioner diagnoses a lumbar radicular syndrome (LRS) (sciatica) with an NRS leg pain of 6 points or more on a 10 points scale, and the duration of pain is longer than 3 weeks and shorter than 8 weeks, the patients are offered to participate in the RCT. If they are willing to consider participating in the RCT, the GP will send the contact details to the study investigator. Patients will be offered at least 48 hours to decide whether they want to be enrolled in the study. The study investigator will contact the patients and explain the study again. If patients are deciding to cooperate, informed consent will be signed. If patients are randomized to continue usual care, the GP will be informed and he/she will conduct conservative treatment as deemed suitable. If the patient is randomized to TEI, the patient is referred to the anaesthesiologist to receive TEI. TEI treatment will be received within 4 days.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Sciatica;
- Leg pain of 6 or more on a 10 point NRS (Numeric Rating Scale) scale with a duration of >3 and <8 weeks;
- Patient is willing to accept the possible costs for the treatment by the pain physician
- Informed consent.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Age under 18 years;
- Condition preventing to receive TEI (for instance, allergy for lidocaine);
- Severe scoliosis;
- TEI received in 6 months before randomization date;
- Surgery for sciatica at the same level;
- Surgery for sciatica at another level within one year before inclusion;

- Pregnancy.

4.4 Sample size calculation

We hypothesize that patients in the intervention group will have a mean NRS for leg pain of 4.0 on a 10-point scale at two weeks after treatment with TEI and patients in the control group will have a mean NRS for leg pain of 5.5 two weeks after randomization. A difference of 1.5 points on the NRS scale will be considered clinically relevant [17]. With a standard deviation of 2.6 (according to results of Joswig [18]), a power of 90% and a level of significance of 5% 64 patients are needed per group. This is a total of 128 patients. With a loss to follow-up of 10% we aim to include 142 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients are referred to the anaesthesiologist to receive TEI within 4 days after randomization.

For injections below L3, where the space around the nerve root is larger and thus dilution of the injectable is more than in the area around the nerve root in the higher lumbar area (above L3), the dosage of the medication will be higher.

For injections at L3 or below :1,5 ml lidocaine 2% and 40mg methylprednisolone acetate is injected transforaminally in close proximity of the nerve root, according to usual care

For injections above L3: 1,5 ml lidocaine 1% and 10mg dexamethasone is injected transforaminally in close proximity of the nerve root, according to usual care.

Administration of the injection will be performed in an outpatient clinic setting and will take 15 minutes. After the procedure, the patient will stay at the recovery room for 30 minutes for monitoring.

5.2 Use of co-intervention

Oral pain reducing medication according to usual care is allowed. This is prescribed, if necessary, by the GP. Since it is a randomized controlled trial, it is reasonable to expect that participants in both treatment arms will demonstrate comparable variation in oral pain medication.

5.3 Escape medication

N.a.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

NRS leg pain: The pain intensity in the leg and the back will be measured with a 10-point horizontal Numeric Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). During each visit the NRS leg pain and NRS back pain will be scored. The patient is not entitled to see the pain scores indicated during previous visit(s). The NRS scores will be measured at baseline and at 1, 2, 4, 10 and 21 weeks after randomization.

The average score for NRS leg pain at two weeks after injection is compared to the average score for NRS leg pain in the prolonged conservative care group, 2 weeks after randomization. This will be calculated again at 4 weeks after randomization.

6.1.2 Secondary study parameters/endpoints

Sciatica is not only characterized by pain in the leg, but also by discomfort in functioning. Therefore the following parameters will also be evaluated.

NRS back pain: The pain intensity in the leg and the back will be measured with a 10-point horizontal Numeric Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). During each visit the NRS leg pain and NRS back pain will be scored. The patient is not entitled to see the pain scores indicated during previous visit(s). The NRS scores will be measured at baseline and at 1, 2, 4, 10 and 21 weeks after randomization.

Oswestry Disability Index (ODI): The functionality of the patient with a focus on walking and daily activities will be measured with the Oswestry Disability Index that is usually measured for sciatica complaints. The scale ranges from 0 (no disability) to 50 (worst disability possible). During each visit the ODI will be scored. The patient is not entitled to see the scores indicated during previous visit(s). The ODI scores will be measured at baseline and at 1, 2, 4, 10 and 21 weeks after randomization.

EuroQoL (EQ-5D): The EuroQoL (five point EQ-5D) will be used for the cost utility analysis. The tool measures five dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Each dimension consists of one item, while three levels are distinguished (no problems, some problems, many problems). Use of the EuroQoL needs to be registered

(euroqol.org). The EuroQol scores will be measured at baseline and at 2, 10 and 21 weeks after randomization.

Quality of Life VAS (Health state utility VAS): To represent the patients perspective, utility will also be estimated using a VAS for the valuation of the patient's health state (ranging from 0 = as bad as death to 100 = perfect health), measured at baseline and at 2, 10 and 21 weeks after randomization.

Likert perceived recovery patient: To measure the perceived recovery a seven-point Likert scale will be used. The score on this scale varies from 'completely recovered' to 'worse than ever'. The Likert scores will be measured at baseline and at 1, 2, 4, 10 and 21 weeks after randomization.

Costs (Cost intervention, health care use, and loss of productivity): Cost diaries will be filled out at 10 and 21 weeks after randomisation. Health care utilization (including physiotherapy, visits to GP and specialists, nursing care and medication), patient costs, and absenteeism will be measured using cost diaries filled out by the patient.

Complications: Post-TEI exacerbation of NRS leg pain (>1 point additional leg pain) that lasts for at least 24 hours will be documented as a clinically relevant complication of TEI. Other rare adverse events from treatment with TEI such as pain at site of injection, persisting numbness, vasovagal reaction, accidental discal puncture, accidental dural puncture or headache will be recorded as well.

Radiological parameters: the level of disc herniation, the size and shape of disc herniation, disc degeneration (Pfirrmann scale), vertebral end plate changes, and facet degeneration (Weishaupt scale) will be evaluated by two independent researchers, blinded to clinical and histological data, on T2 weighted sagittal and transversal MRI.

Histology: During surgery, the herniated disc material will be collected and fixed in 4% formaldehyde solution. For evaluation, the tissue will be subsequently embedded in paraffin blocks. These blocks will be stained with Hematoxylin and used for general macrophage staining (CD68), and subtype macrophage staining: M1(iNOS & CD40) and M2 (Arg1 & CD163), T cell staining (CD45-RO) and B cell staining (CD20). Furthermore, presence of Propionibacterium Acnes and Staphylococcus Epidermidis will be verified by PCR analysis for 16S rDNA. Positive samples will be gram stained for further identification of the bacteria.

All histological data will be quantified by two independent researchers, blinded to clinical and MRI data, and an inter-agreement analysis will be conducted.

6.1.3 Other study parameters

Data with respect to the following variables will be collected at baseline:

- Demographic data;
- Age, gender, length, weight, BMI, tobacco exposure, alcohol abuse;
- History of previous radicular symptoms in the legs;
- Usage of pain medication.

Data with respect to the following items will be collected concerning TEI:

- Timing of administration (days after randomization);
- Number of injections and timing of those;
- NRS leg pain after injection;
- Other complications.

Data during follow up will be collected:

- If an MRI is performed: MRI data;
- If surgery is performed: disc material for histology.

6.2 Randomisation, blinding and treatment allocation

Randomisation will take place using block randomisation in a 1:1 allocation ratio in order to obtain equal study groups. When the patient is enrolled, a randomization envelope will be opened to determine patient allocation. Since this is an open-label randomized controlled trial allocation is not concealed.

6.3 Study procedures

Patients that are diagnosed by the GP with acute sciatica (3-8 weeks after onset of pain, NRS \geq 6) that meet in- and exclusion criteria will be offered the study. If patients are willing to be randomized, they will be contacted by the study investigator. The study investigator will inform the patients again and checks whether patients have access to e-mail. This is done to make sure that they can fill in the questionnaires online (a web-based database with questionnaires is used for data collection (Castor, LUMC)). The study investigator will ask for informed consent. Randomization will take place. If patients are randomized to the intervention group, they will be sent to the anaesthesiologist and planned for TEI within 4 days after randomization without visiting the neurologist. If patients are randomized to the

control group, they will receive oral pain medication according to the care of the general practitioner.

The patient will be invited to the hospital where baseline data will be gathered and questionnaires will be filled in. During this contact the study investigator will guide the patient through the online questionnaire fill-in procedure to get the patient accustomed with this procedure.

Questionnaires will be filled in after 1, 2, 4, 10 and 21 weeks after randomization for both the control group and TEI group.

If leg pain remains severe after the 2 weeks after randomization primary endpoint, patients can be referred to the neurologist if the general practitioner deems it necessary. Patients can be offered surgery if applicable.

If an MRI is made during the process, MRI data will be gathered as mentioned above.

If a lumbar discectomy is performed, disc tissue will be gathered during surgery and analysed as mentioned above.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.5 Replacement of individual subjects after withdrawal

This will not be done. Subjects that refuse TEI after randomisation to the TEI group, will be considered as cross-over subjects. Patients that withdraw during the study will be considered lost-to-follow up patients.

6.6 Follow-up of subjects withdrawn from treatment

These subjects will be followed-up according to study protocol and considered as cross-over subjects.

6.7 Premature termination of the study

N.a.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited Medical Ethical Committee (METC) without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to TEI. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Adverse events from treatment with TEI are rare. The most common adverse events reported in literature are [19]:

- Transient exacerbation of pain: 2.4%
- Pain at site of injection: 1.1%
- Persisting numbness: 0.33%
- Vasovagal reaction: 0.14%
- Accidental discal puncture: 0-1%
- Accidental dural puncture: 2.3%
- (Post dura puncture) headache: 0.33-1%

This includes also includes leg pain/inability as a result of TEI that:

- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in significant disability or incapacity;

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to TEI but could have been based upon appropriate judgement by the investigator.

In literature, arachnoiditis and 'nervous system disorder' have been described as major complications. However, despite the lack of exact data, these complications are considered to be rare [19].

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the subsidizing party without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8. STATISTICAL ANALYSIS

8.1 Primary study parameter(s)

The study data will be analysed according to the intention-to –treat principle. The mean NRS for leg pain will be compared between the two groups using the unpaired t-test. This will also be done at the 4-week time point.

8.2 Secondary study parameter(s)

The absolute decline in NRS leg pain, NRS back pain and ODI and increase in EQ5D from baseline to 2 weeks after randomization will be calculated using t-tests. The same will be done for the baseline to 4 weeks after randomization time point (using t-tests).

Perceived recovery Likert data will be dichotomized (1 and 2 is success, 3-7 is no success) and compared at 2 and 4 weeks after randomization or injection and to 14 and 26 weeks after start of severe leg pain using Chi-square tests.

The 2-week success data will be correlated to the success data after 14 weeks and subsequently for 26 weeks using Chi-square tests to make predictions. Logistic regression analysis will be used to correlate 2-week (and 4-week) success data to the absolute data for NRS leg pain, NRS back pain, ODI, increase in EQ5D at 14 and 26 weeks.

Cost effectiveness analysis:

The economic evaluation will consist of a cost-effectiveness analysis from a healthcare perspective (CEA: costs per extra patient with symptom relieve, i.e. the primary outcome measure) and a cost-utility analysis from a societal perspective (CUA: costs per QALY). Both analyses will be trial-based, using patient reports, with a half-year time horizon. Healthcare use will be valued according to the Dutch guidelines. QALYs will be calculated as the area under the utility curve, estimated using the Dutch tariff for the EQ-5D. As sensitivity analysis, QALYs will also be calculated using the VAS for quality of life (with power transformation). Average costs and patient outcome will be compared according to intention-to-treat, using net-benefit analysis, and using multiple imputation to account for missing data.

8.3 Other study parameters

MRI: the level of disc herniation on MRI will be compared to the clinical diagnosis (made before MRI) and the percentage of clinical diagnosis prediction success can be calculated.

The size and shape of disc herniation, disc degeneration (Pfirrmann scale), vertebral end plate changes, and facet degeneration (Weishaupt scale) will be correlated to baseline clinical data using t-tests.

Histology: the number of M1 and M2 macrophages will be correlated to NRS leg pain and ODI at all time points using t-tests and mixed models analysis.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2018, 9 July 2018, www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patients that present at the GP with acute sciatica (3-8 weeks after onset of pain, NRS ≥ 6) that meet in- and exclusion criteria will be offered the study. If patients are willing to be randomized (48 hours' time of consideration), they will be contacted by the study investigator. The study investigator will inform the patients again and checks whether patients have access to e-mail. This is done to make sure that they can fill in the questionnaires online (a web-based database with questionnaires is used for data collection (Castor, LUMC)). The study investigator will ask for informed consent.

9.3 Compensation for injury

The Spaarne Gasthuis, where the study is conducted has a liability insurance which is in accordance with article 7 of the WMO.

The Spaarne Gasthuis (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.4 Incentives

For each patient that is randomised, the GP, that offered the study to the patient will receive a financial compensation of 25 euros.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be collected using Castor EDC (web based secured system provided by LUMC). Baseline data will be collected during inclusion of the participant and directly registered in Castor by a researcher from the LUMC. Data on TEI, MRI and lumbar surgery will be collected from the electronic patient system Epic in Spaarne Gasthuis by the treating physician and by a researcher from the LUMC and processed in Castor. Specific data on the TEI procedure will be filled in on a paper CRF by the anaesthesiologist and subsequently processed by a researcher from the LUMC in Castor. Other data will be collected at predefined follow-up moments through digital questionnaires that the participants will fill in at home. These will be processed automatically in Castor. Castor EDC will code the patient data into untraceable ID's. All data will be safeguarded and stored for 15 years after the study is finished. All data will be handled according to the guidelines of GRP. This obligates all researchers to comply to the quality assurance standards, which include monitoring, risk assessment, privacy of patient data, and transparency of information to the patient. The LUMC will be responsible for the processing of data.

In order to warrant privacy patient data and disc material will be coded. Only with the key data can be traced back to a specific individual. The key is securely saved at the local research site and only the principal investigator, research monitor and Healthcare and Youth Inspection (Inspectie Gezondheidszorg en Jeugd) will have access to the key. No traceable data will be published. Patients will give permission for these authorities to access the key and their personal data through the informed consent. At any moment patients can withdraw their permission. Data collected before withdrawal of consent will be used. If disc material has been collected, it will be destroyed after withdrawal of consent. Analyses of disc material performed before withdrawal of consent will be used.

10.2 Monitoring and Quality Assurance

Monitoring and quality assurance will be done according to the LUMC standard protocol. The monitoring and quality assurance will be done by a member of the SAINTS research group. A monitoring plan will be created in cooperation with the monitoring coordinator from the LUMC after approval of the protocol by the METC.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

The results from this trial will be published in international peer reviewed journals. Results will be presented on international spine and pain congresses. Furthermore, the results can influence the usual care in the Netherlands and will subsequently be offered to be considered by (inter)national guideline-authors for treatment of sciatica.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

N.a.

11.2 Synthesis

Administration of TEI with dexamethasone has been tested extensively on human beings through numerous (randomized controlled) trials. In the Netherlands, this therapy is now considered usual care for patients suffering from sciatica. Dexamethasone is registered to be used for TEI therapy. The same holds true for the administration of lidocaine.

The study population will only consist of sciatica patients that would have been eligible to receive TEI through usual medical care. In order to minimize risks from treatment with TEI exclusion criteria have been composed: patients that have a condition that prevents them to receive TEI, that have received TEI in 6 months before randomisation or that are pregnant will be excluded from participation. After administration of the injection, patients will shortly stay at the recovery room where they will be monitored. Since TEI treatment is considered usual care additional measurements are not necessary. Current monitoring standards are believed to be sufficient and therefore we do not establish a DSMB or safety committee.

12. REFERENCES

[1] Konstantinou, K., Dunn, K.M. *Sciatica: Review of Epidemiological Studies and Prevalence Estimates*. Spine 2008;33(22):2454-2472.

[2] Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, et al. *Surgery versus prolonged conservative treatment for sciatica*. N Engl J Med 2007;356(22):2245-2256.

[3] Hofstede, S .N., Marang-van de Mheen, P.J., Wentink, M.M., Stiggebout, A.M., Vleggeert-Lankamp, C.L., Vliet Vlieland, T.P., van Bodegom-Vos, L. *Barriers and facilitators to implement shared decision making in multidisciplinary sciatica care: a qualitative study*. Implement Sci 2013;8(1):95

[4] Hofstede, S.N., van Bodegom-Vos, L., Wentink, M.M., Vleggeert-Lankamp, C.L., Vliet Vlieland, T.P., Marang-van de Mheen, P.J. *Most important factors for the implementation of shared decision making in sciatica care: ranking among professionals and patients*. PLoS One 2014;9(4):e94176

[5] Joswig, H., Neff, A., Ruppert, C., Hildebrandt, G., Stienen, M.N. *The Value of Short-Term Pain Relief in Predicting the Long-Term Outcome of Lumbar Transforaminal Epidural Steroid Injections*. World Neurosurg 2017;107:764-771.

[6] Spijker-Huiges, A., Vermeulen, K., Winters, J.C., van Wijhe, M., van der Meer, K. *Epidural steroids for lumbosacral radicular syndrome compared to usual care: quality of life and cost utility in general practice*. Arch Phys Med Rehabil 2015;96(3):381-387.

[7] Kuslich, S.D., Ulstrom, C.L., Michael, C.J. *The Tissue Origin of Low Back pain and Sciatica: A Report of Pain Response to Tissue Stimulation During Operations on the Lumbar Spine Using Local Anesthesia*. Orthop Clin North Am 1991;22(2):181-187.

[8] Takahashi, H., Suguro, T., Okazima, Y., Motegi, M., Okada, Y., Kaiuchi, T. *Inflammatory cytokines in the herniated disc of the lumbar spine*. Spine (Phila Pa 1976) 1996;21(2):218-224.

[9] Donally III, C.J., Varacallo, M. *Lumbosacral Disc Injuries*. [Updated 2018 Oct 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

[10] El Barzouhi, A., Vleggeert-Lankamp, C.L., Lycklama à Nijeholt, G.J., van der Kallen, B.F., van den Hout, W.B., Verwoerd, A.J., Koes, B.W., Peul, W.C. *Magnetic resonance imaging interpretation in patients with sciatica who are potential candidates for lumbar disc surgery*. PLoS One 2013;8(7):e68411.

[11] Verwoerd, A.J., Peul, W.C., Willemsen, S.P., Koes, B.W., Vleggeert-Lankamp, C.L., El Barzouhi, A., Luijsterburg, P.A., Verhagen, A.P. *Diagnostic accuracy of history taking to assess lumbosacral nerve root compression*. Spine J 2014;14(9):2028-2037.

[12] El Barzouhi, A., Vleggeert-Lankamp, C.L., Lycklama à Nijeholt, G.J., van der Kallen, B.F., van den Hout, W.B., Koes, B.W., Peul, W.C. *Reliability of gadolinium-enhanced magnetic resonance imaging findings and their correlation with clinical outcome in patients with sciatica*. Spine J 2014;14(11):2598-2607.

[13] El Barzouhi, A., Vleggeert-Lankamp, C.L., Lycklama à Nijeholt, G.J., van der Kallen, B.F., van den Hout, W.B., Koes, B.W., Peul, W.C. *Influence of low back pain and prognostic value of MRI in sciatica patients in relation to back pain*. PLoS One 2014;9(3):e90800.

[14] Verwoerd, A.J.H., Mens, J., El Barzouhi, A., Peul, W.C., Koes, B.W., Verhagen, A.P. *A diagnostic study in patients with sciatica establishing the importance of localization of worsening of pain during coughing, sneezing and straining to assess nerve root compression on MRI*. Eur Spine J 2016;25(5):1389-1392.

[15] El Barzouhi, A., Verwoerd, A.J., Peul, W.C., Verhagen, A.P., Lycklama à Nijeholt, G.J., van der Kallen, B.F., Koes, B.W., Vleggeert-Lankamp, C.L. *Prognostic value of magnetic resonance imaging findings in patients with sciatica*. J Neurosurg Spine 2016;24(6):978-985.

[16] Djuric, N., Yang, X., Ostelo, R., van Duinen, S., Lycklama à Nijeholt, G.J., van der Kallen, B.F.W., Peul, W.C., Vleggeert-Lankamp, C.L.A. *Modic changes influence the effect of disc inflammation on clinical outcome in sciatica*. Department of Neurosurgery, Leiden University Medical Centre; 2018 (Unpublished report).

[17] Katz, N.P., Paillard, F.C., Ekman, E. *Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions*. J Orthop Surg Res 2015;10(24):1-11.

[18] Joswig, H., Neff, A., Ruppert, C., Hildebrandt, G., Stienen, M.N. *The Value of Short-Term Pain Relief in Predicting the One-Month Outcome of Lumbar Transforaminal Epidural Steroid Injections*. World Neurosurg 2016;96:323-333.

[19] Sectie Pijn- en Palliatieve Geneeskunde van de Nederlandse Vereniging voor Anesthesiologie. (2016). *Protocol Veilig gebruik van epidurale corticosteroïden infiltraties*. Retrieved from <https://www.anesthesiologie.nl/publicaties/protocol-veilig-gebruik-epidurale-corticosteroïden-infiltraties>