Effect of Infection, Modic and Inflammation on Clinical Outcomes in Radiculopathy

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON27285

Source
Nationaal Trial Register

Brief title
EIMICOR

Health condition

For this study, all patients (18-65 yr.) with 12 or more weeks of radicular pain symptoms, that are eligible for surgery according to a neurosurgeon in the participating hospital, will be asked to participate. Patients are eligible if they already planned to undergo surgery for herniated disc.

Sponsors and support

Primary sponsor: Leiden University Medical Center, dept of Neurosurgery
Source(s) of monetary or material Support: EANS Research Fund 2019 (European Association of Neurosurgical Societies)

Intervention

Outcome measures

Primary outcome

1. Pain
The pain experienced by the patients will be measured by two questionnaires to assess back and leg pain: NRS leg pain and NRS back pain. In these questionnaires, the patients will display the amount of pain they have experienced in their back and leg during the week previously to the visit. The pain intensity will be determined on a scale of 0-10. 0 represents 'no pain' and 10 represents 'worst pain imaginable'. Both the NRS back and leg pain score will be measured during every follow-up moment (8, 16, 26, 52 weeks,). Previous test results will not be visible for the patient.

2. Functionality
For estimating functionality of the lumbar patient, the Oswestry Disability index (ODI) will be used. This questionnaire contains 10 topics related to the impact of the pain the patient's life, with 5 grading's for each topic. The total will give a score between 0 (no disability) and 50 (maximum disability possible), which will be calculated to a 1-100% score. For estimating functionality of the cervical patient, the Neck disability index (NDI) will be used, which is an adjusted version of the ODI focused on neck pain instead of back pain.

3. Modic Changes
Type (1,2 or 3) and severity (<50&>50%) of Modic Changes will be scored at baseline.

4. Disc inflammation
Disc material will be stained for the presence of macrophages, for M1 and M2 macrophages, and for B and T cells. Evaluation will be done through counting cells and subsequenlty catagorizing them.

5. Bacterial infection
Bacterial presence in the disc will be verified by a 16s rDNA qPCR analyses for Propionibacterium acnes and staphylococcus epidermidis.

6. Blood samples (from 01-07-2021)
In addition to the frozen disc samples, this study will also collect blood samples for two purposes: the first is to assess the general inflammation (BSE, leukocyte differentiation) and vascular status (Cholesterol) and the second purpose is for future analysis, for which a sample will be stored in the freezer.

Secondary outcome

A possible mediator in this study is the amount and type of pain medication that patients take, either in self care or on prescription from the neurosurgeon or GP as part of the usual care. This could potentially alter the inflammation profile (NSAID's) or could lead to lower perceived pain scores. In addition, it could be that patients with severe inflammation benefit more from anti-inflammatory drugs. Therefore this study will measure participants usage of pain medication as follows:

1. Pharmacological data
participants will be asked to fill in a form regarding the frequency and dosage of pain medication and anti-inflammatory drug usage. This form will also be given to the participants

during the one-year follow-up at 8, 16, 26 and 52 weeks.

2. Osteoarthritis
In order to investigate to what extent Modic Changes are related to clinical features of osteoarthritis, participants will be asked to fill in the Womac questionnaire. The Western Ontario and McMaster Universities Osteoarthritis (Womac) index questionnaire evaluates pain and physical function, con- taining 24 questions about daily functioning and stiffness. The questionnaire will be given to partici- pants at baseline and after one year follow-up.

Other study parameters:
1. Demographic data
From all patients, general information will be collected: age, gender, BMI, ASA, Diabetes, smoking habits.

2. Clinical data
During the intake, the neurosurgeon will assess the duration of the symptoms in weeks.

3. MRI data
Nerve root compression(no or mild, moderate, severe) will be scored on MRI.

Study description

Background summary

Recent findings have suggested that a bacterial infection of the herniated disc aggravates pain symptoms. This bacterial infection is often associated with the presence of Modic changes (MC). Besides, evidence indicates that inflammation is also involved in resorption of herniated tissue.
The objective of this prospective cohort study is to explore the contribution of infection and inflammation in lumbar and cervical radiculopathy. We hypothesize that patients with MC, infection and inflammation will suffer the most and that surgical intervention will have a disappointing outcome. Antibiotic therapy may be more effective in these patients.
Inflammation is thus believed to work in two ways, dependent on the type of inflammatory cells: combined with a bacterial infection the inflammation will be accompanied by pro-inflammatory cytokines that worsen the outcome. In patients without such an infection, the inflammation will be accompanied by cytokines that induce a resorption process that accelerates recovery.
Study population: 320 patients between 18 and 75 years old with either a lumbar (n=160) or cervical (n=160) herniated disc that will be subjected to discectomy.
The present study investigates the effects and interactions of bacterial infection (bacterial cultures), disc inflammation (histological analysis of macrophages, M1 and M2 type), MC and blood biomarkers indicating inflammation or infection on the clinical outcome of patients with cervical or lumbar disc herniation. A mean difference of 2-points on a 10 point NRS scale will be regarded as clinically relevant. Pain reduction over the course of one-year follow-up will be scored.

Study objective

Primary Objective(s):
In a group of sciatica and cervical radiculopathy patients undergoing disc surgery, this study will determine the effects of bacterial infiltration of the disc on patient reported pain scores, in the presence or absence of Modic changes on MRI and histological defined disc inflammation.

Secondary Objective(s):
1. A secondary aim of this study is to assess whether patients that suffer from disc inflammation benefit more from anti-inflammatory drugs than those without inflammation.
2. Another secondary aim of this study is to further explore the inflammation process by characterizing different types of macrophages (M1 and M2) and B and T cells.
3. Furthermore, this study aims to associate the presence of bacterial infection to the presence and type of Modic Changes.
4. At last, the present study assess the general inflammation (BSE, leukocyte differentiation) and vascular status (Cholesterol) in a group of sciatica and cervical radiculopathy patients, during surgery (from 01-07-2021).

Hypothesis of al sub objectives:
- Does the presence and degree of bacterial infection differ between patients with and without Modic changes?
Dudli (2017) revealed that 60% of P. acne infected discs showed a pathological inflammatory response. All of these discs were accompanied by Modic changes in the adjacent endplate. This insinuates that Modic changes are a pathological response to a bacterial infection. Hence, we expect that it is more likely to find a bacterial infection in patients with Modic changes, than in patients without Modic changes.

- Does the presence of infection influence the clinical baseline and outcome data, and does this differ between patients with and without Modic changes?
Because of excreted bacterial products combined with the pro inflammatory cytokines excreted due to the inflammatory response that may occur we expect to find that the presence of infection has a negative effect on the clinical outcomes. However, because Dudli (2017) has shown that only patients with Modic changes show a pathological inflammatory response, we expect that this effect is stronger in patients with Modic changes than in patients without Modic changes.

- Does the presence of Modic changes influence the clinical baseline and outcome data, and does this differ between patients with and without a bacterial infection?
Dudli (2017) found an upregulation of Tropomyosin receptor kinase (Trk) A,B and C, which have been associated with nerve pain, in patients with Modic changes. Based on these findings we would expect a negative of Modic changes on pain symptoms. However, El Barzouhi (2014) found no effect of the presence of Modic changes on back pain. Hence we expect to see no or a small negative effect of Modic changes on the clinical outcomes. In addition, El Barzouhi's findings might be explained by the possibility that Modic changes are still visible on MRI even if the infection is gone. Therefore, we believe that the co-presence of Modic changes and an infection may have a big effect on the clinical outcomes but that Modic

changes alone have a small influence the clinical symptoms.

- Does the presence of Modic changes influence the type of macrophage (M1 or M2) infiltration?
Djuric (2018) et al showed that in patients without Modic changes, macrophage infiltration has a beneficial effect on the clinical outcomes, and that in patients with Modic changes, macrophage infiltration had the opposite effect. We therefore expect to find more pro inflammatory (M1) macrophages in patients with, and more pro resorption (M2) macrophages in patients without Modic changes.

- Does the presence of infection influence the type of macrophage (M1 or M2) infiltration?
P. Acne has been shown to recruit macrophages and induce an inflammatory reaction, which makes it more likely to find M1 macrophages in patients with a bacterial infection. Djuric et al (2018) showed that the presence of Modic changes determined whether patients suffered or benefited from macrophage infiltration, and probably whether their type is M1 or M2. As mentioned before, we hypothesized that Modic changes are a consequence of infection, thus we expect that in patients without an infection we will find a higher degree of M2 macrophages. Taken together, we expect infection to direct the type of macrophages towards M1.

- Is there an interaction between the effect of the presence of Modic change and infection on the type of macrophage (M1 or M2) infiltration?
Based on the findings of Dudli (2017) et al, We expect that an infection without the pro inflammatory response accompanied by Modic changes will lead to less M1 infiltration. We also expect that patients with Modic changes that do not have an active infection will have a lower degree of M1 infiltration and probably a higher degree of M2 infiltration due to the reconsolidation process that is stimulated in the disc. Taken together, we expect to find an interaction effect of infection and Modic changes

- Does the type of macrophage (M1 or M2) influence the clinical outcomes?
M1 macrophages are pro inflammatory and their cytokines are associated with aggravation of the clinical symptoms. M2 macrophages on the contrary, are associated with resorption of waste material and are thought to help with disc resorption, therefore we expect that M1 has a negative effect on the clinical outcomes and M2 has a beneficial effect on the clinical outcomes.

Study design

All participants will be asked to co-operate during the entire follow-up. During follow-up patients will be asked to fill in questionnaires regarding clinical outcome (NRS, ODI/NDI & GPE) and medication status at 8 weeks, 16 weeks, 26 weeks and 52 weeks post-surgery. Patients will receive emails with a
link to the follow up questionnaires around the above mentioned time points.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
Lumbar patients:
- Age 18-75
- a unilateral lumbosacral radicular syndrome, with at least the following criteria:
o Radicular incitement: radiating pain from (a part of the) dermatome L4, L5 and/or S1.
o Present for at least 8 weeks
- MRI verified lumbosacral disc herniation that is corresponding to the side of the symptoms
- Indication for surgery
- Informed consent

Cervical patients:
- Age 18-75
- a unilateral cervical radicular syndrome, with at least the following criteria:
o Radicular incitement: radiating pain from (a part of the) dermatome C45, C56, C67 and/or C7T1.
o Present for at least 8 weeks
- MRI verified cervical disc herniation that is corresponding to the side of the symptoms
- Indication for surgery
- Informed consent

Exclusion criteria

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

Lumbar:
- Previous lumbar spinal surgery or chemonucleolysis
- Paresis of MRC < 4
- History of spinal inflammatory disease
- Instability that requires surgical fixation
- Active infection at the time of surgery
- Usage of Anti-biotics in the past six months
- Epidural steroid injection in the past six months
- Pregnancy
- Inadequate knowledge of the Dutch language

Cervical:
- Previous cervical spinal surgery chemonucleolysis
- Paresis of MRC < 4
- Myelopathy as major complaint
- History of spinal inflammatory disease
- Instability that requires surgical fixation
- Active infection at the time of surgery
- Usage of Anti-biotics in the past six months
- Epidural steroid injection in the past six months
- Pregnancy
- Inadequate knowledge of the Dutch language

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2020
Enrollment:	320
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	18-03-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8464
Other	METC LDD (Leiden, Den Haag, Delft) : P18.211

Study results