Subclinical Propionibacterium Acnes Infection Estimation in the Intervertebral Disc (SPInE-ID)

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RECRUITMENT STATUS
COMPLETED

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STUDY DESCRIPTION

Brief Summary
Subclinical infection of the intervertebral disc after lumbar disc herniation surgery has been correlated to chronic low back pain and vertebral endplate changes. The most commonly reported agent is Propionibacterium acnes. However, the real incidence is unclear, as it has been reported in some series ranging from 3.7% to 46%. Recently, a systematic review concluded that there is a relationship between P. acnes and endplate changes, but, there are so far no studies to verify whether the reported presence of that pathogen in the intervertebral discs is due to local infection or whether intraoperative contamination occurred during the collection of samples. Thus, the main objective of this study is to estimate the incidence of subclinical infection in patients surgically treated for lumbar disc herniation. To this end, a prospective cohort study will be conducted with a minimum of 95 patients between 18 and 65 years of age who have been submitted to surgery after failure of conservative treatment. The extruded disc will be removed and cultured for bacterial identification. As controls, the ligamentum flavum and the multifidus muscle, taken respectively before and after removal of the herniated fragment will also be cultured. Patients will be followed-up for a year and MRI will be done at the end of this period.

Condition or Disease:
- Infection
- Intervertebral Disc Herniation
- Propionibacterium Infection
- Spinal Diseases
- Discitis

Intervention/treatment:
Other: Microdiscectomy

Phase:
N/A

DETAILED DESCRIPTION
INTRODUCTION Low back pain is a frequent condition in the population, as well as vertebral endplates abnormalities, described by Modic et al (1,2), that affect up to 6% of the general population, and, up to 46% of patients with low back pain(3). Modic type I changes are described as vertebral bone marrow edema related to acute low back pain(4). When Modic changes are detected, chances of one presenting unspecific low back pain are 4.5 times higher(1,2).

Subclinical infection caused by low-virulence pathogen can possibly lead to vertebral endplate abnormalities, detected in magnetic resonance imaging (MRI) studies, and differentiation between infection and Modic changes may be difficult(5,6). Subclinical infection can also be associated with increasing low back pain(7). Albert et al(8) reported 62 patients who had undergone surgical treatment and had lumbar disc herniation where 46% of cases had a positive culture. The same authors also reported that 80% of patients with a positive culture for anaerobic pathogens presented Modic type I changes at the adjacent vertebra after a two-year follow-up, against 44% of patients with negative culture. Some studies demonstrated the presence of low-virulence pathogens in intervertebral disc tissue cultures(6,10), most commonly reported to Propionibacterium acnes.

Chronic low back pain and Modic type I changes have been associated with antibiotic regimens for up to 100 days with superior outcomes compared to sham treatment(7). Patients were treated with amoxicillin/clavulanate (500mg/125mg) (7) based on the study where scatica is associated with Propionibacterium acnes(8).

However, Carricojo et al(11) suggest that the presence of P. acnes in the intervertebral discs is due to either external surgical or laboratory contamination. These authors detected positive disc cultures in only 3.7% of cases out of 54 patients. Furthermore, same authors demonstrated that samples of spinal muscle and lumigmentum flavum collected intraoperatively at the end of the procedure had positive cultures in 14.8% of cases with a negative disc culture.

A systematic review performed by Urquhart et al(12) concluded, that there is moderate evidence that a relationship between positive culture with Modic type I changes and low back pain exists, although there was low evidence for relationship of cause. For that, authors concluded that new studies should be made to determine whether pathogens in the disc are originated from external contamination or if they are truly involved in the development of chronic back pain. HYPOTHESIS Lumbard disc herniation is related to subclinical infection of the intervertebral disc Null hypothesis: incidence of subclinical infection is the same as incidence of cases without infection in patients with lumbar disc herniation treated with surgery.

OBJECTIVES Main purpose of this study is to identify if the presence of a infection pathogen in the intervertebral disc is real or if it is intraoperative contamination. Secondary objectives are to analyze clinical prognostic factors in patients and diagnosis of infection. The study also proposes to analyze the relationship between radiological changes (Modic I and II) and infection.

METHODS Study design: An open prospective cohort study will be performed at a single center, (Hospital Israelita Albert Einstein - HAE) taking 1 year for recruiting, and ending 1 year after inclusion of last patient. Patients’ data will be collected with a specific form created for this study. Patients will be summoned for a new magnetic resonance image of the lumbar spine one year after their surgical procedure.

Inclusion criteria: All included patients will go through further treatment of ten sessions of postoperative physical therapy. Preoperativo:

Patients who have failed conservative treatment for lumbar disc herniation undergoing lumbar decompression open surgery (microdiscectomy) will be consecutively included in the study.

Patient enrollment in the study:

Patients accepting their participation will date and sign the Informed Consent Form (ICF). After ICF is properly signed, patient will undergo an interview to complete initial demographic data and pretreatment forms.

Patient recruitment will be carried out for 24 months, when 95 patients shall be included (details of estimated n reported at sample size determination).

Patient allocation:

Patients will undergo surgery according to surgeons’ preference. Attending surgeons will determine chosen operative technique according to their experience and preference.

Blinding:

Patients will not have access to the results of tissue cultures for pathogens, as well as the attending physician.

The radiologist that will analyze imaging studies of performed magnetic resonance will also be blinded to patients’ data or laboratory culture results. A blinded investigator will analyze pain and function scores.

Early stopping of participation in the study:

Patients will be excluded from the study when:

Withdrawn of ICF

Diseased

Patient selection flaw - incompatible eligibility criteria

Lost to follow-up

If patient presents clinical symptoms of infection such as severe lumbar or radicular pain, fever with no other detected foci, abnormal ESR, CRP, leucocytosis, and, altered imaging studies that lead to interruption of blinding of the results of culture exams.

Study stages:

Sample collection:

Included patients will undergo standard fashion general anesthesia and prepped with chlorhexidine solution. Intravenous antibiotics prophylaxis will be administered within first hour before skin incision, according to standard protocol of HAE Infection Control Committee published at the hospital Pharmacutics Manual.

Preoperative blood sample will be collected for leucogram, Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP). Same laboratory will be repeated at 1, 6 and 12 months time-point.

The excised herniated disc fragment will be immediately sent to microbiology laboratory analysis in a universal sterile container (screw cap tube) in no more than 30 minutes to be processed as follows. Same process will be applied to samples of deep muscle and ligamentum flavum at the end of the surgical procedure. Three cultures of the intervertebral disc will be done, as well three of the ligamentum flavum and three of the multifusus muscle for each patient.

Search for pathogens:

Herniated intervertebral disc will be split in three equally sized fragments of over 2x2x5 mm and squashed in a laminar flow cabinet until homogeneous material is achieved. Same process will be carried out for the ligamentum flavum and multifusus muscle samples, although split in three fragments. Tissues will be cultured in specific growth medium and incubated according to the respective culture.

Similar criteria used by the Infectious Diseases Society of America (IDSA) to detect joint replacement infection will be adopted, which is the recommendation on at least two positive tissue cultures by the same pathogen to confirm diagnosis of infection(13).

A - Aerobic culture For aerobic cultures, samples will be cultured in 5% sheep blood agar, chocolate agar and MacConkey agar plate, and will be placed in a 35°C incubator (CO2 atmosphere) for 5 days. If a positive bacteria culture is detected in the plate, the colony will be identified by MALDI TDF (Matrix Assisted Laser Desorption Ionization-Time of Flight) Microflex LT (Bruker Daltonics).

B - Anaerobic culture For anaerobic culture, tissue will be cultured at the Thioiglycolate tube and incubated in a 35°C incubator for up to 21 days. If turbidity occurs at the Thioiglycolate medium, material will be cultured in anaerobic blood agar and incubation at 35°C will be done in an anaerobic atmosphere. After growing of colonies, identification will be done by MALDI TDF.

C - Histological analysis Anatomic pathology analysis of the other fragment of the herniated disc (2x2x5 mm) will be done. Sample will be transported in a universal container with tamponed formalin (10%), followed by dehydration in alcohol diafarnized in xylol and inclusion in paraffin (60-65°C), which will be stained in hematoxylin-eosin (HE) and GRAM staining.

HE: Histological cuts of 4um will be performed, followed by clearing with xylol for 10 minutes twice, embedding with alcohol under increasing concentrations and stained with hematoxylin for 5 minutes, running water for 5 minutes, eosin for 1 minute and running water for 2 minutes followed by assembly of glass microscope slide with Entellan®.

GRAM: Another slide will be embedded with crystal violet for 1 minute, running water for 5 minutes, eosin for 1 minute and running water for 2 minutes followed by assembly of glass microscope slide with Entellan®.

E - Molecular analysis of pathogens Positive cultures that present aerobic or anaerobic pathogens cultured, will be isolated and stored refrigerated in -80°C freezer for posterior molecular analysis.

Molecular typing was performed through Pulse Field Gel Electrophoresis technique of isolated samples according to the protocol described by Oprica et al.(14) using Spe-I restriction enzyme and Bionumerics software for analysis of results.
STUDY DESIGN

Study Type: Observational

Estimated Enrollment: 108 participants

Intervention Model: N/A

Masking: N/A

Primary Purpose: N/A

Observational Model: Cohort

Time Perspective: Prospective

Official Title: Subclinical Propionibacterium Acnes Infection Estimation in the Intervertebral Disc (SPInE-ID)

Actual Study Start Date: May 2017

Actual Primary Completion Date: August 2019

Actual Study Completion Date: May 2021

GROUPS AND COHORTS

<table>
<thead>
<tr>
<th>Groups/Cohorts</th>
<th>Intervention/treatment</th>
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| Microdiscectomy Patients with lumbar disc herniation who failed conservative treatment undergoing surgical treatment through microdiscectomy. | Other: Microdiscectomy

It will be an observational study without interventions. Subjects with diagnose of lumbar disc herniation undergoing open decompression surgery (microdiscectomy) will be included and analyzed. There will be no direct intervention to the patient proposed by the study.

OUTCOME MEASURES

Primary Outcome Measures: 1. Rate of Intervertebral Disc Infection [Time Frame: through study completion, an average of 1 year]

The main objective of this study considers that the intervertebral disc is infected by any type of low virulence pathogen, which leads to Modic changes and chronic low back pain. Thus, calculation of the incidence of infection in lumbar disc herniations will be performed. 1. Incidence of infection rate (IRR) will be calculated as follows: IRR = (number of detected infections) / (total number of included patients)

Secondary Outcome Measures:

1. Low Back Pain [Time Frame: At time of patient recruitment and 1, 3, 6 and 12 months after surgical procedure]

Intensity of low back pain and limitation for daily activities of patients with and without infection will be analyzed through the Numeric Rating Score (NRS) system applied at time of patient recruitment and 1, 3, 6 and 12 months after surgical procedure. Minimal clinically important difference will be considered as an increase of 30% of baseline lumbar pain at first postoperative month, due to possible bias of postoperative pain due to surgical manipulation as well as pain due to the disc herniation itself.

2. EuroQol-5D - [Time Frame: At timing of patient recruitment, and 1, 3, 6 and 12 months after surgery.]

Quality of life at the end of one year for both infected and uninfected groups, with and without Modic changes, will be analyzed through the validated Portuguese version of the EuroQoL (EQ-5D) questionnaire. This measurement tool will be applied at timing of patient recruitment, and 1, 3, 6 and 12 months after surgery.

3. Function [Time Frame: At time of recruitment and 1, 3, 6 and 12 months after surgery.]

Function will be quantified through the Portuguese version of the Oswestry Disability Index (ODI) for lumbar pain that will be applied at time of recruitment and 1, 3, 6 and 12 months after surgery.

4. Modic incidence [Time Frame: 1 year after surgery]

Insurgent Modic changes in patients will be analyzed one year after surgery, as well as its relationship with presence or absence of infection. Incidence of Modic (IM) changes will be calculated for the infection group (IM infec) and for the total group (IM total) as follows: (number of Modic changes in infected IM infec / patients after 1 year) / (total number of infections) IM total = number of Modic changes at final 1 year follow-up / total number of patients

5. Volume of Modic changes [Time Frame: Preop and 12-month postop acquired MRI studies will be compared.]

Modic volume will be measured according to Wang et al(18). Three sagittal slices of the lumbar spine will be considered: midpedal sagittal slice; left pedicle parasagittal slice; and right pedicle parasagittal slice. The parameters examined to quantify Modic changes will include measures of ratios of the region affected by Modic changes to the entire corresponding vertebral body, including maximal width ratio, maximal height ratio, and area ratio. Vertebral body changes will be classified accordingly to Modic changes type I, II, and III[1,2].

6. Adverse effects [Time Frame: Through study completion, an average of 1 year after inclusion]

Fail of surgical treatment (recurrence, instability, need for reoperation, etc.); need for additional physical therapy sessions; superficial infection; drainage; deep venous thrombosis; and, any other possible adverse event that may show up will be included as well.

7. Imaging analysis of disc degeneration [Time Frame: Preop and 12-month postop acquired MRI studies will be compared.]

Disc degeneration will be collected as: normal; degeneration with height preservation; and, degeneration with loss of height.

Biospecimen Retention:

Samples Without DNA

Lumbar Intervertebral Disc, Flavum ligament, Multifidus muscle

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 to 65 Years (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria
Inclusion Criteria:
Subjects between 18 and 65 years of age; both genders; with diagnose of lumbar disc herniation undergoing open decompression surgery (microdiscectomy). Patients willing and able to go through all phases of clinical investigation and rehabilitation will be included. An Informed Consent Form (ICF) must be signed.

Exclusion Criteria:
Patients with previous lumbar disc surgery at the same level at any point of life; patients undergoing chemotherapy; patients with any immune deficiency; patients previously submitted to disc injection and/or discography; patients submitted to previous endoscopic disc surgery; patients with fusion performed at the same stage of decompression surgery; patients with any other infection within the last six months or usage of antibiotics within the last two months; patients with incomplete specific form or data; decline to participate or sign the ICF.

CONTACTS AND LOCATIONS

Contacts

Locations

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Sponsors and Collaborators

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MORE INFORMATION

Keywords provided by Hospital Israelita Albert Einstein:
infection intervertebral disc Propionibacterium acnes spine

Additional relevant MeSH terms:
Infections Communicable Diseases Hernia
Discitis
Intervertebral Disc Pathological Conditions, Anatomical
Displacement Bone Diseases
Spinal Diseases Musculoskeletal Diseases
Disease Attributes Spondylitis
Pathologic Processes Bone Diseases, Infectious