Quantitative Sensory Testing and PET/CT scanning in assessment of surgical outcome for Lumbar Disc Herniation

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2 Background

Low back pain (LBP), defined as pain and discomfort located below the costal margin and above the inferior gluteal folds, with or without leg pain, is associated with great morbidity and significant socio-economic impact in many parts of the world (1-3). The lifetime prevalence of LBP is reported to be as high as 60-85% and an incidence of 5% per year for adults (1, 4, 5).

The underlying pathophysiologies of LBP are many, diverse and often obscure, including: spinal stenosis, infections, inflammation, tumors, fractures, etc. (6, 7). Intervertebral disc herniation (IDH), more specifically lumbar disc herniation (LDH), is a common cause of LBP, irrespective of whether the disc protrudes into the spinal canal and exerts pressure on the lumbar nerve roots or not (8). It is hypothesized that IDH causes a combination of nerve root ischemia and inflammatory processes leading to neoinnervation and neovascularization, which in turn leads to LBP (8-10).

Studies have shown that most LDH can be treated effectively with conservative management and the passage of time. However for the group of patients where pain and disability is of such magnitude or recovery is unacceptably slow, surgical intervention provides effective clinical relief in many cases (11-13). Despite the immediate and effective relief often provided by surgery, the literature indicates that it has limited superiority over conservative regimes on the long-term outcome of 1-2 years (8, 11, 14, 15). Furthermore, as many as 10-40% of patients report unsatisfactory results of lumbar disc surgery, depending on outcome measures (14, 16, 17).

Due to this relative high number of unsatisfactory operative outcomes, great emphasis should be put on pre-operative investigation and diagnostics in order to find the candidates who will most likely benefit from surgery and simultaneously identify those where other interventions would lead to greater gain. Currently, magnetic resonance imaging (MRI) is considered the imaging procedure of choice for patients suspected of LDH (18-21). However, due to inter-observer variations and the inability to determine the relevance of a pathoanatomical abnormality in relation to clinical symptoms, the need for novel diagnostic tools, in particular imaging, in the selection of operative candidates with IDH remains.

It has been hypothesized that chronic LBP may lead to persistent hyperalgesia (22), which may in turn adversely affect the efficacy of surgery. Several studies have been performed to investigate the nature and extend of hyperalgesia in relation to LBP. The findings have previously been of conflicting character, however more recent research indicate that hyperalgesia is a common finding in chronic LBP, but does not constitute a separate risk factor (22-28). With the increasing availability of functional imaging equipment and novel techniques for monitoring cerebral activity (*f*MRI, PET, SPECT), new diagnostic opportunities may help shed light on the mechanisms leading to chronic pain, subsequent development of generalized hyperalgesia and affecting the outcome of spinal surgery (29).

Unfortunately, structural imaging alone, due to its non-specificity and low sensitivity, is of limited value in this setting. Therefore, there is a dire need for newer approaches that are based on hardcore sciences such as molecular and cellular imaging with PET. The utilization of fMRI-based analysis of pain have been tried and the published data are fairly indefensible, and therefore, new frontiers have to be explored for defining the role of functional imaging in this complicated and disabling source of pain in these patients. Currently there is a lack of data in the literature regarding applications of PET in musculoskeletal disorders, in particular spinal diseases, however previous studies have generated data about the role of PET in assessing the effects of pain in the thalamus (30).

3 Objectives

The objective of this thesis is to investigate whether quantitative sensory testing (QST) of experimental pain responses can predict surgical outcome in patients with LDH.

- Can QST be used to identify patients with a change in pain perception and potential abnormal response to painful stimuli?
- Can QST be used to reflect patients pain perception using self-reported questionnaires on pain?
- Is there a correlation between quantitative sensory testing of experimental pain responses and clinical outcome of surgery in LDH patients assess using standardized questionnaires?

4 Methods

4.1 Design

The experimental study design will be a prospective cohort study in accordance with the STROBE guidelines (31). A pilot-study including 15 male and 15 female participants have been conducted in order to assess the setup of QST and to evaluate if PET/CT were a viable way of identifying pain perception and potentially quantifying it. In accordance with previous protocol, data have now been reviewed and evaluated, leading to a modified setup with QST and a dismissal of PET/CT.

Based on the results gained from the pilot-study, it has been found reasonable to continue with further study participants in the QST-part of the study. Therefore, a continuance of QST measurements will be performed on further 70 patients as stated in detail below.

4.2 Study population

Study subjects will be recruited from patients assessed and found eligible for LDH surgery at Center for Spine Surgery and Research, Middelfart, part of the Department of Orthopedics, Vejle, Sygehus Lillebælt.

4.2.1 Inclusion criteria

- Informed consent
- Clinical and radiological indication for LDH surgery, assessed by an experienced spine surgeon
- Age 18-70 years
- No history of previous spine surgery
- No general contra-indication for spine surgery
- No psychiatric disorders requiring medication within the last 3 months

4.2.2 Exclusion criteria

- Psychiatric disorder that in the opinion of the investigators could impact the patient's ability to successfully complete the trial or otherwise interfere with outcomes
- Current malignant disease
- Current chemotherapy

- History of spinal fracture
- Hematologic disease
- Current pregnancy or breast-feeding (pregnancy-tested prior to inclusion)
- Chronic, generalized connective tissue disorders or chronic, non-specific pain disorders (fibromyalgia, whiplash (WAD I-V), etc.)

4.2.3 Subject withdrawal

- The patient has some other clinically significant medical condition that in the opinion of the investigators could impact the patient's ability to successfully complete the trial or otherwise interfere with outcomes
- The patient has, during the follow-up period, received medication or invasive intervention that in the opinion of the investigators could impact the patient's ability to successfully complete the trial or otherwise interfere with outcomes

4.3 Patient course

Patients identified by the attending surgeon as eligible for inclusion (see in- and exclusion criteria previously mentioned) are invited to participate. Patients who express an interest in participating will be given written and oral information on the purpose, nature and implications of study-participation. Information and inclusion of participants will be conducted in accordance with the guidelines of The Health Research Ethics Committee System in Denmark, from which approval will be sought.

Prior to surgery at the Center for Spine Surgery and Research, Middelfart, study subjects will undergo assessment and quantification of pain sensitivity using a standardized QST battery and pain drawing (figure 1). Patients will also be asked to fill-out multiple questionnaires (basic personal information, EQ-5D, OSWESTRY, SF-36, VAS-leg/-back, etc.) as stated in section 5.1 Data collection.

The standardized QST battery consist of 3 different modalities, covering different measurements of pain perception and multiple types of pain stimulus. Initially patients will undergo a simple Pressure Pain Test (PPT) using an electronic/analog pressure pain algometer at the thenar eminence of the hand and the most painful site of the lumbar area, as previously described (25, 32). Patients are instructed to indicate when pain is felt, Pressure Pain Detection Threshold (PPDT). Pain intensity at 140% of PPDT, the Pain Response (PR) is subsequently rated on a VAS. Immediately following both the thenar and lumbar test, a temporal summation test will also be performed. Using a 51,2g PinPrick stimulator, initially a single stimulus will be given, and the patient asked to rate the pain. Thereafter 10 repetitive stimuli will be given and the patient asked to rate the pain of the last stimulus. Temporal summation can then be calculated as the difference in pain following a single stimulus vs the last in a series of 10.

To test for deep mechanic pain sensitivity, a pneumatic double-chamber cuff will be placed around: (i) the arm and (ii) the leg. Cuff inflation rate will be constant and the pain intensity registered continuously on a visual analogue scale (VAS); thresholds of detection and tolerance will be recorded.

Furthermore, patients will undergo a Cold-Pressor Test (CPT) using a water-tub containing refrigerated water at 0-2°C in which they are to submerge their non-dominant hand to the wrist for 3 minutes. During the CPT, pain response will be monitored using a continuous VAS, controlled by the patient. For individuals who fail to tolerate the entire 3 minutes, time of withdrawal will be recorded. Immediately following the CPT, patients will, once again, be tested using the PPT described above. This is performed to analyze Conditioned Pain Modulation

(CPM) in the central nervous system. Following a short break (approx. 3-5 min.), patients will receive an injection of sterile hypertonic saline at the infraspinatus muscle of the scapula. Once again pain response will be measured using a continuous VAS.

	Pain Detection Threshold	Pain Tolerance Threshold	Pain Response	Continuous Pain Response	Complex Pain Modulation
Mechanical	PPT		PPT		PPT
Thermic		CPT		CPT	CPT
Chemical			NaCl	NaCl	

All patients participating in the study will undergo standard operative treatment, either open or microscopically, at Center for Spine Surgery and Research, Middelfart, and scheduled for an outpatient clinical control with a physiotherapist 4-6 weeks post-operative. The examination, assessment and treatment offered are not affected by study participation.

4.4 Facilities

The staff at Center for Spine Surgery and Research, Middelfart will perform initial consultation, assessment, surgery and post-operative treatment.

The Ph.D.-student will perform the initial recruitment and the standardized QST.

5 Data & Statistics

5.1 Data collection

Clinical Tools	At inclusion and pre-operative	6-weeks ambulatory control	6-month ambulatory control	12-month ambulatory control
EQ-5D	x	x		x
Oswestry Disability Index (ODI)	x			x
SF-36	x			x
Standardized QST	x	x	x	
VAS-leg and VAS-back	x	x	x	x
Pain drawing	x	x	x	x
DaneSpine questionnaire		x		x

5.2 Data handling

Collected data will be processed and stored by the research secretariat at Center for Spine Surgery and Research, Middelfart, using EPI-data and in agreement with the requirements of the Danish Data Protection Agency.

5.3 Statistics

Data will be analyzed according to their type using STATA, i.e.; categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics (mean, standard deviation, number of observations, minimum, median, maximum).

5.3.1 Sample size rationale

Based on the data gathered during the initial pilot-study, reverse power-calculations have been performed on variables showing tendency towards significance in Spearman's Rank Correlation and Pearson's Correlations. Based on these calculations an estimated study group of 70-100 patients is needed to secure substantial data for statistical significance.

6 Quality control and quality assurance

The study will be registered at the Ethical Committee of Southern Denmark and the Danish Data Protection Agency.

All patient data, including information on private matters or other confidential information, will be strictly confidential and stored according to the Danish Open Administration Act, the Danish Act on Processing of Personal Data and the Health Act.

The study will be performed in accordance with the guidelines recommended by STROBE (STrenghtening the Reporting of OBservational studies in Epidemiology).

7 Ethics

This study will be a clinical trial conducted according to Danish ethical principles as well as the Declaration of Helsinki.

We take the patients' rights into account, as participation in the study is completely voluntary and can only take place after receiving both oral and written information about the study. Furthermore, all participants must sign a consent form. At any time during the study, the participants can withdraw their consent orally, in writing or by any other clear notification. If the participant chooses to withdraw the consent it will not affect the right to any current or future treatment.

The participants are entitled to bring a member of the family or friend to the informative interview and will be given 24 hours to consider participation before signing the consent form. The Informed Consent form will be signed by all participating patients and stored at the Center for Spine Surgery and Research, Middelfart.

According to the Danish Open Administration Act the participants are entitled to access the research protocols and documents concerning the patient's own participation in the study. This opportunity is available for two years after completion of the study.

The patients have the right to complain and apply for compensation according to the Act on the Right to Complain and Receive Compensation within the Health Service.

The potential clinical relevance of identifying patients with LDH who will not benefit from surgery, would in a combined socio-economical perspective save both society and the individual patient and therefore the exposure of the patients to inflicted pain is found to be justifiable.

8 Finance

Salary and tuition fees for the Ph.D. student are funded by the following sources:

1. One year scholarship from the Faculty of Health Sciences, University of Southern Denmark
2. One year scholarship from Sygehus Lillebælts research committee
3. One year scholarship from IMK Almene Fond

Costs with relation to consultations, operations, admission, data gathering and radiological examinations will be covered by the Center for Spine Surgery and Research, Middelfart.

9 Publication policy

It is the intention to publish the results, whether positive or negative, in relevant international high impact journals. Rules for authorship are as stated in 'Uniform requirements for manuscripts submitted to biomedical journals' at http://www.icmje.org. Generally, first author is the person who supervises the conductance of the respective part of the project, writes the first draft of the manuscript and finishes it for submission. In case of disagreement, project plenum has the final decision.

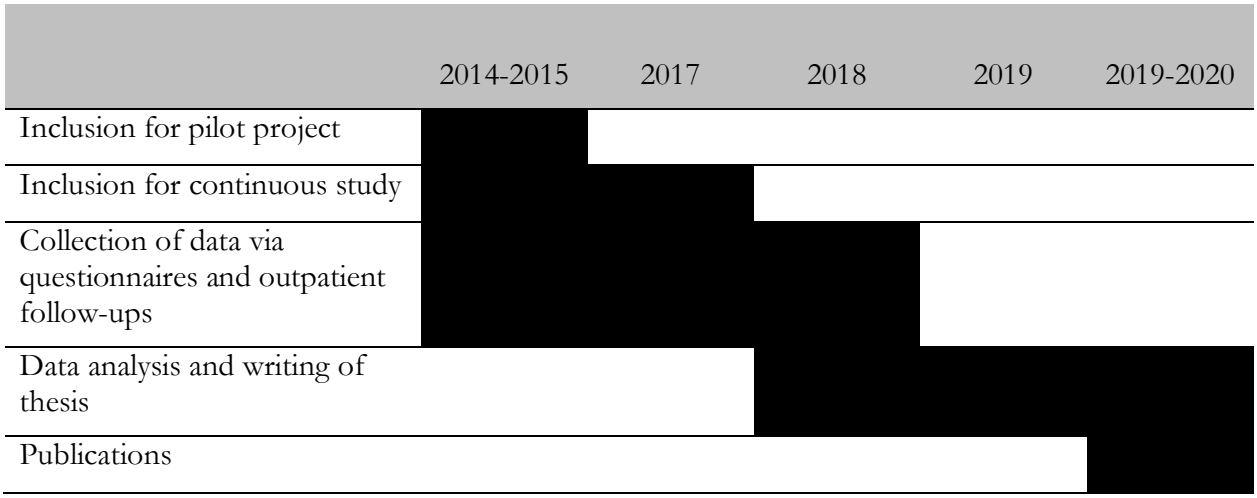
10 Time Schedule

The general set-up at the Center for Spine Surgery and Research is well established and can start including patients immediately after permission is obtained from the local ethical committee.

Marts 2017 – November 2017 – Inclusion and operation of patients

November 2017 – November 2018 – 1-year post-operative follow-up and QST data collection (1 year leave for the completion an introductory position in orthopedic surgery for the Ph.D.-student)

November 2018 – November 2019 – Data processing, statistical analysis, manuscript production and completion of the Ph.D.-thesis



11 Organization and staff

Center for Spine Surgery and Research, Middelfart, Sygehus Lillebælt

- Mikkel Østerheden Andersen, MD, Associate Professor, Senior Surgeon (Principal Supervisor)
- Rikke Rousing, MD, Ph.D. (Co-supervisor)
- Christian Støttrup, MD, Ph.D.-student (Project Manager)

Spine Center of Southern Denmark, Middelfart, Sygehus Lillebælt

- Søren O'Neill, DC, Associate Professor, Ph.D. (Co-supervisor)

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