Uppsala Spinal Stenosis Study (UppSten)

Decompression vs Non-surgical treatment for the lumbar spinal stenosis. An RCT with clinical, radiological, neurophysiological, histologic and biochemical follow-up

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Background

Lumbar spinal stenosis (LSS) is characterized by low back and leg pain, walking disturbances and sometimes instability, impaired balance and numbness of the lower limbs. This condition is caused by degenerative changes in the lumbar spine including bulging discs, osteophytes from the arthritic facet joints and thickened ligamentum flavum which together cause narrowing of the spinal canal and thus affect the lumbar nerve roots. LSS affects mainly older populations and is unusual under 50 years old. This diagnosis is attracting more and more interest due to the aging population with increasing demands for physical activity. LSS is the most common indication for spinal surgery. The surgical treatment involves relieving the pressure from the nerve structures in the stenotic segments through a posterior approach. The hypertrophic ligaments and parts of the facet joints are removed (i.e., decompression). Adding fusion to the decompression for stabilization of the decompressed segment has not been shown to provide superior results than decompression alone [Försth] [Sigmundsson]. In several studies, surgery has been shown to have better results than the conservative treatment [Weinstein] [Malmivaara]. However, methodological difficulties and a large proportion of cross-over in these studies indicate that there is still uncertainty about whether surgery is generally a better option.

After decompression, only 60-70% of patients reported to be satisfied with the result and a minor proportion of them experienced even no improvement at all [Strömqvist]. Conservative treatment has shown in some studies to have good results for some patient groups [Delitto] and other studies have shown that the benefit of the surgical treatment decreases over time [Slätis] and that physical exercise may reduce the need for surgery [Nord]. Moreover, surgery itself has a positive placebo effect that can improve symptoms in some diseases [Harris].

It has been speculated whether the compression of the nerve roots causes in some patients permanent nerve damage with muscle denervation, while in other cases a reinnervation and recovery of the function may occur. Results from neurography and EMG studies have been shown these modalities to have a possible predictive value for the natural process of LSS [Adamova]. If a neurophysiological examination could be able to predict which patients are able to benefit from surgery, many patients could avoid surgery and the risks involved in it.

The degeneration of the lumbar spine is progressively impairing the spinal sagittal balance. The need to make extensive correction and fusion in addition to the decompression in order to restore the sagittal balance is debated among spinal surgeons. The experience gained from previous RCTs is that the patients' back pain is reduced by decompression only [Försth]. Many patients also report that their posture improved after decompression alone.

Previous trials in the connective tissue and blood samples have shown that proinflammatory factors and nociceptors (molecules that induce pain) are upregulated in patients with patellar tendinosis which is an inflammatory condition [Lian] [Schizas] [Schizas]. Changes in the connective tissue that cause LSS are mainly inflammatory (arthritic facet joints and ligamentum flavum) and a possible theory around LSS pathophysiology may be that the nerves are biologically affected by proinflammatory factors and nociceptors. Identification of some of these factors could lead to better explanation of the pathomechanism behind the nerve compression in LSS and to the development of future pharmacological treatments to be used in conjunction with surgery.

Aims

The aim of this study is primarily to evaluate whether surgery with decompression leads to superior results than the non-surgical treatment with structured physical therapy. For this evaluation, the Oswestry Disability Index (ODI) will be used.

The main secondary aim is to investigate by means of Neurography and EMG, whether the degree of neurological affection caused by nerve compression affects the outcome of surgery for LSS.

The questions at issue are:

1. Does decompression provide a better clinical outcome than the non-surgical treatment?
2. Is there any correlation between the grade of the clinical symptoms and the degree of neurological affection measured by ENG/EMG?
3. Is there any connection between the neurological affection and the proinflammatory markers/nociceptors in the blood as well as in histological findings from ligamentum flavum? Are these correlated with the grade of the clinical symptoms?
4. Does decompression provide superior neurological recovery, measured by ENG/EMG, in comparison to the non-surgical treatment?
5. Can decompression improve the spinal sagittal balance?

Inclusion criteria

1. Age 50-85 years.
2. Clinical symptoms of lumbar spinal stenosis (pseudoclaudication) that indicate and motivate surgery. NRS in lower limbs ≥3.
3. MRI with finding of LSS at 1-3 lumbar levels. Dural sac area ≤ 75 mm² or degree of stenosis C or D according to Schizas classification.
4. The surgical treatment to be provided is decompression alone.
5. The patient has given oral and written informed consent to the participation in the study.

Exclusion criteria

1. Degenerative deformity with Cobb angle > 20°.
2. Spondylolysis.
3. Symptomatic osteoarthritis of the lower limbs that affects and limits their function.
4. Arterial insufficiency (claudication intermittent).
5. Past lumbar surgery other than disc herniation.
6. Conditions that affect the spine such as ankylosing spondylitis, Diffuse Idiopathic Skeletal Hyperostosis (DISH), spondylodiscitis/infections, malignancy, neurological diseases.
7. Heart and lung diseases that present a significant risk for surgery or make it impossible for the patient to take part in physical training program (ASA>3).
8. Polyneuropathies.
9. Psychological factors that make the patient incapable of inclusion in the study (eg drug addiction, dementia)

Outcomes

Primary outcome: Oswestry Disability Index (ODI)

Secondary outcome:
Neurophysiology: Primary outcome measure: 1) Motor amplitude (neurography) and 2) Degree of Denervation Activity (EMG). Secondary outcomes: Sensory amplitude, F response latency and H-reflex (neurography), number of motor units (MUNIX) and degree of reinnervation (EMG).

From the Swedish Spine Registry (Swespine): EQ-5D, Back pain (NRS), Leg pain (NRS), Subjective walking ability, Global Assessment (GA), Satisfaction

Objective walking ability (6-Minute Walk Test-6MWT)
Radiological: Lumbar Lordosis (LL) and Sagittal Vertebral Axis (SVA)

Follow-up

6 months, 1, 2 and 5 years

The results at 2 years will be the most important goal of the study, on which the main clinical results will be built. The neurophysiological results can be analyzed and presented after the 6-month follow up.

Power calculation

Totally 150 patients will be included, 75 in each treatment group. The study size has been calculated with power 80% and alpha = 0.05 as well as an ability to detect 12 units (SD19) of difference in the ODI, giving 40 follow-up patients in each group. Experience from previous registry-based RCTs within Swespine, regarding loss to follow-up and cross-over (ie patients admitted to non-surgical treatment who wish to switch to surgical intervention), is taken into account. According to this, the loss is considered to be low (<5% after 2 years) [Försth]. In previous studies, this proportion was comprised of 9 to 40% of the conservatively treated patients [Weinstein] [Malmivaara]. Loss to follow-up and cross-over are estimated to be up to 50%, which leads to 75 patients needed in each group.

Each year, 100-130 patients who meet the inclusion criteria are operated at the Department of Orthopaedics (Uppsala University Hospital and + Enköping Hospital). We estimate that 150 patients will be recruited to the study within a period of 24 months.

Flow-chart

Recruitment	The patient is recruited during an outpatient visit to a surgeon. Oral and written information about the study is given.
ICF	The patient gives oral and written consent. The consent is documented in the patient journal and the written consent is filed in the study document binder.
Baseline data	- PROMs via Swespine Study - 6MWT

	- Scoliosis standing digital X-rays (AP and lateral views) - ENG/EMG - Blood samples for analysis of inflammatory markers (OLINK)
Randomization	Simple block randomization to the two treatment arms.
Treatment arms	A. **Decompression.** Central decompression of the stenotic segments with undercutting of the lateral recesses, free mobilization, and routine follow-up postoperatively by physiotherapist. B. **Non-surgical treatment.** Exercise on exercise bike according to the "Östersund model" [Nord] 30 min, 3 times/week for 4 months.
Follow-up 6 months	- PROMs via Swespine Study - 6MWT - Scoliosis standing digital X-rays (AP and lateral views) - ENG/EMG - Blood samples for analysis of inflammatory markers (OLINK)
Cross-over	Feasibility for cross-over from group B till A after 6-month follow-up.
Follow-up 1,2 years	- PROMs via Swespine Study - 6MWT
Follow -up 5 years	- PROMs via Swespine Study

In the treatment group A, in conjunction with the surgical procedure, ligamentum flavum will be collected (which is routinely removed during the decompression surgery) and will be examined with histological methods regarding proinflammatory markers and nociceptors. An 1x1 cm tissue piece will be dissected and saved. The ligament samples will be examined by immunohistochemistry and with proteomics analysis. Proteomics analysis will be performed in collaboration with Olink Uppsala (www.olink.com) where 92 inflammation-related factors will be investigated. Sample management will be in accordance with the Ethics Examination Act of Human Research (2003: 460) and according to the rules of Uppsala Biobank.

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