

BMJ Open Study protocol for a randomised controlled trial with clinical, neurophysiological, laboratory and radiological outcome for surgical versus non-surgical treatment for lumbar spinal stenosis: the Uppsala Spinal Stenosis Trial (UppSten)

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ABSTRACT

Introduction Symptomatic lumbar spinal stenosis is the most common indication for spinal surgery. However, more than one-third of the patients undergoing surgery for lumbar stenosis report dissatisfaction with the results. On the other hand, conservative treatment has shown positive results in some cases. This trial will compare the outcomes of surgical versus non-surgical treatment for lumbar stenosis. The study includes a multidimensional follow-up, aiming to study the association between outcome and other studied parameters, mainly electromyography and nerve conduction. Moreover, it may contribute to a better understanding of the pathophysiology of lumbar stenosis and to the development of future pharmacological treatments.

Methods and analysis UppSten is a single-centre randomised controlled trial in which 150 patients with symptomatic lumbar spinal stenosis will be randomised into one of two treatment arms. The patients in the surgical arm will undergo laminectomy; the patients in the non-surgical arm will be given a structured physical training programme. The primary outcome of the study will be the Oswestry Disability Index. Secondary outcomes will include motor amplitude and degree of denervation activity obtained by means of nerve conduction studies and electromyography. Patient-reported outcome measures will be also used as secondary outcomes. Blood sample analysis and the investigation of potential inflammation markers are the additional secondary outcome parameters. Laboratory evaluation will include blood sample collection before the treatment initiation and after 6 months. Flavum ligament biopsies will be performed in the surgical group. Finally, tertiary outcomes will include neurophysiological measures, the objective walking ability and radiological evaluation.

Ethics and dissemination The study is approved by the Local Ethics Committee (Dnr 2017–506), the Hospital's Clinical Trials Committee (2018–0001) and the National Biobank Council and Uppsala Biobank (BbA-827-2018-

Strengths and limitations of this study

- To our knowledge, we plan the first randomised controlled trial comparing surgical and non-surgical treatment for lumbar spinal stenosis that aims to evaluate different clinical dimensions based on clinical, radiological, neurophysiological and laboratory measurement.
- If a neurophysiological examination could predict which patients might benefit from surgery, many patients could potentially avoid surgery and the associated risks.
- Identification of inflammation factors could lead to the development of future pharmacological treatments.
- If non-surgical therapy proves less effective than surgical treatment, there is a risk for crossover.

025). The results will be presented in peer-reviewed journals and at international conferences.

Trial registration number NCT03495661

BACKGROUND

Lumbar spinal stenosis (LSS) is characterised by low back and leg pain, walking disturbances and in some cases 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 flavum ligament (FL), which concertedly cause a narrowing of the spinal canal and compression of lumbar nerve roots.^{1–3} LSS mainly affects populations aged >65 years and is unusual in people <50 years.⁴ LSS is attracting increasing interest given that

the world's population is ageing rapidly and increasing demands for physical activity. Today, LSS is the most common indication for spinal surgery among a geriatric population.^{5–7} The goal of surgical treatment in LSS is to decompress the nerve structures in the stenotic segments through a posterior approach. The hypertrophic ligaments and parts of the facet joints are removed (ie, decompression). Adding spinal fusion for stabilisation of the decompressed segment has not been shown to provide superior results compared with decompression alone.^{8–10} Weinstein *et al* performed a study with 289 patients randomised to either surgical or non-surgical treatment. The authors found that at a 6-month follow-up, the cross-over percentage was up to 36% and at 1 and 2-year follow-ups, it was more than 40%.¹¹ In contrast, Slätis *et al*, who randomised 94 patients to surgical and non-surgical procedures, had a lower cross-over percentage but the difference between the two groups decreased significantly over time and at 6 years there was almost no difference.¹² Thus, methodological difficulties and the substantial proportion of cross-over effects in the past studies suggest that there is still uncertainty about whether surgery is the most effective treatment approach.

In one study, only 60%–70% of the patients reported to be satisfied with the result after decompression and a few experienced no improvement.¹³ Atlas *et al* compared surgical and non-surgical treatment for LSS and found similar outcomes between groups at 10 years.¹⁴ Furthermore, several studies have reported beneficial results for conservative treatment in selected patient groups.¹⁵ Other studies indicate that any benefits of surgical treatment decrease over time^{12 16} and that regular physical exercise may reduce the need for surgery in LSS.¹⁷ Moreover, surgery, at least in the short term, has substantial positive placebo effects that can improve symptoms in some diseases.¹⁸

Results from nerve conduction studies (NCSs) and electromyography studies (EMG) have shown that these modalities could have a possible predictive value for the natural course of LSS.¹⁹ If a neurophysiological examination could predict which patients might benefit from surgery, many patients could potentially avoid surgery and the risks, which would introduce the potential for a personalised medical approach in the treatment of LSS.

Previous trials investigating connective tissue and blood samples have shown that inflammation markers and nociceptors are upregulated in patients with patellar tendinitis, which is an inflammatory condition.^{20–22} Changes in the connective tissue that cause LSS are mainly inflammatory and involve the arthritic facet joints and the FL.²³ A feasible theory of the pathophysiology of disability and pain related to LSS may involve biological affection of the nerves as a function of inflammatory factors and nociceptors. Identification of some of these factors could lead to a more unifying picture of the pathomechanism underlying nerve compression in LSS and to the development of future pharmacological treatments to be used instead of or in combination with surgery.

Aims

The null hypothesis is that surgical and non-surgical treatment will be equally effective for patients diagnosed with LSS.

Thus, the primary aim of this study is to evaluate whether surgery with decompression leads to superior results when compared with non-surgical treatment with structured physical therapy. For this evaluation, the Oswestry Disability Index (ODI)²⁴ will be used.

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

The questions at issue are these:

1. Does decompression provide a better clinical outcome than non-surgical treatment?
2. Is there a correlation between grade of the clinical symptoms and severity of neurological affection as measured by NCSs/EMG?
3. Are there any connections between neurological deficits and inflammation markers and nociceptors in the blood as well as in immunohistochemical findings from FL? Are these correlated with grade of the clinical symptoms?
4. Does decompression provide superior neurological recovery, as measured by NCSs/EMG, in comparison with non-surgical treatment?
5. Can decompression improve the sagittal balance of the spine?

METHODS

Trial design

The Uppsala Spinal Stenosis Trial is a single-centre randomised, controlled clinical trial. All patients participating in the study will be treated at the Uppsala University Hospital. The trial was designed according to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.²⁵ A flow chart of the trial is displayed in figure 1.

Sample size calculation

In all, 150 patients will be included (75 in each treatment arm). We need 40 follow-up patients in each group at a power of 80%, a two-sided alpha of 0.05 and an ability to detect 12 units (SD19) of difference in the ODI. We chose a difference of 12 according to our experience from our previous randomised controlled trials (RCT) within the same setting and since a decrease in the ODI score of 15 had been suggested by the Food and Drug Administration in order to indicate minimally important improvement after spinal fusion surgery.^{9 26} An SD of 18 units was shown in our prior RCT and we, therefore, chose a slightly higher value (SD 19) in the planning of our new study.⁹ Moreover, experience from previous registry-based RCTs within the Swedish Spine Register (Swespine) regarding lost to follow-up and crossover (ie, patients admitted to non-surgical treatment who wish to switch to

UppSten Trial

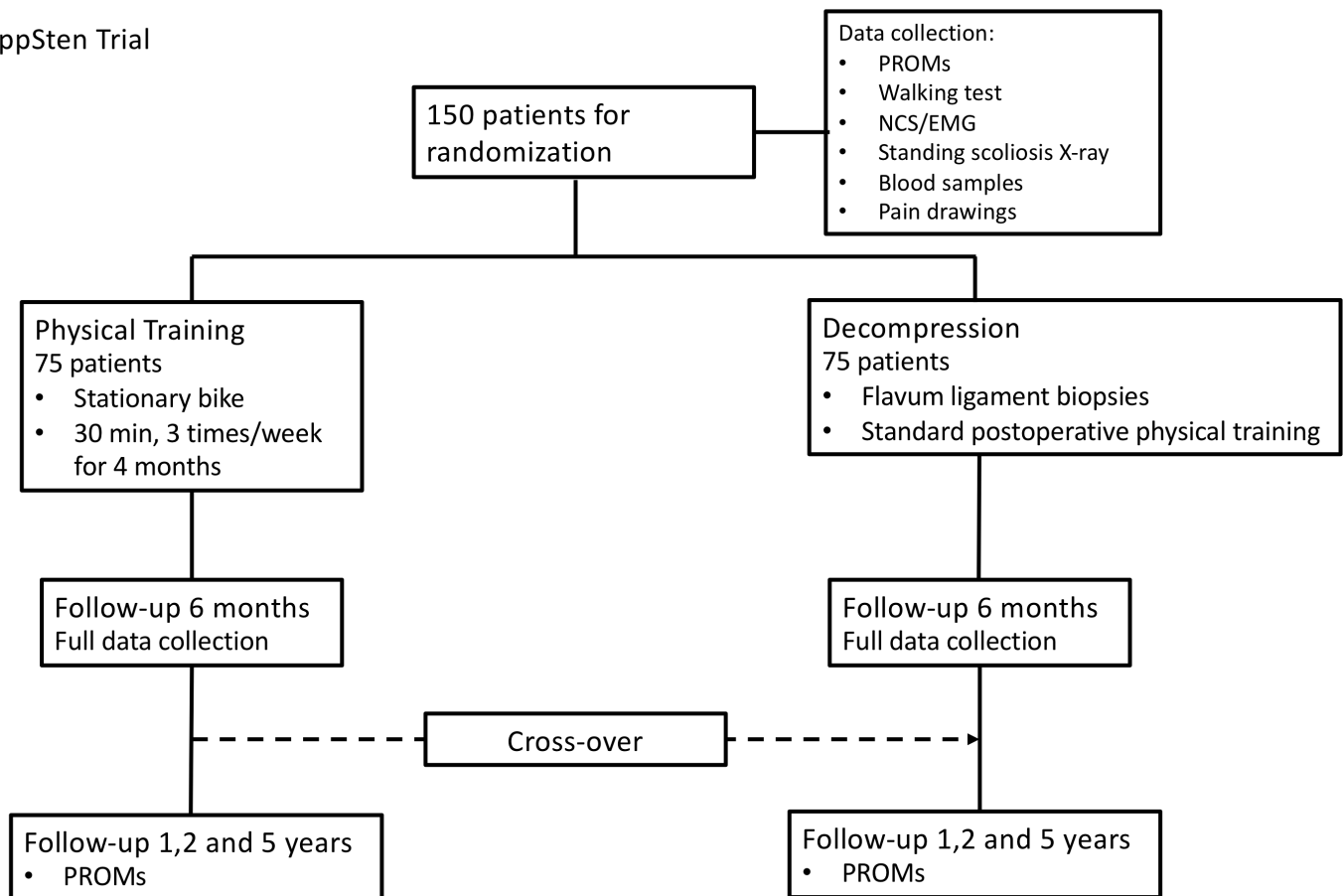


Figure 1 Flow chart of the UppSten trial. EMG, electromyography; NCS, nerve conduction study; PROM, Patient-Reported Outcome Measures.

surgical intervention) is considered. Lost to follow-up is low (<5% after 2 years).⁸ In previous studies, the proportion of patients who crossed over from their treatment assignment varied between 9% and 40%.^{11 16} Lost to follow-up and crossover is estimated to be up to 45% in our study, which means that 75 patients are needed in each group. An interim analysis will be performed when 100 patients have passed the 6-month follow-up in order to decide if an extended inclusion would be needed due to high crossover. Each year, 100–130 patients, who meet the inclusion criteria, are operated at the Department of Orthopaedics, Uppsala University Hospital. We estimate that 150 patients will be recruited to the study within a period of 24 months.

Statistics

The t-test will be used to compare the groups for normally distributed variables and logarithmic transformations will be used for non-normally distributed variables. However, in some instances where the transformation may not assure normality, or the outcome is for instance of an ordinal nature, the Mann-Whitney U test will be needed. For variables that are measured both at baseline and at follow-up, analysis of covariance will be used. The primary outcome will be analysed according to the principle of intention-to-treat and to as-treated analysis.

Linear regression models and logistic regression will be used to determine the level of association between clinical grade and neurophysiological parameters. Finally, a mixed-model analysis will be used in order to deal with missing data.

Patients

A senior orthopaedic spine surgeon will assess the eligibility of all patients aged 50–85 years who are referred to the Department of Orthopaedics at Uppsala University Hospital for LSS. The patients should have a minimum duration of symptoms of 3 months. Inclusion and exclusion criteria are listed in [box 1](#). The patients who are eligible but not included in the trial will be registered and accounted for as well. If the inclusion criteria are met and after oral and written consent (online supplementary appendix 1), the patients will be randomised into one of the two treatment (surgical or non-surgical) arms.

Inclusion and randomisation

The participants will be allocated to either arm of the trial using a permuted block randomisation procedure of variable block sizes. The process will be performed by the internet-based randomisation software WebCRF (AKF, Faculty of Medicine and Health Sciences, PO Box 8905 MTFS, NO-7491 Trondheim, Norway). After inclusion,

Box 1 Inclusion and exclusion criteria**Inclusion criteria**

1. Age 50–85 years.
2. Clinical symptoms of lumbar spinal stenosis (pseudoclaudication) indicating and motivating surgery. Numeric Rating Scale in lower limbs ≥ 3 .
3. MRI with finding of lumbar spinal stenosis at 1–3 lumbar levels. Dural sac area $\leq 75 \text{ mm}^2$ or degree of stenosis C or D according to Schizas's classification.³⁴
4. The surgical treatment to be provided is decompression alone.
5. The patient has given oral and written informed consent to participate.

Exclusion criteria

1. Degenerative deformity with Cobb angle $>20^\circ$.
2. Spondylolysis.
3. Symptomatic osteoarthritis in the lower limbs that affects and limits the patient's function.
4. Arterial insufficiency (claudication intermittent).
5. Former lumbar surgery other than disc hernia.
6. Conditions that affect the spine, such as ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, spondylodiscitis/infections, malignancy and neurological diseases.
7. Heart and lung diseases presenting a significant risk for surgery or making it impossible for the patient to take part in a physical training programme (American Society of Anesthesiologists (ASA) score >3).
8. Polyneuropathies.
9. Psychological factors rendering the patient incapable of inclusion in the trial (eg, drug addiction, dementia).

each participant will receive a code consisting of a letter and a number. The letter indicates the group to which the participant has been assigned and the number corresponds to the allocated ranking within the group. All participant-related documents will be marked with this code. The principal investigator will be responsible for the coding and tagging of the data.

Documentation and data safety

All healthcare contacts will be documented in accordance with the Department of Orthopaedics, Uppsala University Hospital routine procedures. These documents, together with the identity list and the completed forms, will be stored in folders that will be kept in a locked room with access limited to authorised persons. Research officers ensure that all variables from the completed forms are continuously entered into a database. All data management is done in accordance with the General Data Protection Regulation and Good Clinical Practice.

Once the trial is completed, all material belonging to the study will be stored at the clinic for 1 year and then archived for 25 years according to the department's guidelines for the storage of research material.

Treatment arms

Group A: Surgery with decompression. Central decompression of the stenotic segment with undercutting of the lateral recesses. The intervention is done through a 3–4 cm skin incision for one-level, 4–5 cm for two-level

and 6–7 cm for three-level stenosis. The procedure is done under magnification according to the surgeon's own preference (loupes or microscope). After surgery, free mobilisation is allowed. The follow-up includes instructions for physical training and visits to physiotherapist for regular postoperative training with start 4 weeks after surgery.

Group B: Non-surgical treatment with structured physical training programme, that is, solely static bicycle training according to the 'Östersund model'¹⁷ (30 min, 3 times/week for 4 months).

In group A, in conjunction with the surgical procedure, FL will be collected (which is routinely removed during decompression surgery). The ligaments will be examined with immunohistochemical methods for inflammation markers and nociceptors.

Baseline data

The baseline data that will be collected will include data from demographic and comorbidity variables. Generic and specific outcome measures will be collected from the Swespine. The outcome measures that will be used are the ODI, the EuroQol Five-Dimensional descriptive system questionnaire (EQ-5D),²⁷ the Numeric Rating Scale (NRS)²⁸ for low back and leg pain, the subjective walking ability tool, the global assessment (GA) instrument^{29 30} and the patient satisfaction (PS) questionnaire. The latter two are assessment tools of the Swespine.^{6 13 30}

Pain drawings, assessment of anxiety using the Hospital Anxiety and Depression Scale³¹ and evaluation of walking ability using the 6 min walking test (6MWT) will be performed.³² In addition, radiological (standing scoliosis plain X-rays), laboratory (blood samples) and neurophysiological measurements (NCSs/EMG) will be assessed in both groups. FL will be evaluated only in the surgical group.

Crossover

At the 6-month follow-up, there is a possibility of crossover from group B to group A. After crossover to surgery, the after-treatment of these patients will be as in group A.

Radiological evaluation

The radiological evaluation of the lumbar lordosis (LL) and the sagittal vertical axis (SVA) will be performed by an orthopaedic spine surgeon with more than 5 years of experience in spine surgery. LL will be measured by the Cobb angle between the superior endplate of L1 and the S1 plateau. SVA will be calculated as the distance from the posterior–superior angle of the S1 to a vertical plumb line dropped from the C7 centroid.

Laboratory evaluation

Blood samples will be collected from all patients before treatment and at the 6-month follow-up. In the surgical treatment group (group A), an 1×1 cm sample of FL will be dissected and collected from each patient. If the stenosis involves more than one level, the ligament will be collected from the most stenotic segment according to MRI data. If it is not possible to distinguish which level

is most stenotic, the ligament will be chosen at random. The ligament samples will be examined by immunohistochemistry and proteomic analysis while blood samples will be assessed by proteomic analysis. Immunohistochemistry will be performed at the Orthopaedic laboratory, Uppsala University, Uppsala, Sweden. Proteomic analysis will be performed in collaboration with OLINK proteomics, Uppsala Science Park, Uppsala, Sweden (www.olink.com) according to a predetermined inflammation factor panel consisting of 92 proteins. The panel will include inflammation-related biomarkers such as interleukin-1 alpha (IL-1 α), IL-1 beta, IL-1 receptor antagonist, tumour necrosis factor alpha and nociceptors such as glutamate, N-methyl-D-aspartate receptor 1 and substance-P. The exact composition of the panel will be decided on after the enrolment of all patients because at that time point relevant and newly established factors might be of interest (<https://www.olink.com/products/inflammation>).

The samples will be coded numerically to maintain confidentiality and stored safely and only authorised personnel will have access to the safety room's key code. Sample management will be in accordance with the Ethics Examination Act of Human Research (2003:460) and the rules of the Uppsala Biobank.

Outcomes

Primary outcome

Oswestry Disability Index

Secondary outcome

1. Neurophysiology: motor nerve amplitude (NCSs) and degree of denervation activity (EMG).
2. From Swespine: EQ-5D, back pain (NRS), leg pain (NRS), subjective walking ability, GA and PS.

Tertiary outcome

1. Neurophysiology: sensory nerve amplitude, F-response latency and H-reflex (NCSs), number of motor units (MUNIX) and degree of reinnervation (EMG).
2. Objective walking ability (6MWT).
3. Radiological: LL and SVA.

FOLLOW-UP

Six months, 1, 2 and 5 years

The results at the 2-year follow-up are of main concern for the goal of the study and hence on which the main clinical results will be built. The neurophysiological results will be analysed and presented after the 6-month follow-up. During the follow-up, adverse events (AEs) and serious AEs (SAEs) will be documented for both treatment arms. SAEs are defined as life-threatening events or events that result in death or require hospitalisation or result in significant disability.³³

Patient and public involvement

Patients and public were not involved in the design, recruitment and conduction of this study.

Dissemination

The study, regardless of the outcomes, will be submitted for publication in a peer-reviewed journal. Moreover,

the preliminary and final findings will be presented at national and international spinal conferences.

DISCUSSION

The UppSten study is an RCT with three categories of outcome: primary, secondary and tertiary. To our knowledge, it is the first RCT comparing surgical and non-surgical treatment for LSS that incorporates clinical, neurophysiological, laboratory and radiological evaluation.

The goal of the trial is to study the clinical results of surgical versus non-surgical treatment for LSS. The patients randomised to the surgical arm will undergo a decompressive central laminectomy with undercutting of the lateral recesses.

All patients randomised to the non-surgical arm will undergo a structured physical training programme based on static bicycle training.¹⁷

One of the secondary aims of the UppSten trial is to examine whether the neurophysiological evaluations (NCSs/EMG) reveal any correlation with the grade of LSS symptoms. Up to now, the standard treatment for patients with symptomatic clinical and radiological spinal stenosis and a duration of symptoms more than 3 months has been surgical decompression. However, it has been speculated whether the compression of the nerve roots causes permanent nerve damage with muscle denervation in some patients, whereas in other patients a reinnervation and recovery of the function may occur.

The degeneration of the lumbar spine progressively impairs spinal sagittal balance. The need to implement extensive corrections and fusion in addition to the decompression to restore sagittal balance continues to be debated among spinal surgeons. The knowledge gained from past RCTs is that patient back pain is reduced by decompression only.^{8,9} Moreover, according to our experience, many patients report that their posture improved after decompression alone. Thus, the radiological examination intends to help us understand whether decompression surgery can improve the sagittal balance of the spine.

We believe that the UppSten trial will provide useful information about the long-term effects of the two treatment arms for LSS. In addition, the study will examine results from neurophysiological, radiological and immunohistochemical assessments that should help spinal surgeons gain a fuller understanding of the pathophysiology of LSS and formulate more accurate predictions as to which patients have better chances of benefiting from surgery. Up to now (March 2019), 51 patients have been included in the trial.

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Contributors KP and PF wrote the protocol KP, PF and AP designed the study. KP, PF, AP, NS, BS and KM critically reviewed the manuscript.

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Competing interests KP reports grants from Johnson & Johnson, during the conduct of the study.

Patient consent for publication Written patient consent will be obtained from all patients in the trial.

Ethics approval This trial has been approved by the Local Ethics Committee (Dnr 2017–506), the Hospital's Clinical Trials Committee (2018–0001) and the National Biobank Council and Uppsala Biobank (BbA-827-2018-025). UppSten will be conducted in full compliance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

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