Comparative Effectiveness of Microdecompression and Laminectomy for Central Lumbar Spinal Stenosis – An Observational Study

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Study Protocol:
Comparative Effectiveness of Microdecompression and Laminectomy for Central Lumbar Spinal Stenosis – An Observational Study

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Abstract

Introduction: This observational study is designed to test the equivalence between the clinical effectiveness of microdecompression and laminectomy in the surgical treatment of central lumbar spinal stenosis. Lumbar spinal stenosis is the most frequent indication for spinal surgery in the elderly, and as the oldest segment of the population continues to grow its prevalence is likely to increase. However, data on surgical outcomes are limited. Open or wide decompressive laminectomy, often combined with medial facetectomy and foraminotomy, was formerly the standard treatment. In recent years a growing tendency towards less invasive decompressive procedures has emerged. Many spine surgeons today perform microdecompression for central lumbar spinal stenosis.

Methods and analysis: Prospectively registered treatment and outcome data are obtained from the Norwegian Registry for Spine Surgery (NORspine). The primary outcome measure is change in Oswestry Disability Index between baseline and 12-months follow-up. Secondary outcome measures are changes in health-related quality of life measured by the Euro-Qol-5D between baseline and 12-months follow-up, perioperative complications, and duration of surgical procedures and length of hospital stay.

Ethics and dissemination: The study has been evaluated and approved by the regional committee for medical research in central Norway and all participants provided written informed consent. The findings of this trial will be disseminated through peer-reviewed publications.

Trial registration: Clinicaltrials.gov (NCT02006901)

Strengths and limitations of this study

- The main limitation of this study is that analyses are not based on randomized treatment assignments.
- Another potential weakness of the present study is the expected loss to follow-up of approximately 22%.
- The results are strengthened by the use of specific inclusion and exclusion criteria, the large sample size, and the reevaluation of the preoperative diagnostic imaging.

Background

Lumbar spinal stenosis most often results from a gradual, degenerative aging process. It is the most frequent indication for spinal surgery in the elderly, and as the oldest segment of the population continues to grow its prevalence is likely to increase[1-3]. Management of spinal stenosis can be challenging and requires the integration of patients' symptoms, clinical findings and diagnostic imaging. There is growing evidence that decompressive surgery offers an advantage over non-surgical management for selected patients with persistent severe symptoms[4-8]. Today it is generally accepted that surgery is indicated if conservative or non-surgical management fails. Improvement in radiating pain, neurogenic claudication, functional status and quality of life are the main treatment goals. Open or wide decompressive laminectomy, often combined with medial facetectomy and foraminotomy, was formerly the standard treatment[3]. However, in recent years a growing tendency towards less invasive decompressive procedures has emerged. In a study from 2005, unilateral microdecompression for bilateral decompression and bilateral microdecompression were shown to be promising treatment alternatives when compared to open decompressive laminectomy[9]. Since then unilateral microdecompression and bilateral microdecompression have been adopted by many spine surgeons, and as is the case in Norway, more frequently among neurosurgeons than orthopedic surgeons. However, there is still a need to evaluate the benefits and risks of different decompressive surgical procedures for lumbar spinal stenosis.

Aims of the study

The primary aim of this observational study is to test the equivalence of changes in functional outcomes measured with the Oswestry disability index (ODI) between baseline and 12-months follow-up after decompressive laminectomy and

microdecompression with unilateral or bilateral approach in patients with single and two-level central lumbar spinal stenosis using data from the Norwegian Registry for Spine Surgery (NORspine). Secondary outcome measures are changes in health-related quality of life (HRQL) measured with the Euro-Qol-5D (EQ-5D) between baseline and 12-months follow-up, perioperative complications, duration of surgical procedures and length of hospital stays.

Patients and methods

Study population

Data for this cohort study will be collected through the Norwegian Registry for Spine Surgery (NORspine), which was established in 2006 and is a comprehensive clinical registry for quality control and research. Participation in the registration by either providers or patients is not mandated, nor is participation required as a necessary condition for a patient to gain access to health care or for a provider to be eligible for payment for the health care service. Follow-up time from the date of the operation (baseline) in this study is 12 months.

Inclusion criteria

1. Diagnosis of central lumbar spinal stenosis
2. Operation in ≤2 lumbar levels with either open decompressive laminectomy, bilateral microdecompression or unilateral microdecompression for bilateral decompression in the time period between October 2006 and December 2011
3. Included in the NORspine registry

Exclusion criteria

1. History of lumbar fusion
2. Previous surgery in the lumbar spine
3. Discectomy as part of the decompression
4. Associated pathological entities such as disc herniation, spondylolisthesis or scoliosis.

Ethics and dissemination

The study has been evaluated and approved by the regional committee for medical research in central Norway and all participants provided written informed consent. The Data Inspectorate of Norway approved the registry protocol. The findings of this trial will be disseminated through peer-reviewed publications.

Primary outcome measure

The primary outcome measure is change in functional outcome between baseline and 12-months follow-up measured with version 2.0 of the Oswestry disability index (ODI)[10], translated into Norwegian and tested for psychometric properties by Grotle et al[11]. ODI is one of the principal condition-specific outcome measures used in the

management of spinal disorders. It has been extensively tested, shown good psychometric properties, and considered applicable in a wide variety of settings. ODI contains 10 questions on limitations of activities of daily living. Each variable is rated on a 0- to 5-point scale, summarized, and converted into a percentage score. Scores range from 0 to 100, with lower score indicating less severe pain and disability.

Secondary outcome measures

Secondary outcome measures are:

1. Changes in HRQL measured with the EQ-5D between baseline and 12-months follow-up
2. Perioperative complications
3. Duration of surgical procedures and hospital stays

Euro-Qol-5D (EQ-5D) is a generic and preference-weighted measure of HRQL[12]. The Norwegian version of EQ-5D has shown good psychometric properties[13]. EQ-5D evaluates 5 dimensions: mobility, self-care, activities of daily living, pain, and anxiety and/or depression. For each dimension, the patient describes 3 possible levels of problems (none, mild-to-moderate, and severe). This descriptive system therefore contains $3^5 = 243$ combinations or index values for health status. EQ-5D has been validated for patient populations similar to that in our study[13]. Total score ranges from –0.6 to 1, where 1 corresponds to perfect health and 0 to death. Negative values are considered to be worse than death.

The surgeons provide the following complications and adverse events to the NORspine registry: intraoperative hemorrhage requiring blood replacement, unintentional durotomy, cardiovascular complications, respiratory complications, anaphylactic reactions, and wrong level surgery. Patients report the following complications if they occur within three months of surgery: wound infection, urinary tract infection, pneumonia, pulmonary embolism, and deep venous thrombosis.

Data collection and registration by the NORspine registry protocol

On admission for surgery, the patients complete the baseline questionnaire, which includes questions about demographics and lifestyle issues in addition to the outcome measures. Information about marital status, educational level, employment status, body-mass index and tobacco smoking is available in the NORspine registry. During the hospital stay, using a standard registration form, the surgeon records data concerning diagnosis, comorbidity, *American Society of Anesthesiologists* (ASA) grade, duration of symptoms, treatment, and image findings. A questionnaire is distributed by regular mail 3 and 12 months after surgery, completed at home by the patients, and returned in the same way. The patients who do not respond receive one reminder with a new copy of the questionnaire. The patients complete preoperative questionnaire data and postal follow-up questionnaires without any assistance from the surgeon.

Diagnostic imaging

In the NORspine registry surgeons provide data concerning preoperative diagnostic imaging and the results of these investigations. For patients with available preoperative magnetic resonance images we will review the images and perform a morphologic

grading of the severity of spinal stenosis as described by Schizas et al[14]. This morphological grading from A to D is based on the cerebrospinal fluid/rootlet ratio as seen on axial T2 weighted magnetic resonance images. The original publication defines four subgroups of Grade A. We will not use these subgroups since they all are defined as no or minor stenosis. In the morphological grading A to D, we define grade A as no stenosis, grade B as relative stenosis and grade C and D as significant stenosis. The clinicians who review the preoperative magnetic resonance images and perform the morphological grading of the severity of spinal stenosis will be blinded with regards to treatment allocation (laminectomy or microdecompression).

Surgical procedures

There is variation in the surgical management of lumbar spinal stenosis, and in the following only a general description is provided for each procedure. When a decompressive laminectomy (Group 1) is performed the spinous process and the laminae of the involved level(s) as well as the medial aspects of the facet joints are resected[9]. Microdecompression (Group 2) can be performed using a bilateral or unilateral approach depending on the surgeon's preference and the individual patient's anatomy and symptoms. Unlike a decompressive laminectomy, the spinous process and the supra- and interspinous ligaments are left intact when performing a microdecompression[9]. Bilateral microdecompression means resection of the bone from the inferior aspect of the cranial lamina, and, occasionally, from the superior aspect of the subjacent lamina. Resection of the medial aspect of the facet joint is performed to alleviate the lateral recess. Flavectomy is performed to expose the spinal canal. The same procedure is then repeated on the contralateral side. When performing a unilateral microdecompression for bilateral decompression, the spinous process is undercut in addition to the ipsilateral decompression. By angling the microscopic view and occasionally tilting the operating table following ipsilateral decompression, resection of the contralateral ligamentum flavum and the medial aspects of the contralateral facet joints are possible[9].

Statistical analyses

This study will use mixed linear models to test the equivalence of the clinical effectiveness of microdecompression and laminectomy. If the population effect of treatment on changes is less than or equal to 8, the treatments are considered equal with respect to effectiveness. The minimal clinical important difference for change in the mean ODI score is considered to be in the range of 8 to 10 points [15-17]. Assuming a correlation of 0.5 between baseline and follow up measurements and a standard deviation of 18 for the individual measurements, the study will have 90% power with 132 patients in each treatment group. The minimal clinical important difference for ODI in patients with lumbar spinal stenosis in the same study population will be analyzed in a separate ongoing study. In the analyses of primary and secondary outcome measures adjustments for the number of levels operated (one or two), age, body mass index, and preoperative ODI will be made. Supplementary analyses with adjustments for baseline covariates and for the propensity to receive microdecompression will be done. We plan to conduct subgroup analyses to compare the clinical effectiveness of microdecompression and laminectomy in patients aged ≥70 years. In addition, we plan to conduct subgroup analyses to compare the clinical effectiveness of

microdecompression and laminectomy in obese patients (Body-mass index ≥30). Statistical significance level is defined as P≤0.05 with no adjustments made for multiple comparisons. Baseline and follow up measurements will be assumed normally distributed provided this assumption is confirmed by Q-Q plots. To evaluate the magnitude of change in EQ-5D score effect sizes will be estimated according to the method of Kazis et al[18]. An effect size of 0.8 or more is considered to be large.

Missing data

For the primary outcome (change in ODI between baseline and 12-month follow-up) we will perform both a complete case analysis and a full information analysis using mixed linear models. In the complete case analysis for the primary outcome patients with missing ODI data at 12-month follow-up will be excluded. A study on an equivalent patient population showed no difference in outcomes between responders and non-responders[19].

Study limitations

The main limitation of this study is that analyses are not based on randomized treatment assignments. However, the results are strengthened by the use of specific inclusion and exclusion criteria, the large sample size, and the reevaluation of the preoperative diagnostic imaging[20]. Another potential weakness of the present study is the expected loss to follow-up of approximately 22%, which is relatively high[19]. A third possible limitation is the growing tendency towards microdecompression, especially among neurosurgeons, during the study period.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement

The authors report no disclosures.

Authors' contributions

All authors read and approved the final manuscript. Dr. Gulati has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

USN: Study design, collection of data, statistics and writing. ASJ: Study design, statistics and writing. OS: Study design and writing. CW: Collection of data. VR: Collection of data. GL: Collection of data. TKS: Study design and collection of data. Writing. ØS: Study design

and statistics. SMC: Study design, statistics and writing. ØPN: Study design and writing. SG: Original concept of the trial, study design, collection of data, statistics and writing.

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References

1. Deyo RA. Treatment of lumbar spinal stenosis: a balancing act. *The spine journal : official journal of the North American Spine Society.* Jul 2010;10(7):625-627.
2. Ciol MA, Deyo RA, Howell E, Kreif S. An assessment of surgery for spinal stenosis: time trends, geographic variations, complications, and reoperations. *Journal of the American Geriatrics Society.* Mar 1996;44(3):285-290.
3. Gunzburg R, Szpalski M. The conservative surgical treatment of lumbar spinal stenosis in the elderly. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Oct 2003;12 Suppl 2:S176-180.
4. Amundsen T, Weber H, Nordal HJ, Magnaes B, Abdelnoor M, Lilleas F. Lumbar spinal stenosis: conservative or surgical management?: A prospective 10-year study. *Spine.* Jun 1 2000;25(11):1424-1435; discussion 1435-1426.
5. Atlas SJ, Keller RB, Robson D, Deyo RA, Singer DE. Surgical and nonsurgical management of lumbar spinal stenosis: four-year outcomes from the maine lumbar spine study. *Spine.* Mar 1 2000;25(5):556-562.
6. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the maine lumbar spine study. *Spine.* Apr 15 2005;30(8):936-943.
7. Malmivaara A, Slatis P, Heliovaara M, et al. Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial. *Spine.* Jan 1 2007;32(1):1-8.
8. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *The New England journal of medicine.* Feb 21 2008;358(8):794-810.
9. Thome C, Zevgaridis D, Leheta O, et al. Outcome after less-invasive decompression of lumbar spinal stenosis: a randomized comparison of unilateral laminotomy, bilateral laminotomy, and laminectomy. *Journal of neurosurgery. Spine.* Aug 2005;3(2):129-141.
10. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. *Physiotherapy.* Aug 1980;66(8):271-273.
11. Grotle M, Brox JI, Vollestad NK. Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability Index. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine.* Sep 2003;35(5):241-247.

12. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health policy (Amsterdam, Netherlands).* Dec 1990;16(3):199-208.

13. Solberg TK, Olsen JA, Ingebrigtsen T, Hofoss D, Nygaard OP. Health-related quality of life assessment by the EuroQol-5D can provide cost-utility data in the field of low-back surgery. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Dec 2005;14(10):1000-1007.

14. Schizas C, Theumann N, Burn A, et al. Qualitative grading of severity of lumbar spinal stenosis based on the morphology of the dural sac on magnetic resonance images. *Spine.* Oct 1 2010;35(21):1919-1924.

15. Brox JI, Reikeras O, Nygaard O, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. *Pain.* May 2006;122(1-2):145-155.

16. Hellum C, Johnsen LG, Storheim K, et al. Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study. *BMJ.* 2011;342:d2786.

17. Knutsson B, Michaelsson K, Sanden B. Obesity is associated with inferior results after surgery for lumbar spinal stenosis: a study of 2633 patients from the Swedish spine register. *Spine (Phila Pa 1976).* Mar 1 2013;38(5):435-441.

18. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Medical care.* Mar 1989;27(3 Suppl):S178-189.

19. Solberg TK, Sorlie A, Sjaavik K, Nygaard OP, Ingebrigtsen T. Would loss to follow-up bias the outcome evaluation of patients operated for degenerative disorders of the lumbar spine? *Acta orthopaedica.* Feb 2011;82(1):56-63.

20. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *The New England journal of medicine.* Jun 22 2000;342(25):1887-1892.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 2-3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 2-3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 3-5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 3-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 3** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **Page 5** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 3-4**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 3-5**
Bias	9	Describe any efforts to address potential sources of bias **Page 5-6**
Study size	10	Explain how the study size was arrived at **Page 5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5**
		(*c*) Explain how missing data were addressed **Page 6**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **Page 6** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 6**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(Not available yet as this is a study protocol. Will be provided in the final article)**
		(b) Give reasons for non-participation at each stage **(Not available yet as this is a study protocol. Will be provided in the final article)**
		(c) Consider use of a flow diagram **(Not available yet as this is a study protocol. Will be provided in the final article)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 4 (Not available yet as this is a study protocol. Will be provided in the final article)**
		(b) Indicate number of participants with missing data for each variable of interest **(Not available yet as this is a study protocol. Will be provided in the final article)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 4 (Not available yet as this is a study protocol. Will be provided in the final article)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **(Not available yet as this is a study protocol. Will be provided in the final article)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 5 (Not available yet as this is a study protocol. Will be provided in the final article)**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Page 5 (Not available yet as this is a study protocol. Will be provided in the final article)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(Not available yet as this is a study protocol. Will be provided in the final article)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 2,6**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(Not available yet as this is a study protocol. Will be provided in the final article)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 6 (Not available yet as this is a study protocol. Will be provided in the final article)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 6**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Abstract

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- The results are strengthened by the use of specific inclusion and exclusion criteria, the large sample size, and the reevaluation of the preoperative diagnostic imaging.

Background

Lumbar spinal stenosis most often results from a gradual, degenerative aging process. It is the most frequent indication for spinal surgery in the elderly, and as the oldest segment of the population continues to grow its prevalence is likely to increase[1-3]. Management of spinal stenosis can be challenging and requires the integration of patients' symptoms, clinical findings and diagnostic imaging. There is growing evidence that decompressive surgery offers an advantage over non-surgical management for selected patients with persistent severe symptoms[4-8]. Today it is generally accepted that surgery is indicated if conservative or non-surgical management fails. Improvement in radiating pain, neurogenic claudication, functional status and quality of life are the main treatment goals. Open or wide decompressive laminectomy, often combined with medial facetectomy and foraminotomy, was formerly the standard treatment[3]. However, in recent years a growing tendency towards less invasive decompressive procedures has emerged. In a study from 2005, unilateral microdecompression for bilateral decompression and bilateral microdecompression were shown to be promising treatment alternatives when compared to open decompressive laminectomy[9]. Since then unilateral microdecompression and bilateral microdecompression have been adopted by many spine surgeons, and as is the case in Norway, more frequently among neurosurgeons than orthopedic surgeons. However, there is still a need to evaluate the benefits and risks of different decompressive surgical procedures for lumbar spinal stenosis.

Aims of the study

The primary aim of this observational study is to test the equivalence of changes in functional outcomes measured with the Oswestry disability index (ODI) between baseline and 12-months follow-up after decompressive laminectomy and microdecompression with unilateral or bilateral approach in patients with single and two-level central lumbar spinal stenosis using data from the Norwegian Registry for Spine Surgery (NORspine). Secondary outcome measures are changes in health-related quality of life (HRQL) measured with the Euro-Qol-5D (EQ-5D) between baseline and 12-months follow-up, perioperative complications, duration of surgical procedures and length of hospital stays.

Patients and methods

Study population

Data for this cohort study will be collected through the Norwegian Registry for Spine Surgery (NORspine), which was established in 2006 and is a comprehensive clinical registry for quality control and research. Participation in the registration by either providers or patients is not mandated, nor is participation required as a necessary condition for a patient to gain access to health care or for a provider to be eligible for payment for the health care service. Patients operated between October 2006 and December 2011 will be screened for study eligibility. Follow-up time from the date of the operation (baseline) in this study is 12 months.

Inclusion criteria

1. Diagnosis of central lumbar spinal stenosis
2. Operation in ≤2 lumbar levels with either open decompressive laminectomy, bilateral microdecompression or unilateral microdecompression for bilateral decompression in the time period between October 2006 and December 2011
3. Included in the NORspine registry

Exclusion criteria

1. History of lumbar fusion
2. Previous surgery in the lumbar spine
3. Discectomy as part of the decompression
4. Associated pathological entities such as disc herniation, spondylolisthesis or scoliosis.

Ethics and dissemination

The study has been evaluated and approved by the regional committee for medical research in central Norway and all participants provided written informed consent. The Data Inspectorate of Norway approved the registry protocol. The findings of this study will be disseminated through peer-reviewed publications.

Primary outcome measure

The primary outcome measure is change in functional outcome between baseline and 12-months follow-up measured with version 2.0 of the Oswestry disability index (ODI)[10], translated into Norwegian and tested for psychometric properties by Grotle et al[11]. ODI is one of the principal condition-specific outcome measures used in the management of spinal disorders. It has been extensively tested, shown good psychometric properties, and considered applicable in a wide variety of settings. ODI contains 10 questions on limitations of activities of daily living. Each variable is rated on a 0- to 5-point scale, summarized, and converted into a percentage score. Scores range from 0 to 100, with lower score indicating less severe pain and disability.

Secondary outcome measures

Secondary outcome measures are:

1. Changes in HRQL measured with the EQ-5D between baseline and 12-months follow-up
2. Perioperative complications
3. Duration of surgical procedures and hospital stays

Euro-Qol-5D (EQ-5D) is a generic and preference-weighted measure of HRQL[12]. The Norwegian version of EQ-5D has shown good psychometric properties[13]. EQ-5D evaluates 5 dimensions: mobility, self-care, activities of daily living, pain, and anxiety and/or depression. For each dimension, the patient describes 3 possible levels of problems (none, mild-to-moderate, and severe). This descriptive system therefore contains $3^5 = 243$ combinations or index values for health status. EQ-5D has been validated for patient populations similar to that in our study[13]. Total score ranges from –

0.6 to 1, where 1 corresponds to perfect health and 0 to death. Negative values are considered to be worse than death.

The surgeons provide the following complications and adverse events to the NORspine registry: intraoperative hemorrhage requiring blood replacement, unintentional durotomy, cardiovascular complications, respiratory complications, anaphylactic reactions, and wrong level surgery. Patients report the following complications if they occur within three months of surgery: wound infection, urinary tract infection, pneumonia, pulmonary embolism, and deep venous thrombosis.

Data collection and registration by the NORspine registry protocol

On admission for surgery, the patients complete the baseline questionnaire, which includes questions about demographics and lifestyle issues in addition to the outcome measures. Information about marital status, educational level, employment status, body-mass index and tobacco smoking is available in the NORspine registry. During the hospital stay, using a standard registration form, the surgeon records data concerning diagnosis, comorbidity, *American Society of Anesthesiologists* (ASA) grade, duration of symptoms, treatment, and image findings. A questionnaire is distributed by regular mail 3 and 12 months after surgery, completed at home by the patients, and returned in the same way. The patients who do not respond receive one reminder with a new copy of the questionnaire. The patients complete preoperative questionnaire data and postal follow-up questionnaires without any assistance from the surgeon.

Diagnostic imaging

In the NORspine registry surgeons provide data concerning preoperative diagnostic imaging and the results of these investigations. For patients with available preoperative magnetic resonance images we will review the images and perform a morphologic grading of the severity of spinal stenosis as described by Schizas et al[14]. This morphological grading from A to D is based on the cerebrospinal fluid/rootlet ratio as seen on axial T2 weighted magnetic resonance images. The original publication defines four subgroups of Grade A. We will not use these subgroups since they all are defined as no or minor stenosis. In the morphological grading A to D, we define grade A as no stenosis, grade B as relative stenosis and grade C and D as significant stenosis. The clinicians who review the preoperative magnetic resonance images and perform the morphological grading of the severity of spinal stenosis will be blinded with regards to treatment allocation (laminectomy or microdecompression).

Surgical procedures

There is variation in the surgical management of lumbar spinal stenosis, and in the following only a general description is provided for each procedure. When a decompressive laminectomy (Group 1) is performed the spinous process and the laminae of the involved level(s) as well as the medial aspects of the facet joints are resected[9]. Microdecompression (Group 2) can be performed using a bilateral or unilateral approach depending on the surgeon's preference and the individual patient's anatomy and symptoms. Unlike a decompressive laminectomy, the spinous process and the supra- and interspinous ligaments are left intact when performing a microdecompression[9]. Bilateral microdecompression means resection of the bone from

the inferior aspect of the cranial lamina, and, occasionally, from the superior aspect of the subjacent lamina. Resection of the medial aspect of the facet joint is performed to alleviate the lateral recess. Flavectomy is performed to expose the spinal canal. The same procedure is then repeated on the contralateral side. When performing a unilateral microdecompression for bilateral decompression, the spinous process is undercut in addition to the ipsilateral decompression. By angling the microscopic view and occasionally tilting the operating table following ipsilateral decompression, resection of the contralateral ligamentum flavum and the medial aspects of the contralateral facet joints are possible[9].

Statistical analyses

This study will use mixed linear models to test the equivalence of the clinical effectiveness of microdecompression and laminectomy. If the population effect of treatment on changes is less than or equal to 8, the treatments are considered equal with respect to effectiveness. The minimal clinical important difference for change in the mean ODI score is considered to be in the range of 8 to 10 points [15-17]. Assuming a correlation of 0.5 between baseline and follow up measurements and a standard deviation of 18 for the individual measurements, the study will have 90% power with 132 patients in each treatment group. The minimal clinical important difference for ODI in patients with lumbar spinal stenosis in the same study population will be analyzed in a separate ongoing study. In the analyses of primary and secondary outcome measures adjustments for the number of levels operated (one or two), age, body mass index, and preoperative ODI will be made. Supplementary analyses with adjustments for baseline covariates and for the propensity to receive microdecompression will be done. We plan to conduct subgroup analyses to compare the clinical effectiveness of microdecompression and laminectomy in patients aged ≥70 years. In addition, we plan to conduct subgroup analyses to compare the clinical effectiveness of microdecompression and laminectomy in obese patients (Body-mass index ≥30). Statistical significance level is defined as $P \leq 0.05$ with no adjustments made for multiple comparisons. Baseline and follow up measurements will be assumed normally distributed provided this assumption is confirmed by Q-Q plots. To evaluate the magnitude of change in EQ-5D score effect sizes will be estimated according to the method of Kazis et al[18]. An effect size of 0.8 or more is considered to be large.

Missing data

For the primary outcome (change in ODI between baseline and 12-month follow-up) we will perform both a complete case analysis and a full information analysis using mixed linear models. In the complete case analysis for the primary outcome patients with missing ODI data at 12-month follow-up will be excluded. A study on an equivalent patient population showed no difference in outcomes between responders and non-responders[19].

Study limitations

The main limitation of this study is that analyses are not based on randomized treatment assignments. However, the results are strengthened by the use of specific

inclusion and exclusion criteria, the large sample size, and the reevaluation of the preoperative diagnostic imaging[20]. Another potential weakness of the present study is the expected loss to follow-up of approximately 22%, which is relatively high[19]. A third possible limitation is the growing tendency towards microdecompression, especially among neurosurgeons, during the study period.

Conclusion

In this article, we present a protocol for an observational study designed to test the equivalence between the clinical effectiveness of microdecompression and laminectomy in the surgical treatment of central lumbar spinal stenosis. Prospectively registered treatment and outcome data are obtained from the Norwegian Registry for Spine Surgery (NORspine). We have discussed some of the methodological issues pertinent to the successful execution of this surgical observational study.

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Authors' contributions

All authors read and approved the final manuscript. Dr. Gulati has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

USN: Study design, collection of data, statistics and writing. ASJ: Study design, statistics and writing. OS: Study design and writing. CW: Collection of data. VR: Collection of data. GL: Collection of data. TKS: Study design and collection of data. Writing. ØS: Study design and statistics. SMC: Study design, statistics and writing. ØPN: Study design and writing. SG: Original concept of the study, study design, collection of data, statistics and writing.

Competing interests statement

The authors report no disclosures.

Current status

We believe that publishing the study protocol will enable readers of the final study to compare what was originally intended with what was actually done, thus preventing post-hoc revisions of study aims. Data for this cohort study including 12-months follow-up will be obtained from NORspine in 2014. We will then screen all patients in the registry with a diagnosis of lumbar spinal stenosis for study eligibility. Further, available MR investigations will be retrieved and undergo blinded review. Data collection will be completed by the end of 2014.

References

1. Deyo RA. Treatment of lumbar spinal stenosis: a balancing act. *The spine journal : official journal of the North American Spine Society.* Jul 2010;10(7):625-627.
2. Ciol MA, Deyo RA, Howell E, et al. An assessment of surgery for spinal stenosis: time trends, geographic variations, complications, and reoperations. *Journal of the American Geriatrics Society.* Mar 1996;44(3):285-290.
3. Gunzburg R, Szpalski M. The conservative surgical treatment of lumbar spinal stenosis in the elderly. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Oct 2003;12 Suppl 2:S176-180.
4. Amundsen T, Weber H, Nordal HJ, et al. Lumbar spinal stenosis: conservative or surgical management?: A prospective 10-year study. *Spine.* Jun 1 2000;25(11):1424-1435; discussion 1435-1426.
5. Atlas SJ, Keller RB, Robson D, et al. Surgical and nonsurgical management of lumbar spinal stenosis: four-year outcomes from the maine lumbar spine study. *Spine.* Mar 1 2000;25(5):556-562.
6. Atlas SJ, Keller RB, Wu YA,et al. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the maine lumbar spine study. *Spine.* Apr 15 2005;30(8):936-943.
7. Malmivaara A, Slatis P, Heliovaara M, et al. Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial. *Spine.* Jan 1 2007;32(1):1-8.
8. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *The New England journal of medicine.* Feb 21 2008;358(8):794-810.
9. Thome C, Zevgaridis D, Leheta O, et al. Outcome after less-invasive decompression of lumbar spinal stenosis: a randomized comparison of unilateral laminotomy, bilateral laminotomy, and laminectomy. *Journal of neurosurgery. Spine.* Aug 2005;3(2):129-141.
10. Fairbank JC, Couper J, Davies JB, et al. The Oswestry low back pain disability questionnaire. *Physiotherapy.* Aug 1980;66(8):271-273.
11. Grotle M, Brox JI, Vollestad NK. Cross-cultural adaptation of the Norwegian versions of the Roland-Morris Disability Questionnaire and the Oswestry Disability Index. *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine.* Sep 2003;35(5):241-247.
12. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health policy (Amsterdam, Netherlands).* Dec 1990;16(3):199-208.
13. Solberg TK, Olsen JA, Ingebrigtsen T, et al. Health-related quality of life assessment by the EuroQol-5D can provide cost-utility data in the field of low-back surgery. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* Dec 2005;14(10):1000-1007.
14. Schizas C, Theumann N, Burn A, et al. Qualitative grading of severity of lumbar spinal stenosis based on the morphology of the dural sac on magnetic resonance images. *Spine.* Oct 1 2010;35(21):1919-1924.

15. Brox JI, Reikeras O, Nygaard O, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. *Pain.* May 2006;122(1-2):145-155.

16. Hellum C, Johnsen LG, Storheim K, et al. Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study. *BMJ.* 2011;342:d2786.

17. Knutsson B, Michaelsson K, Sanden B. Obesity is associated with inferior results after surgery for lumbar spinal stenosis: a study of 2633 patients from the Swedish spine register. *Spine (Phila Pa 1976).* Mar 1 2013;38(5):435-441.

18. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Medical care.* Mar 1989;27(3 Suppl):S178-189.

19. Solberg TK, Sorlie A, Sjaavik K, et al. Would loss to follow-up bias the outcome evaluation of patients operated for degenerative disorders of the lumbar spine? *Acta orthopaedica.* Feb 2011;82(1):56-63.

20. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *The New England journal of medicine.* Jun 22 2000;342(25):1887-1892.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 2-3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 2-3**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 3-5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 3-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 3** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **Page 5** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 3-4**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 3-5**
Bias	9	Describe any efforts to address potential sources of bias **Page 5-6**
Study size	10	Explain how the study size was arrived at **Page 5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5**
		(*c*) Explain how missing data were addressed **Page 6**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **Page 6** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 6**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(Not available yet as this is a study protocol. Will be provided in the final article)**
		(b) Give reasons for non-participation at each stage **(Not available yet as this is a study protocol. Will be provided in the final article)**
		(c) Consider use of a flow diagram **(Not available yet as this is a study protocol. Will be provided in the final article)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 4 (Not available yet as this is a study protocol. Will be provided in the final article)**
		(b) Indicate number of participants with missing data for each variable of interest **(Not available yet as this is a study protocol. Will be provided in the final article)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Page 4 (Not available yet as this is a study protocol. Will be provided in the final article)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **(Not available yet as this is a study protocol. Will be provided in the final article)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 5 (Not available yet as this is a study protocol. Will be provided in the final article)**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Page 5 (Not available yet as this is a study protocol. Will be provided in the final article)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(Not available yet as this is a study protocol. Will be provided in the final article)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 2,6**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(Not available yet as this is a study protocol. Will be provided in the final article)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 6 (Not available yet as this is a study protocol. Will be provided in the final article)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 6**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.