Management for lumbar spinal stenosis: Protocol for a network meta-analysis and systematic review

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Abstract

Introduction: Lumbar spinal stenosis (LSS) is caused by structural changes of the spine, which lead to several severe symptoms, including back pain, leg pain, numbness and tingling in the legs, as well as reduced physical function. However, there is little evidence suggesting whether a patient with LSS should be treated with surgery. If surgery is recommended, which type of surgery benefits the patient most? To answer these questions, we will conduct a network meta-analysis and a systematic review to compare surgical and nonsurgical interventions in terms of efficacy as well as safety in adult patients with LSS. Methods and analysis: We will search the PubMed, Cochrane library, and EMBASE databases for articles published prior to October 10, 2019. We will search for randomized controlled trials assessing surgical and nonsurgical interventions for adult patients with degenerative LSS without any language restrictions. The primary outcome measures will be pain and disability. The secondary outcomes will include adverse events (number of events or number of people with each type of adverse event), reoperations, complications, blood loss and operation time. We will obtain the full texts of the potentially relevant studies and independently assess them. The quality of evidence will be evaluated according to the Grading of Recommendations Assessment, Development and Evaluation framework. A random-effects network meta-analysis will be performed to analyze all the evidence under the frequentist framework, and the ranking results will be presented. We will generate plots depicting the network geometry using Stata. The network meta-analysis will be performed according to the Bayesian framework. Ethics and dissemination Ethics approval is not required. The research will be published in a peer-reviewed journal.

Keywords
disability, lumbar spinal stenosis, non-surgery treatment, NMA, pain, surgery

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Introduction

Lumbar spinal stenosis (LSS) is a very common disease that is usually caused by a degenerative process.1,2 LSS is accompanied by clinical syndromes including buttock or lower extremity pain caused by a gradual narrowing of the spinal canal, including disk bulging or protrusion (but not herniated disks) and degenerative olisthesis. In LSS patients, the gradual narrowing of the spinal canal causes low back pain and leg pain, which worsen when they walk. LSS is the most common reason adults over 65 years old seek medical treatment.3,4 Nonsurgical interventions are initially recommended to treat LSS patients with mild to moderate symptoms. Surgery is introduced when nonsurgical interventions are not successful. However, some studies have demonstrated that surgery benefits LSS patients more than nonsurgical interventions do.5–7 In contrast, there is evidence suggesting that surgery is associated with more adverse events, such as infection, nerve injury, restenosis, and segmental instability.5 Nonsurgical treatments of LSS include drugs, physical therapy, spinal injections, lifestyle changes and multidisciplinary rehabilitation.9 In addition, there are many surgical options for patients with LSS, including decompression, decompression plus fusion, endoscopic decompression, inter spinous process spacer device, laminotomy, minimally invasive decompression, and split spinous process decompression.10,11

Patients with persistent severe pain and progressive neural dysfunction seem to benefit from decompressive surgery.12–15 The previously reported efficacy and adverse effects of surgical and nonsurgical treatment for LSS are inconsistent,10,16 so no expert consensus has been established on the ideal treatment for LSS patients. Therefore, there is an urgent need to conduct evidence-based medical research to guide clinical practice. However, there are many different interventions, so a traditional meta-analysis cannot provide the information needed to answer the above questions. A Bayesian network meta-analysis, also known as a mixed treatment comparison,17 is a potential solution. Network meta-analyses (NMAs) are an extension of conventional pairwise meta-analyses that enable the simultaneous pooling of data from clinical trials comparing at least two treatments. Furthermore, the inference on the relative efficacy of each treatment is strong when both direct and indirect comparisons are included.18,19 We plan to conduct a comprehensive NMA comparing the safety and efficacy of different treatment modalities to provide a complete ranking of different interventions by safety and efficacy for patients with LSS. The protocol is as follows.

Methods and analysis

Criteria for eligible studies for this review

The protocol was written according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).20 Any changes made to this protocol will be updated in the version registered in PROSPERO with the registration number CRD42020154247.

Types of participants

Adult LSS patients over 18 years old will be included in this research, without sex restrictions. LSS will be confirmed by the clinical presentation and imaging findings. The complexity of symptoms and signs will be defined as neurogenic lameness or radiculopathy or multiple root symptoms, which are neuroanatomically consistent with areas of pathological stenosis, suggesting high confidence in the diagnosis of “symptomatic LSS.” Cases of LSS caused by disc herniation will be included in our study. The exclusion criteria will be as follows: nonspecific low back pain and root pain secondary to primary pathological conditions rather than congenital or degenerative LSS; isthmic spondylolisthesis; and postfracture stenosis. For studies involving mixed clinical populations, the study authors will be contacted to obtain relevant data. If the authors do not respond or subgroups are not included, those studies will be excluded.

Types of interventions

All studies comparing any type of surgical (decompression, with or without spinal fusion, any kind of device or prosthesis) or nonsurgical (e.g., exercise, manipulation, mobilization, physical therapy, drugs, acupuncture, bracing, education and cognitive-behavioral treatments) procedures will be included.

Outcome measures

The outcome data will be divided by short-term (<12 months) and long-term (≥12 months) follow-up assessments. The NMA will be performed separately for these two periods. For studies reporting results at multiple time points, the data reported at the time points closest to 3 months and 12 months of follow-up will be included in the primary analysis.

Primary outcomes

The primary outcomes will be as follows:

1) Disability and functional status, as measured by a back pain-specific scale (e.g., Roland Morris Disability Questionnaire (RMDQ), Oswestry Disability Index (ODI)).

2) Pain intensity, as measured by a visual analog scale or other pain scale (e.g., visual analog scale (VAS), numerical rating scale (NRS), McGill pain scale).21,22 The VAS will be considered the first choice, and the NRS will be considered the second choice.23
Secondary outcomes
The secondary outcomes will be as follows:
1. reoperation rate; 2. operation time; 3. length of hospital stay; 4. perioperative blood loss; and 5. complications.

Types of studies
For our analysis, we will include only randomized controlled trials comparing different interventions. Randomized research involves the true random selection of participants and the use of computer-generated sequences, closed envelopes, blocking randomization or a similar method to assign participants to groups. To reduce bias, studies with high risk of bias corresponding to the randomization process will be excluded.

Search strategy
Electronic searches. We will use the updated search strategy recommended by the Cochrane Back and Neck Review Group for identifying RCTs.24 The PubMed, Embase, Scopus, Cochrane Library, Web of Science, and ScienceDirect electronic databases will be searched for randomized trials comparing at least two different treatments that were published prior to 11 October 2019. No restrictions regarding language or publication status will be used.

Reference lists and other sources
The reference lists of all the included studies, relevant systematic reviews and meta-analyses, and guidelines will be screened for additional eligible studies.

Identification and selection of studies
Two authors will independently review the search results by reading the titles and abstracts. The full texts of potentially relevant research will be obtained and independently evaluated in this study. We will resolve disagreements through discussion with a third senior review author.

Data extraction
Two authors will independently extract relevant data using a standardized form.24 In addition, a pilot test will be performed before the formal data extraction step. The demographic characteristics, type of intervention, treatment time, follow-up time, and outcome measures listed above will be extracted. All data will be collected in custom Excel spreadsheets.

Measurement of treatment effect
The trials will be grouped according to the type of surgical interventions, the outcomes, and the time points of assessment. We will extract the sample size, means (final values) and standard deviations (SDs) of continuous results and quantify the treatment effect as the mean difference (MD) or standardized mean difference (SMD) if different methods are used to evaluate the same outcome. For the dichotomous results, the number of cases and the total sample size will be used to estimate the hazard ratio (RR). Therefore, we will use the MD, SD or RR and 95% confidence interval (CI) to measure the treatment effect.

Relative treatment ranking
Each intervention will be ranked using a cumulative grade curve and a surface at the average level.25 A level-heat map will be used to display the ranking results for each intervention.26

Unit of analysis issues
We will not include cluster randomized trials or crossover trials. If multiple pain measurements are reported, we will extract the most severe measurement at baseline. For disability, we will choose the scale defined in the study as the primary outcome. In terms of data synthesis, the follow-up period will be divided into short-term (time points closest to 3 months) and long-term periods (time points closest to 12 months).

Dealing with missing outcome data and missing statistics
In the case of incomplete or missing data, we will contact the corresponding author. For continuous outcomes, if only the SE, p-value or CI is reported, we will convert them to the SD. If the median and interquartile range (IQR) are reported, we will calculate the SD by dividing the IQR by 1.35 and consider the median equal to the mean. If data are reported as a chart rather than a table, we will estimate the means and standard deviations. If SDs are not reported, we will contact the corresponding author. If SDs for the follow-up measurements are missing, we will use the baseline measurements for the follow-up measurements. Finally, if no variability measures are reported anywhere in the text, we will estimate the SD based on the data reported in other studies with similar populations and risk of bias. For the dichotomy outcomes, we will first try to contact the corresponding author to obtain the relevant data. If the author does not respond or cannot provide the relevant data, informative missing ORs (IMORs) will be used to explore the uncertainty of the results under the random missing hypothesis.27

Risk of bias assessment
Two reviewers will independently assess the risk of bias of the included studies. Differences will be resolved through discussion. Otherwise, a decision will be made by the third
reviewer. If the third reviewer deems it necessary, we will contact the author for more information. We will use the “risk of bias” assessment tool, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions and the Cochrane Back and Neck Review Group. The response options for each signaling question are as follows: yes, probably yes, probably no, no and no information. Based on the answers to all the signaling questions within a given domain, we will score each study as having “high,” “low” or “unclear” risk of bias for the domain.

Data analysis

A descriptive summary of the characteristics of the study, patients, and interventions will be provided. A summary of the findings table will be created in Review Manager, and we will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines to assess the quality of the evidence for each outcome measure. If the data are insufficient, we will conduct a narrative review on some of the comparisons. A network diagram will be drawn to describe the available interventions. The node size reflects the number of patients per intervention. The width of the line indicates the number of comparisons. Pairing and NMA will be performed by effectiveness and safety.

Pairwise meta-analyses

Traditional pairwise meta-analyses will be performed with a random-effects model with the DerSimonian and Laird inverse-variance method for every direct comparison. For some subgroups, we will also perform pairwise meta-analyses if NMAs cannot be performed. The heterogeneity will be assessed by using I² and T².

Assessment of the transitivity assumption

Before conducting NMAs, we will evaluate potential baseline effect modifiers (age, sex, educational level, baseline physiological function, smoking habits, body mass index (BMI), comorbidities, and past treatments) to assess their effects on the comparisons. If any differences are found, we will conduct a meta-regression to explore the impact on the outcomes.

Network meta-analyses

Random-effects NMAs will be performed according to the frequency domain framework, combining direct comparisons with indirect comparisons. It is assumed that the heterogeneity parameters for each intervention are the same. In a future study, a prediction interval map will be generated to reflect the uncertainty of the results.

Assessment of inconsistency

The Bucher method will be used as a local method, and the design-by-treatment interaction model will be used as a global method. If an inconsistency is found, the node splitting method will be used to determine the original cause of the inconsistency.

Exploring sources of heterogeneity or inconsistency with subgroup analyses and meta-regression

For the two main outcomes (disability and pain intensity), in addition to the long-term follow-up evaluation, subgroup analysis and meta-regression will be performed for three short-term and long-term categories. The subgroup analysis will be performed to compare different surgical methods belonging to the decompression group, assuming that different surgical methods will affect the outcomes.

Sensitivity analyses

For the four main outcomes (including physiological function and all-cause mortality), a sensitivity analysis was conducted for the following types of studies: (1) only studies with a low risk of bias; (2) studies with data imputed through either IMDoM or IMOR; (3) studies without a nonactive comparison group; (4) studies receiving no commercial funding; and (5) studies without unpublished data.

Publication bias

If the number of studies included is larger than 10, the comparison adjustment funnel plot will be used to test the publication bias. A meta-regression will be performed using sample size and effect estimates to detect small study effects.

Statistical software

All analyses (the pairwise meta-analysis will be performed only with Review Manager 5.3, and the NMA will be performed with both Stata and WinBUGS) will be performed with Stata and WinBUGS. We will generate plots depicting the network geometry using Stata, version 14.0 (Stata Corp). NMA will be performed according to a Bayesian framework using Markov chain Monte Carlo methods with WinBUGS, version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Strengths and limitations of this study

1) This is the first network meta-analysis to assess the efficacy and safety of surgical and conservative treatment for adults with lumbar spinal stenosis.

2) The main advantage is that only randomized controlled trials will be included in the analysis, yielding reliable results.
3) This article includes the results of both direct and indirect comparisons.
4) The differences in the standards of complications reported by different researchers may cause heterogeneity.

Author contributions
F-LW, YL, C-PZ, and S-GS contributed equally to this work. All authors conceived the study. F-LW, YL, C-PZ, S-GS, X-DY, L-LS, and J-XQ contributed to the study concept and design. F-LW, YL and C-PZ drafted the manuscript. F-LW, S-GS, K-LZ, M-RD, H-RG, Y-FY, HW, SQ and BA developed the search strategy. X-XL, S-KG, Q-YG and S-DW designed and revised the protocol. All authors read and approved the final manuscript as submitted.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics and dissemination
We will publish the research in a peer-reviewed journal after completing it.

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Patient and public involvement
Patients will not be involved.

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