STUDY PROTOCOL

Written in line with PRISMA-P 2015 statement

Title

The natural course of clinical pain and disability following first time lumbar fusion surgery: study protocol of a systematic review

Registration

To be registered in PROSPERO. A protocol following the PRISMA-P statement (Moher et al., 2015) and Cochrane handbook (Higgins, 2011) informed the conduct of this systematic review, which will be reported in line with the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

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Contributions

JBS is leading protocol development, analyses and dissemination. NK and TH are first and second reviewers. All authors contribute following the four International Committee of Medical Journal Editors criteria for authorship:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Amendments

Important protocol amendments post registration will be recorded and included in dissemination.

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No sources of support or funding were provided for this review. Authors are academic staff at Radboud University Medical Centre, University of Birmingham, Bern University Hospital, and Maastricht University Medical Centre.

INTRODUCTION

Rationale

Lumbar spinal fusion (LSF) is a surgical procedure which aims to decompress and stabilize the lumbar spine in various degenerative spinal disorders such as spinal stenosis, lumbar spondylolisthesis, disc herniation, and discogenic low back pain.(Bydon et al., 2014; Fu et al., 2009; Ong, Auerbach, Lau, Schmier, & Ochoa, 2014) Several techniques of LSF are available, ranging from simple to complex procedures.(Deyo et al., 2010) Between 1998 and 2008, the national bill for spinal fusion increased from $4.3 billion to $33.9 billion (US dollars).(Rajaee, Bae, Kanim, & Delamarter, 2012) Hospitalizations for spinal fusion in the US increased from 61,000 in 1993 to 296,211 in 2002 and over 451,000 in 2012 according to results presented by the US Department of Health and Human Services.(Kalakoti et al., 2015) Furthermore, Deyo et al. (Deyo et al., 2010) report especially an increase of complex fusion procedures in patients with lumbar stenosis from 1.3 per 100,000 to 19.9 per 100,000 Medicare beneficiaries in the US between 2002 and 2007.

Aging and surgical advancement are likely to contribute to a further raise in use of increasingly complex procedures and number of operations.(Virk, Sandhu, & Khan, 2012) Positive effects of LSF are reported in some randomized controlled trials (RCTs) in patients with chronic low back pain and disc degeneration.(Brox et al., 2003; Fritzell, Hagg, Wessberg, & Nordwall, 2001) More recently, a small randomized controlled trial (n = 41) of Ohtori et al. (Ohtori et al., 2011) shows a large decrease

in pain over a two-year period after LSF in patients with chronic discogenic low back pain. However, the positive effect of LSF in patients with chronic low back pain seems to decrease at longer follow-up.(Fritzell, Hagg, Jonsson, & Nordwall, 2004) In addition, a randomized controlled trial by Brox et al. (Brox et al., 2006) in patients with chronic low back pain and previous surgery for disc herniation, reporting no difference in back specific pain and disability compared to LSF. Despite some positive results, several studies analysing cost-effectiveness report a questionable cost-effectiveness of LSF. For example, Mummaneni et al. (Mummaneni et al., 2014) report a gain of $224,420 per quality-adjusted life year (QALY) over a one-year period for single level LSF in patients with grade 1 spondylolisthesis. This seems not cost-effective assuming a $50,000/QALY threshold (Freeman, Steele, Sach, Hegarty, & Soegaard, 2007; Hirth, Chernew, Miller, Fendrick, & Weissert, 2000), though results improve over a two-year period. Results of the Spine Patient Outcomes Research Trial show a gain of one QALY at a cost of $115,600 over a two-year period (Tosteson et al., 2008) and one QALY at a cost of $66,300 over a four-year period (Tosteson et al., 2011) for single level LSF in patients with degenerative spondylolisthesis. Graft-specific complications (5.4%-10.0% in first postoperative year (Carragee, Hurwitz, & Weiner, 2011; Haid, Branch, Alexander, & Burkus, 2004; Rihn et al., 2009)) and revisions (2.0% - 6.9%) (Burkus et al., 2011; Cahill et al., 2011; Dimar et al., 2009; Jorgenson, Lowe, France, & Sabin, 1994; Vaccaro, Stubbs, & Block, 2007) are frequent and can drastically decrease cost-effectiveness.(Virk et al., 2012) Therefore, LSF might not be effective for the entire heterogeneous group of patients with chronic low back pain and disc degeneration.(Willems, 2013)

In summary, LSF is increasingly used in the treatment of degenerative lumbar spinal disorders while evidence shows a questionable cost-effectiveness and long-term effect of LSF. In addition, postoperative rehabilitation shows disappointing results with moderate to severe symptoms and disability on long term(Abbott, Tyni-Lenne, & Hedlund, 2010; Brox et al., 2006; Christensen, Laurberg, & Bunger, 2003; Skold, Tropp, & Berg, 2013), high rehospitalisation rates(Deyo et al., 2010), and high dis-satisfaction scores(Abbott et al., 2010). Knowledge about the natural course is needed to improve understanding of recovery after LSF. First, the natural course of clinical pain and disability after LSF could be analysed accurately when outcomes on both short term and long term are provided. To the knowledge of the authors, no overview of the natural course after LSF exists. Secondly, a clear trend in recovery after LSF could indicate optimal timing for rehabilitation. This is important, because exercises six weeks after surgery are possible without endangering internal spinal fixation devices. (Rohlmann, Graichen, & Bergmann, 2002) Nevertheless, Oestergaard et al. showed inferior efficacy of rehabilitation(Oestergaard et al., 2013) and lower pain and disability outcomes (Oestergaard et al., 2012) when rehabilitation started six weeks after LSF compared to

twelve weeks postoperatively in patients with degenerative lumbar spinal disorders. Therefore, it could be advised to not intervene in the first weeks after surgery when the natural course is satisfactory. In conclusion, knowledge of the natural course of clinical pain and disability after LSF is needed to improve understanding of recovery after LSF and inform postoperative management. Therefore, the main objective of this systematic review is to systematically review the natural course of clinical pain and disability in patients with degenerative disorders of the lumbar spine after first time lumbar spinal fusion surgery.

Objective

To systematically review the natural course of clinical pain and disability (WHO, 2011) in adult patients with degenerative disorders of the lumbar spine, such as spinal stenosis, disc herniation or discogenic low back pain after first time lumbar fusion surgery, reported in prospective controlled trials or prospective cohort studies.

METHODS

Eligibility criteria

Participants

Adult patients with degenerative disorders of the lumbar spine, such as spinal stenosis (including spondylolisthesis)(Kreiner et al., 2013), disc herniation(Kreiner et al., 2014) or discogenic low back pain who have undergone first time lumbar spinal fusion surgery.

I suggest analysing and reporting results per patient category. The results of studies reporting outcomes of mixed patient categories will be presented as "category: blended" or according to the majority of patients belonging to a patient category as described above.

Note: Discogenic low back pain secondary to a degenerated disc that meets all of the following criteria:

- Advanced single- or two-level disease noted on an MRI and plain radiographs of the lumbar spine, characterized by signs of degeneration of the disc with high intensity zones (HIZ, as a sign of rupture of the annulus fibrosus), black discs, or Modic changes (defined as bone edema of the vertebral endplates above and below the disc space in question) as compared to other normal or mildly degenerative levels (characterized by normal plain radiographic appearance and no signs of degeneration on MRI).
- Presence of symptoms for at least one year AND that are not responsive to structured multi-modal non-operative treatment over that period that should at least include physical therapy or a rehabilitation program but may also include (but not limited to) pain management, injections, cognitive behavioral therapy, and active exercise programs.
- Absence of active significant psychiatric disorders, such as major depression, requiring pharmaceutical treatment.
- Primary complaint of axial pain, with a possible secondary complaint of lower extremity pain.

Outcome measures

Measurements reported on one or more outcome(s) of pain or disability (WHO, 2011) at baseline and one or more follow-up time-point(s).

Studies

Prospective controlled trials and prospective cohort studies.

Retrospective cohort studies and RCTs have their limitations for answering the current research question. It could be thought that there would be a 'recall bias' (retrospective) or treatment bias (patients dissatisfied by receiving treatment under study / not under study) or selection bias (both retrospective and RCT).

Information sources

The search will employ sensitive topic-based strategies designed for each database to 30 September 2015. There will be no language or geographical restrictions.

Databases:

- CINAHL, EMBASE, MEDLINE, ZETOC Databases
- Selected Internet sites and Indexes: Turning Research into Practice
- National Research Register
- Cochrane Back Review Group
- Science Citation Index and Social Science Citation Index
- Unpublished research: British National Bibliography for Report Literature, Dissertation Abstracts, Index to Scientific and Technical Proceedings, National Technical Information Service, System for Information on Grey Literature.

Search strategy

The search strategy will include 1] the intervention/population terms, 2] study outcome terms and 3] a strategy for searching MEDLINE for observational studies.

Intervention terms: lumbar fusion, spinal fusion, posterolateral fusion, interbody fusion, anterior fusion, posterior fusion, transforaminal fusion, transpsoas fusion, facet fusion, pedicle fusion, cage fusion, vertebrae fusion, oblique, minimal invasive fusion, mini-open fusion.

Study outcome terms: natural course, clinical course, natural history, pain, neuralgia, sciatica, back pain, referred pain, radicular pain, McGill pain questionnaire, numeric rating scale, NRS, visual analogue scale, VAS, Oswestry low back pain disability questionnaire, Oswestry disability index, ODI, Quebec back pain disability scale, QBPDS, Roland disability questionnaire, Roland Morris disability questionnaire, Roland-Morris disability questionnaire, Roland Morris low back pain and disability questionnaire, walk test(s), walk-test(s), walk distance, timed up and go test, TUG, performance oriented mobility assessment, POMA, elderly mobility scale, EMS.

Observational study terms (as provided by SIGN): epidemiologic studies, case control studies, cohort studies, case control, follow up studies, observational studies, longitudinal, prospective.

Box 1 details an example of searches that will be used: the Medline OvidSP search.

Example of Medline OvidSP search strategy 1948—31 September 2015

Patient-intervention terms

1. Spinal Fusion/
2. ((Spin* adj3 fusion?) or (fusion? adj3 spin*) or (spondylosyndes?s) or (spondylodes?s) or ((spin* or vertebra?) adj3 arthrodes?s)).ti,ab,kf.
3. ((lumbar or posterolateral or interbody or anterior or posterior or transforam?nal or transpsoas or facet or pedicle or cage or verterbra? or oblique) adj3 fusion?).ti,ab,kf.
4. ((minim* invasive adj5 fusion?) or (mini-open adj5 fusion?)).ti,ab,kf.

Outcome terms

1. ((Natural history) or ((natural or clinical) adj3 course)).ti,ab,kf.
2. pain/ or back pain/ or low back pain/ or neuralgia/ or sciatica/ or pain, referred/ or pain, postoperative/
3. (pain? or ache? or ((backache? lower) or (back ache? lower) or (back pain? lower) or (backpain? lower)) or ((backache? low) or (back ache? low) or (back pain? low) or (backpain? low)) or ((ache? lower back) or (pain? lower back)) or ((ache? low back) or (pain? low back)) or ((lower backache?) or (lower back ache?) or (lower back pain?) or (lower backpain?)) or ((low backache?) or (low back ache?) or (low back pain?) or (low backpain?)) or lumbago or ((pain? radiating) or (radiating pain?)) or (neuralgia? or neuralgic?) or ((nerve pains?) or (pain? nerve)) or ((neuropathic pain?) or (pain? neuropathic)) or sciatica or ((neuralgi? sciatic?) or (sciatic? neuralgi?)) or ((referred adj3 pain) or (pain adj3 referred)) or ((postoperative adj3 pain?) or (pain adj3 postoperative))).ti,ab,kf.
4. activities of daily living/ or disability evaluation/
5. ((daily living activit*) or (activit* daily living) or (activit* of daily living) or (living activit* daily) or adl or (disability evaluation?) or (evaluation? disability)).ti,ab,kf.
6. pain measurement/ or pain perception/ or visual analog scale/
7. ((pain assessment) or (pain scale) or (McGill pain questionnaire) or MPQ or (SF-MPQ) or (numeric rating scale) or NRS or (NRS-11) or (NRS-101) or (numeric rating score) or (visual analogue scale) or VAS or (visual analogue score) or (visual analog* scale) or (analog* visual scale) or (scale visual analog*)).ti,ab,kf.
8. (questionnair* or (Oswestry adj5 disability index) or ODI or mODI or OSW or mOSW or (Oswestry adj5 disability questionnaire) or ODQ or (Quebec adj5 disability scale) or QBPDS or QUE or QDS or (Roland adj5 disability questionnaire) or (Roland-Morris adj5 disability questionnaire) or (Roland-Morris adj5 disability questionnaire) or RDQ or RDQ-11 or RDQ-18 or RDQ-25 or M-RDQ or mRDQ or RMDQ or RMDQ-11 or RMDQ-18 or RMDQ-24 or M-RMDQ or mRMDQ).ti,ab,kf.
9. exercise test/ or walking/
10. ((physical performance assessment?) or (walk test?) or (walk-test?) or (walk distance) or 6MWT or 6MWTD or 2MWT or 5MWT or 12MWT or 15MWT or 10MWT or 10MTWT or

FWT or 10MSWT or SPWT or (timed adj5 test) or TUG or (performance oriented mobility assessment) or POMA or (elderly mobility scale) or EMS).ti,ab,kf.

Study terms

1. epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or (case control).tw. or (cohort adj (study or studies)).tw. or (cohort analy$).tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or longitudinal.tw. or prospective.tw.

Study records

Data management

Records will be managed through EndNote; specific software for managing bibliographies.

Selection process

Two reviewers (NK/TH) will search information sources independently and assess identified studies for inclusion, facilitated by grading each eligibility criterion as eligible/not eligible/might be eligible(van Tulder, Furlan, Bombardier, & Bouter, 2003). The study will be considered potentially relevant when it cannot be clearly excluded on the basis of its title or abstract (Higgins, 2011) following discussion between the two independent reviewers. Full text will be obtained of potentially eligible studies, studies with insufficient information in their abstract or in a situation of disagreement. A study will be included when both reviewers independently assess it as satisfying the inclusion criteria on the basis of its full text. A third reviewer (AR) will mediate in the event of disagreement following discussion.(Higgins, 2011)

Data collection process

Using a standardised form managed in Microsoft Access, one reviewer (NK) will extract the data. A random selection of 10% of the data will be checked by the second reviewer (TH) for accuracy. If any error occurs, a second (and so on) 10% of the data will be checked for errors.

Data items

Data extracted for each study will include the following summary data: participants (setting and area), sample size, inclusion and exclusion criteria, design, outcomes (including scale and name of questionnaire/instrument), patient characteristics, surgical procedure, clinical care pathway, and follow-up dates.

In addition, data will be collected regarding possible determinants for effect modification such as:

- Simple (anterior interbody fusion or posterolateral fusion of one or two levels) or complex (360^{o} spinal fusion by a single incision (posterior or transforaminal lumbar interbody fusion); or any combination of anterior with either transverse process or posterior fusion techniques; or any fusion of more than two levels) procedure.(Deyo et al., 2010) Patients after a complex procedure are hypothesized to have an inferior natural course than patients after a complex procedure.(Fritzell, Hagg, & Nordwall, 2003)
- Open or minimally invasive surgery. Patients after open surgery are hypothesized to have an inferior natural course.(Vertuani et al., 2015)
- Severity and time of complaints before surgery. Patients with a higher leg pain intensity (Abbott, Tyni-Lenne, & Hedlund, 2011) and/or longer time of complaints before surgery (Lara-Almunia, Gomez-Moreta, & Hernandez-Vicente, 2015) are hypothesized to have an inferior natural course of pain.
- Work status before surgery. Patients with psychologically stressful work (Katz, 2006), and/or classified as 'currently not in paid employment' (Wilson-MacDonald et al., 2008), and/or patients with a low household income at time of injury (DeBerard, Masters, Colledge, Schleusener, & Schlegel, 2001) are hypothesized to have an inferior natural course.
- Pain catastrophizing, operationalized as pain-related negative thinking.(Abbott et al., 2011) Patients with a high level of pain catastrophizing are hypothesized to have an inferior natural course.(Wilhelm et al., 2015)
- Depression. Patients with a depression before surgery and/or high scores on depression scales are hypothesized to have an inferior natural course of disability.(Wilhelm et al., 2015)
- Smoking. Patients classified as 'current smokers' are hypothesized to have an inferior natural course.(Wilson-MacDonald et al., 2008)
- Levels affected. Patients with a 2 or 3-level fusion are hypothesized to have an inferior natural course.(Turner et al., 1992)
- Age. Patients with a higher age are hypothesized to have an inferior natural course.(DeBerard et al., 2001)
- Obesity. Patients with obesity are hypothesized to have a similar natural course.(Lingutla et al., 2015)

Outcomes and prioritisation

Primary outcomes of interest are pain and disability. Secondary outcomes are work absenteeism, quality of life, adverse events, and health service utilisation. Outcomes are presented for short term

(≤ 3 months follow-up), medium term (> 3 months, ≤ 12 months), and long term (> 12 months). Long-term outcomes are considered outcomes of main interest.

There will be help of minimal important change values as provided by Ostelo et al. (Ostelo et al., 2008) to interpret results and draw conclusions regarding a satisfying or disappointing natural course of clinical pain and disability after lumbar spinal fusion.

- Visual Analogue Scale: 15 points on a 0 to 100 scale
- Numerical Rating Scale: 2 points on a 0 to 10 scale
- Roland Disability Questionnaire: 5 points on a 0 to 24 scale
- Oswestry Disability Index: 10 points on a 0 to 100 scale
- Quebec Back Pain Disability Questionnaire: 20 points on a 0 to 100 scale

Risk of bias in individual studies

Risk of bias for each included study will be independently assessed by the same initial reviewers. The third reviewer will mediate in situations of disagreement. Cohen's κ will be used to assess agreement between reviewers. All tools and processes will be piloted prior to use. Risk of bias will be assessed using a modified version of the QUIPs tool (original: (Hayden, van der Windt, Cartwright, Cote, & Bombardier, 2013)).

Data

Continuous outcome data will be presented at original scale or converted to a 0–100 scale if appropriate. Recovery rates will be reported consistent with the definitions used in the included studies. All authors will be contacted to request either raw data or additional summary statistics to those reported if necessary. All results will be reported in the context of overall study quality.

Synthesis

If enough studies are included, a meta-analysis will be conducted using pain and/or disability outcome data. Pooled estimates of outcomes will be calculated. Variance weighted pooled means will be calculated for continuous data. Variance weighted pooled proportions will be calculated for dichotomous data.

Meta-biases

Assessment of any publication bias across studies (e.g. publication bias across studies, selective reporting within studies) will be reported.

Confidence in cumulative evidence

The strength of the overall body of evidence will be assessed using an adapted version of GRADE.(Huguet et al., 2013)

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Scoping search findings

Authors and year	
Rao et al. 2015 (Rao et al., 2015)	Stand-alone anterior lumbar interbody fusion for treatment of degenerative spondylolisthesis
Sivaraman et al. 2015 (Sivaraman et al.)	Prospective Study of Posterior Lumbar Interbody Fusion With Either Interbody Graft or Interbody Cage in the Treatment of Degenerative Spondylolisthesis
Lara-Almunia et al. 2015 (Lara-Almunia et al., 2015)	Posterior lumbar interbody fusion with instrumented posterolateral fusion in adult spondylolisthesis: description and association of clinico-surgical variables with prognosis in a serie of 36 cases
Siepe et al. 2015 (Siepe et al., 2015)	Anterior stand-alone fusion revisited: a prospective, clinical, X-ray and CT investigation
Gu et al. 2015 (Gu et al., 2015)	Clinical and radiological outcomes of unilateral versus bilateral instrumentation in two-level degenerative lumbar diseases
Fei et al. 2015 (Fei et al., 2015)	Comparison between posterior dynamic stabilization and posterior lumbar interbody fusion in the treatment of degenerative disc disease: a prospective cohort study
Udby and Bech-Azeddine 2015 (Udby & Bech-Azeddine, 2015)	Clinical outcome of stand-alone ALIF compared to posterior instrumentation for degenerative disc disease: A pilot study and a literature review
Malham et al. 2015 (Malham, Parker, Goss, & Blecher, 2015)	Clinical results and limitations of indirect decompression in spinal stenosis with laterally implanted interbody cages: results from a prospective cohort study
Saeed et al. 2014 (Saeed, Khan, Wazir, Inam, & Satar, 2014)	The use of locally harvested bone chips as a graft in spine fusion surgery
Hey and Hee 2015 (Hey & Hee, 2015)	Open and minimally invasive transforaminal lumbar interbody fusion: comparison of intermediate results and complications
Bohinski et al. 2010 (Bohinski, Jain, & Tobler, 2010)	Presacral retroperitoneal approach to axial lumbar interbody fusion: a new minimally invasive technique at L5-S1: Clinical outcomes, complications, and fusion rates in 50 patients at 1-year follow-up
Pimenta et al. 2008 (Pimenta, Pesantez, & Oliveira, 2008)	Silicon matrix calcium phosphate as a bone substitute: early clinical and radiological results in a prospective study with 12-month follow-up
Alijani et al. 2015 (Alijani et al., 2015)	Posterior lumbar interbody fusion and posterolateral fusion: analogous procedures in decreasing the index of disability in patients with spondylolisthesis
Lauweryns and Raskin 2015	Prospective analysis of a new bone graft in lumbar interbody fusion: results of a 2-year prospective

(Lauweryns & Raskin, 2015)	clinical and radiological study
Rodgers et al. 2012 (Rodgers, Gerber, & Rodgers, 2012)	Clinical and radiographic outcomes of extreme lateral approach to interbody fusion with beta-tricalcium phosphate and hydroxyapatite composite for lumbar degenerative conditions
Marchi et al. 2012 (Marchi, Oliveira, Coutinho, & Pimenta, 2012)	The importance of the anterior longitudinal ligament in lumbar disc arthroplasty: 36-month follow-up experience in extreme lateral total disc replacement
Jhala et al. 2014 (Jhala, Singh, & Mistry, 2014)	Minimally invasive transforaminal lumbar interbody fusion: results of 23 consecutive cases
Lee et al. 2014 (Lee, Kim, Ju, Lee, & Kim, 2014)	Posterior lumbar interbody fusion using a unilateral cage: a prospective study of clinical outcome and stability
Horsting et al. 2012 (Horsting, Pavlov, Jacobs, Obradov-Rajic, & de Kleuver, 2012)	Good functional outcome and adjacent segment disc quality 10 years after single-level anterior lumbar interbody fusion with posterior fixation
Adogwa et al. 2012 (Adogwa et al., 2012)	Extent of intraoperative muscle dissection does not affect long-term outcomes after minimally invasive surgery versus open-tranforaminal lumbar interbody fusion surgeray: a prospective longitudinal cohort study
Kok et al. 2012 (Kok, Donk, Wapstra, & Veldhuizen, 2012)	The memory metal minimal access cage: a new concept in lumbar interbody fusion-a prospective, noncomparative study to evaluate the safety and performance
Kok et al. 2012 (Kok, Grevitt, Wapstra, & Veldhuizen, 2012)	The memory metal spine system in a posterior lumbar interbody fusion (PLIF) procedure: a prospective, non-comparative study to evaluate the safety and performance
Àbdul et al. 2011	Clinico-radiological profile of indirect neural decompression using cage or auto graft as interbody construct in posterior lumbar interbody fusion in spondylolisthesis: which is better?

Studies identified from scoping search: n=23 (but at least one reporting same study)