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BMJ Open Minimally invasive surgery versus open surgery in the treatment of lumbar spondylolisthesis: study protocol of a multicentre, randomised controlled trial (MISOS trial)

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ABSTRACT

Introduction Patients with symptomatic spondylolisthesis are frequently treated with nerve root decompression, in addition to pedicle screw fixation and interbody fusion. Minimally invasive approaches are gaining attention in recent years, although there is no clear evidence supporting the proclamation of minimally invasive spine surgery (MISS) being better than open surgery. We present the design of the MISOS (Minimal Invasive Surgery versus Open Surgery) trial on the effectiveness of MISS versus open surgery in patients with degenerative or spondylolytic spondylolisthesis.

Methods and analysis All patients (age 18–75 years) with neurogenic claudication or radicular leg pain based on low-grade degenerative or spondylolytic spondylolisthesis with persistent complaints for at least 3 months are eligible. Patients will be randomised into mini-open decompression with bilateral interbody fusion with percutaneous pedicle screw fixation (MISS), or conventional surgery with decompression and instrumented fusion with pedicle screws and bilateral interbody fusion (open). The primary outcome measure is Visual Analogue Scale of self-reported low back pain. Secondary outcome measures include improvement of leg pain, Oswestry Disability Index, patients' perceived recovery, quality of life, resumption of work, complications, blood loss, length of hospital stay, incidence of reoperations and documentation of fusion. This study is designed as a multicentre, randomised controlled trial in which two surgical techniques are compared in a parallel group design. Based on a 20 mm difference of low back pain score at 6 weeks (power of 90%, assuming 8% loss to follow-up), a total of 184 patients will be needed. All analyses will be performed according to the intention-to-treat principle.

Ethics and dissemination The study has been approved by the Medical Ethical Review Board Southwest Holland in August 2014 (registration number NL 49044.098.14) and subsequently approved by the board of all participating hospitals. Dissemination will include peer-reviewed publications and presentations at national and international conferences.

Trial registration number NTR 4532, pre-results.

Strengths and limitations of this study

- The Minimal Invasive Surgery versus Open Surgery (MISOS) trial evaluates the effectiveness of percutaneous pedicle screw fixation versus open surgery in patients with degenerative or spondylolytic spondylolisthesis.
- The trial is the largest, multicentre, randomised trial on minimal invasive surgery versus open surgery in patients with spondylolisthesis.
- Methodological strengths include appropriate sample size calculation based on difference in early postoperative low back pain.
- It is not feasible to blind the patients for the allocated treatment.
- There is no economical evaluation.

INTRODUCTION

Background and rationale

Patients with degenerative or spondylolytic spondylolisthesis of the lumbar spine usually present with radicular leg pain or neurogenic claudication, with or without low back pain. Whenever conservative management fails, patients are offered surgery. In case of stable spondylolisthesis documented on dynamic radiographs, patients can be treated with decompression alone, and the modest difference in favour of additional instrumentation does not justify the associated higher costs for implants and longer duration of surgery.¹ In case of unstable spondylolisthesis, most patients will be treated with nerve root decompression in addition to pedicle screw fixation and interbody fusion. However, this surgical approach usually implies large skin incisions with detachment of the paravertebral muscles, which may result in disabling postoperative low back pain and higher complications with consequent longer rehabilitation period.²

Worldwide, minimally invasive spine surgery (MISS) is becoming more and more popular. The rationale behind minimally invasive techniques is less tissue damage, reduced back pain leading to a shorter rehabilitation period, and faster return to work and resumption of daily activities.³ Despite numerous studies on minimally invasive lumbar fusion techniques, level 1 evidence on outcome of MISS versus open surgery is scarce. There is no evidence supporting the proclamation of small (minimally invasive) being better. There is only one randomised controlled trial, of low quality, on minimally invasive lumbar fusion, performed by Wang *et al.*⁴ They reported 41 cases who underwent minimally invasive transforaminal lumbar fusion versus 38 patients who underwent open surgery. There was no difference in pain between both groups during the follow-up of 2 years, although the Oswestry Disability Index (ODI) score in patients treated with MISS was significantly better during the first 12 months. This difference, however, diminished over time.

Recently, two reviews on minimally invasive fusion versus open surgery have been published,^{5 6} and one review specifically focused on spondylolisthesis.⁷ Overall, MISS was associated with less blood loss and shorter hospitalisation, and there was no difference in terms of outcome, fusion rates and complications. However, the results should be interpreted carefully since the included studies displayed heterogeneous patient populations and neither review contained a level 1 randomised controlled trial.

In the MISOS (Minimal Invasive Surgery versus Open Surgery) trial, patients with degenerative or spondylolytic spondylolisthesis will be randomised into mini-open decompression with bilateral interbody fusion with percutaneous pedicle screw fixation (MISS), or conventional open surgery with decompression and instrumented fusion with pedicle screws and bilateral interbody fusion (open). We hypothesise that patients treated with MISS have a faster speed of recovery with less low back pain at 2 weeks and 6 weeks after surgery, and similar outcome at 1 year after surgery, as compared with patients treated with open surgery. We will especially focus on the short-term results because that is the period in which possible differences in speed of recovery may become clear in case of less invasive techniques. The presented protocol follows the recommendations outlined in the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines for randomised controlled trials.

Research aim and objectives

Despite numerous studies on minimally invasive lumbar fusion techniques, level 1 evidence on outcome of MISS versus open surgery is scarce. The objective of our trial is to determine whether minimally invasive lumbar fusion will result in faster recovery and less low back pain compared with conventional open surgery in patients with degenerative or spondylolytic spondylolisthesis. The

Box Inclusion and exclusion criteria

Inclusion criteria

- ▶ Age between 18 and 75 years
- ▶ Neurogenic claudication or radicular leg pain with or without low back pain
- ▶ Degenerative or spondylolytic spondylolisthesis grade I or II with spinal stenosis
- ▶ Persistent complaints for at least 3 months, regardless of conservative treatments
- ▶ Be able to understand the Dutch language and comprehend the questionnaires and patient information
- ▶ Written informed consent given

Exclusion criteria

- ▶ Previous spine fusion surgery at the same level
- ▶ Osteoporosis
- ▶ Active infection or prior infection at the surgical site
- ▶ Active cancer
- ▶ Spondylolisthesis greater than grade III
- ▶ More than one symptomatic level that needs fusion
- ▶ Pregnancy
- ▶ Contraindication for surgery
- ▶ Severe mental or psychiatric disorder
- ▶ Alcoholism
- ▶ Inadequate knowledge of Dutch language
- ▶ Morbid obesity (body mass index >40)

primary outcome measure is short-term low back pain at 2 weeks and 6 weeks.

METHODS AND ANALYSIS

Study design and settings

This study is designed as a multicentre, randomised controlled trial in which patients with symptomatic spondylolisthesis (degenerative or spondylolytic) will be allocated into minimally invasive pedicle screw fixation versus open surgery. In order to recruit enough patients, the study will be performed in three neurosurgical centres in the Netherlands: Medical Center Haaglanden in The Hague, Haga Hospital in The Hague, and University Medical Center Groningen, Groningen.

Patient selection

All patients (age between 18 and 75 years) with neurogenic claudication or radicular leg pain based on low-grade (Meyerding grades I and II) degenerative or spondylolytic spondylolisthesis with persistent complaints for at least 3 months are eligible for the study. Additional inclusion and exclusion criteria are shown in the box.

Randomisation

Randomisation will be computer-generated and will be performed prior to surgery at the outpatient clinic. A predefined block size will be used to ensure balanced group sizes at the end of the inclusion period. When surgery is rescheduled the patient stays in the same randomisation group (intention to treat), and the original date

of surgery is documented. Blinding is not feasible because of differences in surgical wounds.

Surgical intervention

All patients in both groups will be operated with the aid of spinal navigation (O-arm (Medtronic) or 3D-Orbic C-arm (Siemens)) and will be positioned on a radiolucent spine table. In case of the standard open procedure, a long midline skin incision (10–15 cm) is made, after which the paravertebral muscles are detached from the midline and retracted laterally in order to expose the facet joints and pedicle entry point. After the pedicle screws are positioned, the disc will be removed bilaterally and packed with autogenous bone chips, followed by bilateral placement of polyetheretherketone (PEEK) posterior lumbar interbody fusion (PLIF) cages. In case of the minimally invasive surgery, a small midline incision (3–5 cm) will be made to perform mini-open decompression and placement of bilateral PEEK PLIF cages. In addition, two small paramedian incisions will be made on both sides for percutaneous pedicle screw fixation.

All participating surgeons have performed at least 20 procedures of MISS prior to the start of the trial.

Outcome measurements

Primary outcome

The primary outcome is the score on the Visual Analogue Scale (VAS) of low back pain (ranging from 0 to 100 mm) in the short term (2 weeks and 6 weeks after surgery). Pain will be assessed on a horizontal 100 mm scale varying from 0 mm, 'no pain', to 100 mm, 'the worst pain imaginable'. Patients do not see the results of earlier assessments and will score the pain experienced at the visit. Reliability, validity and responsiveness of VAS have been shown.⁸ The minimal clinically important difference of the VAS for pain is 20 mm.⁹

Secondary outcome

Several secondary outcome measures will be documented.

Oswestry Disability index

The ODI is one of the principal condition-specific outcome measures used in the management of spinal disorders.¹⁰ In this study we will use the current version 2.1a. The ODI is the most commonly used outcome measures in patients with low back pain. It has been extensively tested, showed good psychometric properties and is applicable in a wide variety of settings. There are 10 questions (items), each with six possible answers, and each answer option receives a score of 0–5 points, yielding a score range between 0 and 50, which is scaled to a 100% range. The questions are designed in a way to realise how the back or leg pain is affecting the patient's ability to manage in everyday life.

Patients' perceived recovery

This is a 7-point Likert scale measuring the perceived recovery, varying from 'complete recovery' to 'worse than ever'. This outcome scale has been used in previous studies and is regarded valid and responsive

to change.¹¹ 'Complete recovery' and 'almost complete recovery' will be defined as good outcome (Likert 1 and 2).

Neurological outcome

All patients will be examined neurologically at 3 months' follow-up.

VAS of leg pain

This parameter will measure the experienced pain intensity in the leg during the week before visiting the researcher. Pain will be assessed on a horizontal 100 mm scale, varying from 0 mm, 'no pain', to 100 mm, 'the worst pain imaginable'. Patients do not see the results of earlier assessments and will score the pain experienced at the visit. Reliability, validity and responsiveness of VAS have been shown.⁸

Quality of life (EQ-5D)

The EuroQol (EQ-5D) measures five dimensions (mobility, self-care, daily activities, pain/discomfort, anxiety/depression) on a 3-point scale (no, some or extreme problems). For each health state described by the patients, a utility score can be calculated that reflects society's valuation of that health state. The Dutch tariff for the EQ-5D will be used.¹² Whereas the EQ-5D provides society's assessment of patients' health, the patients themselves will also assess their own health on VAS, ranging from 0.0 (as bad as death) to 1.0 (optimal health). Both the EQ-5D and the VAS will be reported in questionnaires filled out at home.

Resumption of work

Hypothetically, MISS may result in faster recovery and earlier return to work. Therefore, patients will be asked on every follow-up moment whether they have resumed their work activities.

The following are other outcome measures that will be documented:

Incidence of reoperations

In general, reoperation is considered as bad outcome and therefore used as an outcome measure. The incidence of reoperation in both groups will be measured.

Complications

A systematic assessment of complications (including wound infection, deep venous thrombosis, urine tract infection, haematoma and progressive neurological deficit) will be carried out by the surgeon. Moreover, surgeons will be asked for perioperative complications like cerebrospinal fluid leakage, nerve root damage and exploration on the wrong disc level. During the complete course of the study, all adverse events will be reported.

Surgical parameters

Blood loss, time of surgery and length of hospital stay will be documented in all patients.

Fusion

For the assessment of fusion we will use conventional dynamic X-ray. The flexion–extension plane images will be analysed and quantified using FXA (Functional X-Ray Analysis). The software allowed measurement of rotation on flexion–extension films with an accuracy of $\pm 1^\circ$. Absence of range of motion of the index disc level will be documented as indicator of fusion. We defined fusion as rotation $\leq 2^\circ$ and ≤ 1.25 mm translation on flexion–extension film.¹³

Correction of spondylolisthesis

Based on the preoperative and postoperative X-rays, we will analyse the correction of spondylolisthesis in all patients.

Sample size

The sample size calculation is based on a difference in low back pain score of 20 mm at 6 weeks after surgery (60 mm for open surgery vs 40 mm for minimally invasive surgery). Assuming an SD of 40 mm, 85 patients will be needed in both groups ($\alpha=0.05$; $\beta=0.10$). Including 8% loss to follow-up, a total of 184 patients will need to be randomised.

Data collection, management and analysis

All patients will be analysed preoperatively, as well as 2 weeks, 6 weeks, 3 months, 6 months, 12 months and 24 months postoperatively, according to the assessment schedule in table 1.

The data from initial visits, hospitalisation and follow-up visits will be entered into a database via an electronic data capture system (Castor EDC). The data will be recorded and analysed without any personal identifiers by using coded information. The source documents and identifiers will be archived in a security facility and permission for accessing data will be documented per investigator.

All analyses will be performed according to the intention-to-treat principle. Differences between groups at baseline will be assessed by comparing means, medians or percentages, depending on the type of variable. The outcomes for function (ODI) and pain (VAS) will be analysed with a repeated-measures analysis of variance using a first-order autoregressive covariance matrix. The estimated consecutive scores will be expressed as means and 95% CIs. Kaplan-Meier survival analysis will be used to estimate time elapsed between randomisation and recovery, and curves will be compared using the log-rank test. A Cox model will be used to compare rates of recovery by calculation of an HR. The level of significance will be $p < 0.05$.

Safety monitoring and adverse events

The study will be monitored by the Trial Coordinator Center of Haaglanden Medical Center. At least one monitoring visit per year per centre will be conducted. During the complete study period, all adverse events will be reported. Adverse events are defined as any undesirable

Table 1 Visit plan of the MISOS trial		Intake	Surgery	FU 2 weeks	FU 6 weeks	FU 3 months	FU 6 months	FU 12 months	FU 24 months
Inclusion/exclusion criteria		X							
Demographics		X							
Basic physical examination		X							
Neurological examination		X				X			
Randomisation			X						
X-ray		X				X	X	X	X
MRI		X							
VAS low back pain		X		X		X	X	X	X
VAS leg pain		X		X		X	X	X	X
ODI		X		X		X	X	X	X
Patients' perceived recovery				X		X	X	X	X
EQ-5D				X		X	X	X	X
Complications			X						
Reoperation				X			X	X	X

EQ-5D, EuroQoL, five dimensions; FU, follow-up; MISOS, Minimal Invasive Surgery versus Open Surgery; ODI, Oswestry Disability Index; VAS, Visual Analogue Scale.

experience occurring to a participant, whether or not related to the intervention.

ETHICS AND DISSEMINATION

Recently, three reviews on minimally invasive spondylolysis versus open spondylolysis have been published, of which one review specifically on spondylolisthesis.^{5–7} The clinical outcome, fusion rates and complication rates are comparable between minimally invasive interbody fusion surgery and open fusion surgery, although MISS is associated with reduced blood loss and shorter hospital stay. However, these results should be interpreted carefully since the included studies displayed heterogeneous patient populations and neither review contained a level 1 randomised controlled trial. This lack of evidence was the basis of the MISOS trial. The objective of our trial is to determine whether minimally invasive lumbar fusion will result in faster recovery and less low back pain compared with conventional open surgery. We plan to disseminate our findings through presentations at national and international spine conferences, and we will submit findings for publication in peer-reviewed international journals. Recruitment of patients has started in September 2015 and will be finished when all 184 patients have been followed up for 2 years, which is expected at the end of 2019.

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Contributors MA designed the protocol, contributed to acquisition of data, is primary investigator and coordinator of the trial. JW, JK and GdR have contributed to acquisition of data. All authors read and approved the final manuscript.

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Competing interests None declared.

Ethics approval Medical Ethical Review Board Southwest Holland.

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