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Findings from a pilot randomized trial of spinal decompression alone or spinal decompression plus instrumented fusion

THE SPINAL FUSION INDICATIONS AND OUTCOMES RANDOMISED TRIAL (SPINOUT-F) FEASIBILITY STUDY

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Aims

Symptomatic spinal stenosis is a very common problem, and decompression surgery has been shown to be superior to nonoperative treatment in selected patient groups. However, performing an instrumented fusion in addition to decompression may avoid revision and improve outcomes. The aim of the SpInOuT feasibility study was to establish whether a definitive randomized controlled trial (RCT) that accounted for the spectrum of pathology contributing to spinal stenosis, including pelvic incidence-lumbar lordosis (PI-LL) mismatch and mobile spondylolisthesis, could be conducted.

Methods

As part of the SpInOuT-F study, a pilot randomized trial was carried out across five NHS hospitals. Patients were randomized to either spinal decompression alone or spinal decompression plus instrumented fusion. Patient-reported outcome measures were collected at baseline and three months. The intended sample size was 60 patients.

Results

Of the 90 patients screened, 77 passed the initial screening criteria. A total of 27 patients had a PI-LL mismatch and 23 had a dynamic spondylolisthesis. Following secondary inclusion and exclusion criteria, 31 patients were eligible for the study. Six patients were randomized and one underwent surgery during the study period. Given the low number of patients recruited and randomized, it was not possible to assess completion rates, quality of life, imaging, or health economic outcomes as intended.

Conclusion

This study provides a unique insight into the prevalence of dynamic spondylolisthesis and PI-LL mismatch in patients with symptomatic spinal stenosis, and demonstrates that there is a need for a definitive RCT which stratifies for these groups in order to inform surgical decision-making. Nonetheless a definitive study would need further refinement in design and implementation in order to be feasible.

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Introduction

Symptomatic spinal stenosis is common in the ageing population, and approximately 29,000 people required hospital admission for treatment of this condition across the NHS between April 2014 and March 2015.[1] Approximately 20% of those with severe spinal stenosis report associated symptoms of severe pain in the lower back and leg, affecting their activities of daily living. In

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addition to the physical limitations, patients often suffer significant psychological challenges including sleep deprivation and exhaustion.

Decompression surgery has been demonstrated to be superior to nonoperative treatment in selected patient groups,[2-4] with approximately 18,000 such surgeries performed in the NHS in England each year. However, in randomized trials, up to 20% to 25% of these surgical procedures require subsequent surgery.[5,6] In selected sub-groups, specifically those with spinopelvic malalignment or mobile degenerative spondylolisthesis, performing instrumented fusion at the same time as decompression may be preferable in terms of improving outcome and preventing many such revision procedures. However, this increases the complexity and risk profile of the procedure.

The variety of anatomical degenerative changes in the lumbar spine that cause stenosis, coupled with a subjective and variable patient experience of symptoms, means that appropriate patient selection for either decompression alone, or decompression with instrumented fusion, represents a significant challenge faced by surgeons, and the superiority of one treatment over the next remains unclear. Studies to date have failed to adequately stratify for subgroups of patients, including those with spinopelvic mismatch and spondylolisthesis, and hence have not been able to satisfactorily inform surgeons. Three randomized controlled trials (RCTs) comparing decompression alone with decompression and fusion for spinal stenosis have shown conflicting results, reflecting a discrepancy demonstrated by other studies in similar degenerative lumbar conditions,[7-9] and demonstrate an underlying failure to account for the spectrum of disease causing spinal stenosis. Furthermore, other studies have failed to report subgroup classification of patient diagnosis, details of the operative procedures, and improvement according to the preoperative diagnosis.[10]

In addressing these current shortfalls, a new study must consider the preoperative diagnosis and individual spinal anatomical characteristics to make an evidence-based recommendation for treatment of each subgroup. The aim of this study was therefore to establish whether a definitive RCT comparing decompression alone to decompression with instrumented fusion in patients with spinopelvic malalignment or degenerative spondylolisthesis, and a well-defined clinical status, was feasible. Here, we report on the prevalence of the subgroups of interest such as a mobile spondylolisthesis and spinopelvic malalignment, neither of which were considered in the published RCTs.

Methods

The feasibility study consisted of a pilot trial of decompression with instrumented fusion versus decompression only in two patient subgroups, along with patient focus group consisting of participants in the pilot trial, which was intended to provide patient input into the design and conduct of a definitive trial. The study registration number is: ISRCTN15462386 - CPMS ID 40853; the NHS Health Research Authority (East Midlands - Leicester South Research Ethics Committee, reference 19/EM/0068) approved the study.

Initial screening criteria required patients to be aged 40 years or above with radicular leg pain or claudication symptoms equal or greater in intensity to back pain, of greater than five months duration who have failed nonoperative treatment. Following initial screening, at least one of the following secondary inclusion criteria had to be satisfied: patients with MRI-confirmed neural compression in the lateral recess or exit foramen; central spinal stenosis with cross-sectional area of the dural sac of < 70 mm^2 on MRI at one or two levels corresponding to L3/4, L4/5 or L5/S1; or complete effacement of cerebrospinal fluid at one or two levels corresponding to L3/4, L4/5, or L5/S1. Furthermore, patients had to have either a confirmed diagnosis of spinopelvic malalignment, measured as pelvic incidence-lumbar lordosis mismatch of > 10° measured on upright sagittal radiograph from L1 to S1, degenerative spondylolisthesis with an increase of the listhesis on the upright sagittal radiograph compared to the supine MRI to > 25%, an absolute value increase of > 5 mm, or kyphotic collapse on upright sagittal radiograph.

Excluded from the study were patients with isthmic spondylolisthesis, those who had undergone previous spinal surgery in the thoracolumbar spine, patients with a degenerative scoliosis > 10°, current smokers, BMI ≥ 35 kg/m^2, a clinical history of osteoporotic fracture, a neurological disorder affecting function, e.g. multiple sclerosis, Parkinson's disease, or patients with a systemic illness affecting physical function, such as inflammatory arthritis. Recruitment for the study took place at five hospital sites across the UK, intended to achieve a recruitment rate of 12 patients per centre per year, and a total intended sample size of 60 patients. This would also allow extrapolation to estimate the number of sites that would be required for a definitive study.

Following informed consent, patients were randomized to either spinal decompression alone or spinal decompression plus instrumented fusion. Randomization was performed using a web-based randomization system, stratified by subtype and site. Due to the diverse management options, neither participants nor treating clinicians were blinded.

The following patient-reported outcome measures were collected at baseline and were planned to be collected at three months: the visual analogue scale for back and leg pain, Oswestry Disability Index (ODI),[11] Measure yourself Medical Outcome profile,[12] and

Table I. Breakdown of screening data for the SpInOuT–F study (total screened = 90).

Inclusion criteria	n (%)
Initial criteria (all must be satisfied to be eligible)	
Age > 40 yrs	88 (98)
Radicular leg pain or claudication symptoms of greater or equal intensity to back pain symptoms for which surgery is considered an option	85 (94)
Failed nonoperative management	83 (92)
Passed initial screening criteria	77 (86)
Secondary criteria A (at least one must be satisfied to be eligible)	
Confirmed neural compression in the lateral recess or exit foramen	53 (59)
Central spinal stenosis with cross sectional area of the dural sac of < 70 mm^2 on MRI at one or two levels corresponding to L3/4, L4/5, or L5/S1	55 (61)
Complete effacement of CSF at one or two levels corresponding to L3/4, L4/5, or L5/S1	9 (10)
None of the above	3 (3)
Secondary criterion B (at least one must to be satisfied to be eligible)	
A confirmed diagnosis of spinopelvic malalignment measured as PI-LL mismatch of > 10° measured on upright sagittal radiograph	27 (30)
Degenerative spondylolisthesis with an increase of the listhesis on the upright sagittal radiograph compared to the supine MRI of > 25%, or an absolute value of > 5 mm or kyphotic collapse on upright sagittal radiograph, indicating a higher degree slip	23 (26)
Neither of the above	31 (34)
Passed initial screening and surgical criteria	52 (58)
Exclusion criteria	
Isthmic spondylolisthesis	1 (1)
Previous spinal surgery in the thoracolumbar spine	12 (13)
Degenerative scoliosis of the lumbar spine of > 10°	9 (10)
Current smoker	2 (2)
Clinical history of osteoporotic fracture or chronic oral steroid use	0 (0)
Evidence of neurological disorders (e.g. multiple sclerosis, Parkinson's) or systemic illness (e.g. inflammatory arthritis) that affect physical function	2 (2)
Unable to give informed consent	0 (0)
Unfit for elective surgery	2 (2)
Participation in other studies	0 (0)
Eligible for study	31 (34)
Patients approached to participate in study	24 (27)
Patients did not consent to take part	10 (11)
Preference for decompression surgery alone	2 (2)
Preference for decompression surgery with instrumented fusion	1 (1)
Patient did not wish to be randomized	1 (1)
Other	6 (7)
Total randomized	6 (7)

PI-LL, pelvic incidence-lumbar lordosis.

the Euroqol five-level five-dimension questionnaire (EQ-5D-5L).[13,14]

Interventions. Two routinely used procedures in the management of spinal stenosis were performed: spinal decompression alone, or decompression in addition to instrumented fusion with pedicle screws, plus or minus an interbody device. A panel of surgeons comprising the site's principal investigators agreed on the surgical and positional approach in each case to ensure consistency.

Statistical analysis. The intended sample size was 60 patients, which would be sufficient to estimate consent proportion with anticipated 95% Wilson confidence interval width of 10% to 20%. No formal statistical analysis of the data between groups was planned for the feasibility study. Descriptive analysis of outcome data was carried out using summary measures.

Results

The pilot trial was open for recruitment between June 2019 and March 2020 across five sites. Recruitment was slower than anticipated, and there was disparity between the numbers assessed at each site, ranging from 0 to 43. A total of 90 patients were screened, and 77 (86%) satisfied all of the initial screening criteria (Table I). More than half the patients had either lateral recess or foraminal stenosis, or central stenosis at one or two levels. There was a high prevalence of mobile spondylolisthesis and spinopelvic malalignement in the study group. Of 90 patients screened, 23 (26%) demonstrated mobile spondylolisthesis and 27 (30%) showed spinopelvic malalignment according to the criteria used (PI-LL > 10°). Overall, 52 patients (58%) passed the initial screening and secondary inclusion criteria, and, following application

Table II. Baseline demographic characteristics for participants in the SpInOuT pilot trial.

Variable	Value
Mean age, yrs (SD)	70 (13)
Mean height, m (SD)	1.7 (0.1)
Mean weight, kg (SD)	85 (12.8)
Mean symptom duration, mths (SD)	64 (67)
Sex, n (%)	
Female	2 (33)
Male	4 (67)
Spinopelvic malalignment > 10°, n (%)	6 (100)
With spondylolisthesis, n (%)	5 (83)
Dynamic spondylolisthesis, n (%)	4 (67)
Central stenosis, n (%)	4 (67)
Lateral recess stenosis, n (%)	6 (100)
Foraminal stenosis, n (%)	4 (67)

SD, standard deviation.

of the exclusion criteria, 31 were eligible for the study (Table I). Of these, 24 were approached to participate in the study. Following a number who declined to participate, the total number randomized was six patients (Table II). Of these, four were male and two were female. The mean age was 70.3 years (SD 13.0). The mean duration of symptoms was 63.8 months (SD 67.0). All six of the patients had spinopelvic malalignment > 10° and five had spondylolisthesis, four of which were dynamic. The study showed low recruitment, with the impact of the COVID-19 pandemic on elective surgery bringing about the official closure of recruitment on 31 March 2020. At this point, eight patients were awaiting preoperative assessment, which would have been likely to have resulted in randomization, and ten patients did not consent to participate. One patient subsequently underwent surgery during the study period, which was the procedure they were randomized and consented for.

Given the small number of randomized patients, resulting in only one patient undergoing surgery, follow-up data were not collected, it was not possible to assess completion rates, assess quality of life, or imaging outcomes as intended.

Discussion

The number of patients recruited for the study across all five sites was lower than expected. The expected rate of recruitment of 12 patients per centre per year was not met, the reasons for which were multifactorial. It was logistically challenging for the surgical team to capture patients at the point of referral for eligibility screening, and opportunities to recruit patients were therefore missed prior to decisions being made about their treatment. Assessment of pelvic parameters and spondylolisthesis, fundamental to the study for stratification of patients into the different groups, needed to be carried out by a member of the surgical team, which was not always realistic. Additionally, of the five recruitment sites, none were open for recruitment for a full 12-month period secondary to COVID-19. Variability in the referral pathways sites also limited efficiency, and to succeed in recruiting sufficient patients, a trial of this nature requires a consistent pathway across sites that enables patients to be screened at the point of referral. Delays in surgical waiting time also contributed to the low number of patients recruited. This effect was undoubtedly augmented even further secondary to the COVID-19 pandemic in the tail end of the pilot trial's recruitment period. A future study that includes stratification in the randomization protocol would have to specifically resolve practical challenges related to timely screening and recruitment in a consistent pathway across sites.

However, despite its limitations, the study did provide a unique insight into the prevalence of dynamic spondylolisthesis (26%) and PI-LL mismatch (30%) in a prospective study population which, to our knowledge, has not been reported before.

Previous RCTs and studies reporting on degenerative lumbar conditions have not adequately addressed variability in the causes of spinal stenosis, or reported on subgroup classification of preoperative diagnosis, details of surgical procedures, and subsequent outcome according to preoperative diagnosis.[10] There are currently three RCTs which have compared decompression and fusion and decompression alone for spinal stenosis, which demonstrate conflicting results. Försth et al[6] investigated whether fusion as an adjunct to decompression resulted in better clinical outcomes than decompression alone in 247 patients, with or without degenerative spondylolisthesis. At two-year follow-up, there was no significant difference between the treatment groups in the ODI score and change in the score between the preoperative and postoperative timepoints. In the second RCT, Ghogawala et al[15] compared laminectomy alone to laminectomy plus fusion for 66 patients with lumbar degenerative spondylolisthesis across five centres. After two years, the increase in 36-Item Short-Form Health Survey questionnaire (SF-36) scores was significantly greater in the laminectomy plus fusion group than in the laminectomy-alone group. Furthermore, the laminectomy-alone group had a 34% rate of revision (reoperation) for clinical instability compared to 14% in the laminectomy plus fusion group. Notably, the two trials comparing interventions for stenosis caused by spondylolisthesis showed conflicting results. The differences in the groups in the study by Ghogawala et al[15] were mainly seen in the SF-36, a non-disease-specific outcome measure, and the number of patients was relatively small compared to the other trials. In addition, the revision rate in the laminectomy group is higher than reported in other studies,[16] as acknowledged by the authors. In the third study, Austevoll et al[17] compared decompression alone to decompression with

instrumented fusion, reporting on 262 patients with stenosis caused by spondylolisthesis. Reduction in the ODI scores was comparable for both groups and demonstrated noninferiority of decompression alone. One explanation for the findings in all of the studies may be the spectrum of disease encompassed by degenerative spondylolisthesis, ranging from stable to highly unstable. A systematic review by Simmonds et al,[18] of clinical and biomechanical analyses evaluating stability and surgical outcomes of dynamic spondylolisthesis, identified clinical and radiological predictors of stability and developed an instability classification based on these. A trial comparing different treatment of degenerative spondylolisthesis should therefore stratify for this, as appropriate treatment may vary based on predicted stability.

In 2007, the Spine Patient Outcomes Research Trial (SPORT) reported on 501 patients with spinal stenosis and degenerate spondylolisthesis and concluded that surgical treatment showed greater improvement in pain and function than patients treated non-surgically. 'Instability' was defined in the study as a change of more than 10° of angulation, or more than 4 mm of translation of the vertebrae between flexion and extension of the spine, and was present in 8% of patients in the combined randomized and observational cohorts.[19] This differed from our definition of dynamic spondylolisthesis as we specifically excluded flexion/extension radiographs to eliminate the possibility of false negative values, instead measuring an increase in olisthesis on the upright sagittal radiograph compared to the supine MRI to > 25%, an absolute value increase of > 5 mm or kyphotic collapse on upright sagittal radiograph, and may account for the difference in the prevalence of this condition that was observed. The trial by Austevoll et al[17] recorded 20% of patients has having 'instability', defined as dynamic slippage of 3 mm, or ≥ 10° angulation on dynamic upright radiographs, in keeping with our findings. A previous prospective study comparing flexion-extension (FE) radiographs to the difference between upright lateral radiographs and supine MRI (ultrasound (US)) demonstrated that the ability to identify 'instability' was improved using US compared to FE, with mobility significantly higher in the US group.[20] The motion characteristics at diseased and adjacent levels of single-level degenerative spondylolisthesis have previously been studied using kinematic MRI. Lumbar instability was characterized as > 4 mm translational motion when moving from 30° flexion to 20° extension on upright MRI. Instability was found to be present in 32% of degenerative spondylolistheses present at either L3/4, L4/5, or L5/S1.[21] Considering the higher threshold value for translational motion used in our study, these results would appear to corroborate our findings.

Spinopelvic malalignment, specifically the difference between pelvic incidence and lumbar lordosis (PI-LL mismatch), has been identified as a biomechanic factor leading to increased shear stress and, clinically, to a higher risk of revision surgery after lumbar fusions.[22,23] Spinopelvic mismatch was defined in our study according to a cut-off value of 10°, above which patients have a higher risk for revision surgery.[23] This is consistent with the sagittal modifier in the SRS-Schwab classification of PI-LL ≥ 10°, which has been correlated with clinical outcome.[24] Our study found a prevalence of spinopelvic mismatch of 30% in the study population. Data on prevalence in the literature are varied and dependent upon age and pathology, and even in asymptomatic patients sagittal alignment of the spine and pelvis is highly variable.[25] A multicentre analysis of 773 adult spinal deformity patients with a mean age of 54 years, conducted by the International Spine Study Group, noted mean PI-LL to be -10.1°, although there was substantial variability with a SD of 20.4°.[26] In a study relating sarcopenia to spinal sagittal imbalance in patients with spinopelvic mismatch, Ohyama et al[27] recorded a prevalence of 42% of patients with spinopelvic mismatch in patients without sarcopenia, compared with 37% in patients with sarcopenia. However, inclusion for the study necessitated age > 65 years, and included patients who had previously undergone lumbar decompression and would account for a higher prevalence than noted in the study we present. There is a relative paucity of data on the prevalence of spinopelvic mismatch in patients with degenerative stenosis, and our study based on prospective screening data for a pilot trial indicates that it affects almost one in three patients with spinal stenosis considering surgery. The pitfalls of failing to account for this when performing fusion surgery, and the consequences for developing adjacent segment disease should the malalignment be maintained, have been well documented in the literature,[22,23,28,29] and underline the importance of our findings, especially as the current evidence may not necessarily support performing fusion in patients with degenerative spondylolisthesis in the first place because there is no difference in clinical outcome.

To summarize, this feasibilty study provided a unique insight into the prevalence of dynamic spondylolisthesis and PI-LL mismatch in patients with symptomatic spinal stenosis. Dynamic spondylolisthesis is found in one in four patients with spinal stenosis, and may have confounded the pertinent RCTs comparing fusion to non-fusion for spinal stenosis and/or spondylolisthesis. However, its clinical role at this point remains unclear. PI-LL mismatch appears to be a prevalent feature in patients with spinal stenosis considering surgery, and is found in one in three patients. Given the evidence that fusion in spinal stenosis does not improve the clinical outcome and the higher risk for revision surgery found across several studies in patients with PI-LL mismatch, this feature should not be overlooked, and must be accounted for in surgical

decision-making. It is clear that a definitive RCT which stratifies for these groups is required to inform surgical decision-making with regard to clinical outcome. A definitive study would need further refinement in terms of design and implementation in order to significantly improve recruitment and be successful.

Take home message

- One-third of patients with degenerative spinal stenosis present either with a mobile spondylolisthesis or a pelvic incidence-lumbar lordosis mismatch.
- A definitive randomized controlled trial which stratifies for these groups is required to ascertain their clinical significance, and to inform surgical decision-making with regard to clinical outcome.

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