Microdiscectomy compared with transforaminal epidural steroid injection for persistent radicular pain caused by prolapsed intervertebral disc: the NERVES RCT

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Scientific summary

The NERVES RCT

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Scientific summary

Background

Sciatica is defined as leg pain in the distribution of a lumbosacral nerve root. Estimates of caseload vary substantially within the literature because of difficulties in definition and poor data capture. Sciatica has a lifetime prevalence of up to 43%, an annual incidence of 5% and a point prevalence of up to 13%. Over 90% of sciatica is due to a prolapsed intervertebral disc, and in the majority of cases those affected are young, working adults, with the average age of sciatica patients being the early 40s. It may be helpful to consider two groups of patients: (1) patients who have acute sciatica that lasts < 6 weeks and may be self-limiting with little or no impact on the patient's work, and (2) patients who have persistent sciatica that lasts > 6 weeks and has a tremendous impact on the patient's working ability. Although studies have shown that most cases of sciatica resolve spontaneously within a year, 30% of patients still experience persistent troublesome symptoms after this, and 20% of patients leave work as a result. For patients with severe sciatica, work days lost can be as high as 15 days per calendar month. Current National Institute for Health and Care Excellence guidance recommends investigating sciatica persisting > 6 weeks using specialised radiological investigations, such as magnetic resonance imaging. Surgical removal of the disc prolapse in the form of microdiscectomy is widely accepted as the gold-standard treatment option worldwide, but this is an expensive treatment with risks and with long delays for patients in accessing surgical treatment. Previous studies of epidural steroid injections for sciatica have been disappointing, suggesting little or no benefit beyond 2–3 weeks post injection. By administering the epidural steroid injection closer to the site of the problem, injection by the transforaminal route (i.e. transforaminal epidural steroid injection) may be a far more effective treatment than either caudal or interlaminar epidural steroid injection. Although care pathways exist for the treatment of sciatica, there is tremendous variation in practice across the UK, depending on treatment availability and clinician preference. This largely arises from the lack of 'level 1' evidence available in the literature to formulate these guidelines, and has led to variability in commissioning of epidural steroid injection within the UK and variations in clinician preference of surgery over epidural steroid injection. Moreover, Danish Health Authority guidelines recommend against the use of injections owing to low-level evidence of their effectiveness for sciatica within 12 weeks of onset. To address this controversial issue we compared two invasive treatments for sciatica, both of which are recommended by expert pathway/guidelines:

1. surgical lumbar microdiscectomy
2. transforaminal epidural steroid injection.

Objectives

Primary objective

- To compare the clinical effectiveness of surgical microdiscectomy with transforaminal epidural steroid injection for sciatica of < 12 months' duration secondary to prolapsed intervertebral disc, at 18 weeks post randomisation.

Secondary objectives

- To compare the cost-effectiveness of microdiscectomy with transforaminal epidural steroid injection for the treatment of sciatica secondary to prolapsed intervertebral disc.
- To compare health-related quality-of-life outcomes for both treatments.

Methods

Trial design

The NErve Root Block VErsus Surgery trial is a pragmatic, multicentre, Phase III randomised trial, with an internal pilot phase, comparing microdiscectomy with transforaminal epidural steroid injection for sciatica of < 1 year symptom duration.

Participants

Participants were recruited from 11 specialist multidisciplinary clinics receiving patients from pooled tertiary referrals from general practitioners, allied health professionals and non-spinal consultants.

Patients were eligible for inclusion in the trial if they met the following criteria:

- They had been diagnosed with lower extremity radiculopathy (sciatica).
- They had sciatica secondary to prolapsed intervertebral disc (proven by magnetic resonance imaging).
- The duration of their symptoms was between 6 weeks and 12 months. [Note that, if symptoms were episodic, then 'duration of symptoms' refers to the initial incidence of severe symptoms (i.e. the disc prolapse). It does not refer only to the most recent episode.]
- They had leg pain non-responsive to conservative, non-invasive management.
- They were aged 16–65 years.
- They had previously undergone at least one form of conservative (non-operative) treatment (including but not limited to medication, physiotherapy and modification of daily activities) but this had not provided adequate relief of pain/symptoms.
- They provided written, informed consent.

Patients were excluded from the trial if they met any of the following criteria:

- They had a serious neurological deficit (e.g. foot drop/possible cauda equina compression).
- They had previously undergone spinal surgery at the level of the prolapsed intervertebral disc.
- Their current episode of sciatica had lasted longer than 12 months.
- They were aged < 16 years or > 65 years.
- They had not previously undergone any form of conservative treatment.
- Patients with a contraindication for surgery and/or injection.
- They were known to be pregnant.

Contraindications to both groups of treatment were assessed on an individual case-by-case basis by the local health-care team as per routine NHS practice using the current drug Summaries of Product Characteristics and according to local policy.

Trial procedures

Informed, written consent was obtained from participants. Participants were randomised between groups in a 1 : 1 ratio, with variable block randomisation stratified by centre. Blinding was not possible because of the nature of the intervention.

A screening log was maintained at each trial centre, which recorded all individuals screened for the trial and the eventual outcome. Reasons for non-recruitment were documented (e.g. not eligible, declined consent) and the information was used for monitoring purposes. Patients were asked if they would like to provide a reason for non-consent, although they were not obliged to provide one. Reasons for non-participation that relate to patient preference were recorded with the undesired treatment listed when possible.

Data collected at the baseline visit included:

- medical and spinal surgical history
- a participant-completed questionnaire booklet [incorporating the Oswestry Disability Questionnaire; the modified Roland–Morris (for sciatica); the Core Outcome Measures Index; visual analogue scores for leg and back pain; the EuroQol-5 Dimensions, five-level version; and a Resource Use Questionnaire].

Treatment started within 6 weeks of randomisation when possible and no later than 12 weeks after randomisation. Data collected at the treatment visit included:

- treatment details
- a participant-completed Resource Use Questionnaire booklet.

Normal clinical practice usually includes a 3-month post-treatment follow-up. Therefore, participants were followed up at approximately 18 weeks post randomisation to align with routine clinical practice, and then at 30, 42 and 54 weeks. Participants could have also been seen at other times as clinically indicated. Additional visits outside the trial protocol were recorded.

The 18- and 54-week follow-ups were face-to-face clinic visits when possible, and the 30- and 42-week follow-ups were postal questionnaires sent to participants for completion and return.

Data collected at the follow-up visits included:

- work status, concomitant medications, related adverse events and additional treatments
- a participant-completed questionnaire booklet.

Outcome measures

Primary outcome

The primary outcome was the participant-completed Oswestry Disability Questionnaire score (a condition-specific outcome measure with > 30 years of scientific validation) at 18 weeks post randomisation.

Secondary outcomes

Secondary outcomes were Oswestry Disability Questionnaire score at 30, 42 and 54 weeks and visual analogue scale scores for leg and back pain, modified Roland–Morris score, Core Outcome Measures Index score and a Likert scale assessing participant satisfaction at 54 weeks. Health-related quality of life was assessed using the EuroQol-5 Dimensions, five-level version, which was also used for estimating quality-adjusted life-years for the cost-effectiveness analysis.

Sample size

A total of 172 participants were required to detect a clinically important difference of 10 points between the two groups on the Oswestry Disability Questionnaire at a 5% significance level and with 90% power. This assumed a standard deviation of 20 points based on a similar population in previous published trials. The initial target sample size for the trial was 200 patients, which would allow for a 10% rate of missing outcome data. As this initial sample size calculation did not account for the analysis being adjusted for baseline values of the Oswestry Disability Questionnaire, the sample size was recalculated after outcome data were received for 47 participants. A blinded analysis of the correlation between baseline and follow-up Oswestry Disability Questionnaire scores was carried out to adjust the sample size calculation. Based on the observed correlation of 0.49, the revised sample size to achieve 90% power was 66 participants per group. Allowing for 10% loss to follow-up gave a revised target of 74 participants per group (148 participants in total).

Statistical methods

The primary outcome (i.e. Oswestry Disability Questionnaire score at 18 ± 6 weeks post randomisation) was compared between groups using a linear regression model, adjusted for the randomisation stratification variable centre and baseline Oswestry Disability Questionnaire score. Oswestry Disability Questionnaire score at all follow-up visits, visual analogue scale scores for back and leg pain, modified Roland–Morris score and Core Outcome Measures Index score were analysed using a repeated-measures mixed-effects model, adjusting for baseline outcome measure, treatment arm, time (fitted as a continuous variable) and a time–treatment arm interaction (if significant). Site was fitted as a random effect. The Likert scale for satisfaction with care was analysed using the Mann–Whitney *U*-test. Employment status was analysed using a chi-squared test. The intention-to-treat principle was applied as far as was practically possible (i.e. where data were available). The analysis set for the primary outcome included all participants with a valid Oswestry Disability Questionnaire score (at least 8 out of 10 items) at baseline and at 18 ± 6 weeks post randomisation.

A sensitivity analysis was carried out using multiple imputation to assess the robustness of the analysis to missing primary outcome data. Safety data on adverse events and serious adverse events are presented descriptively, with no inferential statistics.

A post hoc analysis was carried out using joint modelling of the longitudinal outcomes (i.e. Oswestry Disability Questionnaire scores, visual analogue scale scores for back and leg pain, modified Roland–Morris score and Core Outcome Measures Index score) and the time to study dropout for each outcome to address the possibility of informative dropout.

Economic evaluation

The economic analysis adopted the perspective of the NHS in England. Resource use was estimated from routine NHS data, trial case report forms and patient-completed questionnaires, comprising Hospital Episode Statistics data, medication usage and self-report cost data at 12-weekly intervals. Utilities were estimated from responses to the EuroQol-5 Dimensions, five-level version, multiattribute utility instrument. Costs were valued in Great British pounds and based on 2017/18 prices. Inflation indices were applied as necessary. No discounting was applied as the time horizon of analysis was approximately 12 months. When possible, missing utility data were estimated through interpolation; otherwise missing cost and utility data were multiply imputed. Regression analyses were used to estimate mean total costs and quality-adjusted life-years. The primary outcome of the economic evaluation was the incremental cost per quality-adjusted life-year of microdiscectomy compared with transforaminal epidural steroid injection. Uncertainties in costs, quality-adjusted life-years, the incremental results and resulting cost-effectiveness metrics were evaluated using a non-parametric bootstrap of the patient-level data. Scenario analyses were conducted to test the impact on the incremental cost-effectiveness ratio, including out-of-pocket costs and productivity losses arising from time off work that approximated a societal perspective, alternative quality-adjusted life-year valuation methods, the impact of varying the doses of 'when-needed' medications and including only sciatica-related costs.

Results

Clinical results

There was no statistically significant difference between the groups for the primary end point. The adjusted estimate of the effect of microdiscectomy compared with transforaminal epidural steroid injection at 18 weeks on Oswestry Disability Questionnaire score was −4.25 (95% confidence interval −11.09 to 2.59) points. At 18 weeks, the Oswestry Disability Questionnaire scores was improved in 87% of participants in the microdiscectomy group compared with 90% of participants in the transforaminal epidural steroid injection group. Among these participants, Oswestry Disability Questionnaire scores improved by > 10 points in approximately 74% of those in the surgical group and 68% of those in the transforaminal epidural steroid injection group. The mean reduction in Oswestry

Disability Questionnaire score at 18 weeks was slightly greater in the surgical group (i.e. 26.74 points), but was similar to the improvement seen following transforaminal epidural steroid injection (i.e. 24.52 points). There was no significant difference in the two treatments at any time point up to 1 year and on any outcome domain (i.e. Oswestry Disability Questionnaire score, visual analogue scale scores for back and leg pain, modified Roland–Morris score and Core Outcome Measures Index score were not significant). There was a slight preference in terms of participant satisfaction for microdiscectomy, with a median score of 1 (i.e. 'completely satisfied') for microdiscectomy compared with a median score of 1.5 (i.e. between 'completely satisfied' and 'somewhat satisfied') for transforaminal epidural steroid injection.

Additional treatment

Prior to primary outcome evaluation, 14 participants (17.5%) who received transforaminal epidural steroid injection subsequently received microdiscectomy. Overall, 28 participants (35%) received microdiscectomy in addition to transforaminal epidural steroid injection.

Post hoc

There was no statistically significant difference between groups for the joint models of the longitudinal outcomes (i.e. Oswestry Disability Questionnaire score, visual analogue scale scores for back and leg pain, and modified Roland–Morris score) and the time to study dropout. The joint model for Core Outcome Measures Index suggests a significant treatment effect of −0.78 (95% confidence interval −1.54 to −0.02) once adjusted for informative dropout, but this is less than the minimum clinically important difference of 2.2.

Safety

Four out of 105 participants who received microdiscectomy experienced a related serious adverse event (i.e. 3.8%). No serious adverse events were associated with transforaminal epidural steroid injection.

Economic analysis

The mean total cost associated with microdiscectomy over the 54-week trial was £6919 (95% confidence interval £5503 to £8046). The mean total cost associated with transforaminal epidural steroid injection over the 54-week trial was £4706 (95% confidence interval £3821 to £5516). The mean total quality-adjusted life-years gained was 0.616 (95% confidence interval 0.570 to 0.671) and 0.559 (95% confidence interval 0.503 to 0.620) in the microdiscectomy and transforaminal epidural steroid injection groups, respectively. The mean incremental costs and quality-adjusted life-years were £2212 (95% confidence interval £629 to £3677) and 0.057 (95% confidence interval −0.009 to 0.124), respectively. This results in an incremental cost-effectiveness ratio of £38,737 per quality-adjusted life-year gained and, at a threshold of £20,000 per quality-adjusted life-year, an incremental net health benefit loss of 0.054 quality-adjusted life-years. The probability of microdiscectomy being cost-effective at £20,000 per quality-adjusted life-year is 0.17, and the probability of microdiscectomy being cost-effective at a higher threshold of £30,000 per quality-adjusted life-year is 0.37.

Conclusions

Both microdiscectomy and transforaminal epidural steroid injection are effective in producing clinically significant improvements in pain and disability associated with sciatica secondary to a prolapsed intervertebral disc, if treated within 12 months of symptom onset. There is no evidence that microdiscectomy is associated with better improvements in pain and disability than transforaminal epidural steroid injection. Microdiscectomy is unlikely to be cost-effective at a threshold of £20,000 per quality-adjusted life-year.

Recommendations for future research

- A longer-term outcome assessment of trial patients beyond 12 months to determine rate of long-term relapse is required.
- A thorough health economic/safety evaluation of a proposed clinical pathway, whereby transforaminal epidural steroid injection precedes microdiscectomy (except for individual circumstances) for persistent sciatica, is needed.

Trial registration

This trial is registered as ISRCTN04820368 and EudraCT 2014-002751-25.

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