Posterior cervical foraminotomy versus anterior cervical discectomy for Cervical Brachialgia: the FORVAD RCT

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/OTOH7720.

Primary conflicts of interest: Peter Hutchinson declares participation in the Health Technology Assessment (HTA) Intellectual Property Panel (2016–8) and in HTA Prioritisation Committee B (in hospital, 2016–22). Deborah Stocken declares membership of the Efficacy and Mechanism Evaluation (EME) Funding Committee (2020–present).

Published October 2023
DOI: 10.3310/OTOH7720

Scientific summary

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Health Technology Assessment 2023; Vol. 27: No. 21
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NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

As people age, degenerative disease affects the intervertebral discs, facet joints and ligamentum flavum in the cervical spine. Consequently, the nerve root foramina may change shape and the nerve roots become compressed, causing a syndrome called cervical radiculopathy. Cervical radiculopathy is characterised by neck pain and cervical brachialgia, with the symptom of pain originating in the neck and radiating down into the upper arm. The reported incidence of cervical brachialgia is 1.79 cases per 1000 per year, with > 110,000 cases of brachialgia annually in the UK. Cervical brachialgia typically affects people aged 40–60 years, with up to 15% of patients unable to work because of the pain.

In most patients, brachialgia is self-resolving with conservative management strategies. However, if symptoms persist 6 weeks to 3 months after onset, two of the available surgical techniques used (in the UK) to treat cervical brachialgia are posterior cervical foraminotomy (PCF) and anterior cervical discectomy (ACD). The most common and current standard operation is ACD, approaching from the front of the neck. The procedure is effective, but there is a high incidence of significant, potentially permanent, complications, including dysphagia and hoarse voice, which can be devastating to a patient's quality of life. Alternatively, PCF can be undertaken from the back of the neck. Unlike ACD, PCF avoids risk to the structures in front of the spine including the carotid artery, sympathetic trunk, recurrent laryngeal nerve, larynx and pharynx, but may result in higher levels of postoperative neck pain and a greater need for revision surgery.

Controversy therefore exists over which procedure is superior for the treatment of cervical brachialgia, and the decision on which procedure to use is frequently left to surgeon preference. The posterior cervical FORaminotomy Versus Anterior cervical Discectomy in the treatment of cervical brachialgia (FORVAD) trial aimed to robustly compare the two procedures, with the ambition of providing definitive evidence that would guide surgical decision-making for patients with cervical brachialgia symptoms requiring surgical intervention.

Objectives

The primary objective of the trial was to determine whether PCF is superior to ACD in terms of improving clinical outcome, as measured by the Neck Disability Index (NDI) at 52 weeks post operation, among patients with persistent cervical brachialgia for whom conservative management has failed. The secondary objectives were comparison of the two surgeries in terms of NDI score, patient-reported neck and upper-limb pain, dysphagia and globus, hoarse voice symptoms, incidence of revision surgery, cost effectiveness over 52 weeks post operation, the extent and severity of a patient's spinal cord functional impairment, and incidence of surgical complications up to 6 weeks post operation. The exploratory objectives were to explore the impact of variations in the optional surgical components of PCF (open or minimal-access surgery) and ACD (surgery with or without a plate) on NDI and EuroQol-5 Dimensions, three-level version (EQ-5D-3L) scores.

Design

The FORVAD trial was a UK multicentre, Phase III, parallel-group, superiority, individually randomised controlled trial comparing the clinical effectiveness and cost effectiveness of PCF with those of ACD among patients experiencing symptomatic unilateral cervical brachialgia for at least 6 weeks, with confirmed nerve root compression on magnetic resonance imaging or computerised tomography myelography. Neither participants nor medical or clinical trial staff in the FORVAD trial were blinded to

the treatment allocated. The trial incorporated an internal pilot phase to assess the feasibility of trial delivery against prespecified recruitment criteria.

Participants were randomised (1 : 1) to receive PCF or ACD via minimisation incorporating a random element, with minimisation factors of centre, duration of upper-limb symptoms and smoking status. Participants were followed up in clinic at day 1 and 6 weeks post operation, and by post at 12, 26, 39 and 52 weeks post operation. The target sample size was 252 participants (126 per trial arm). This number was required to have 90% power to detect the minimum clinically important difference of 10% (5 points) in the change in NDI score at 52 weeks post operation, assuming a between-patient standard deviation of 23 units, two-sided 5% significance level and 10% loss to follow-up.

For the analysis of the primary outcome measure, it was intended to use a multilevel linear regression model incorporating random effects with respect to centre, and adjusting for baseline (day 0) NDI score and minimisation factors (duration of upper limb symptoms and smoking status). The statistical analysis plan was amended prior to final analysis of the data to account for the restricted sample size owing to the early closure of the trial and was limited to descriptive summaries.

Setting

The trial aimed to recruit from 15 NHS hospitals throughout the UK. Participating surgeons were expected to perform both trial procedures and were required to have performed a minimum of 10 of each surgical procedure and to have completed a bespoke training package on the e-brain platform [www.ebrain.net (accessed 25 April 2022)].

Participants

Patients were eligible to participate if they had been diagnosed with unilateral cervical brachialgia that had persisted for at least 6 weeks, resultant from single-level nerve entrapment, and conservative management had previously failed. Patients with cervical myelopathy, spinal cord compression or who had previously had cervical spine surgery were excluded. Eligibility waivers were not granted in this trial.

Interventions

Pre-operative investigations and preparation were as per individual site protocol. Participants received either PCF or ACD. Minimal- and open-access techniques were permitted for PCF. For ACD, the choice of fusion material and the decision to use a plate were left to surgeon discretion. Postoperative care was also as per individual site protocol.

Main outcome measures

The primary outcome measure was the patient-reported percentage NDI score at 52 weeks post operation. Secondary patient-reported outcomes (collected at baseline; at days 1 and 6; and at 12, 26, 39 and 52 weeks post operation) were collected using the Numerical Rating Scale–Neck Pain (NRS-NP), the Numerical Rating Scale–Arm Pain (NRS-AP), the validated PainDETECT, the Eating Assessment Tool-10 items (EAT-10), the Glasgow–Edinburgh Throat Scale (GETS) and the Voice Handicap Index-10 items (VHI-10) tools. Secondary clinical outcomes included a restricted version of the American Spinal Injury Association (ASIA) assessment scale, intraoperative and postoperative complications, incidence of reoperations within 52 weeks of operation and assessment of hoarse voice from additional voice recordings collected from randomly selected participants using the grade, roughness, breathiness, asthenia and strain scoring system. Exploratory outcomes included whether participants receiving PCF received minimal- or open-access surgery, and whether participants receiving ACD received surgery with or without a plate. Patient-reported outcomes were recorded using the EQ-5D-3L, which, alongside collected health resource use data, informed cost-effectiveness analysis.

Results

Owing to slower than expected accrual, the trial closed to recruitment after randomising 23 participants, 14 to PCF and 9 to ACD, from 11 sites. Therefore, results from the trial should be interpreted with caution because of the small sample size. The median NDI scores at baseline and 52 weeks were 44.0 [interquartile range (IQR) 36.0–62.0] and 25.3 (IQR 20.0–42.0) in the PCF group, respectively, indicating a reduction (improvement) from baseline. In the ACD group, the median scores at baseline and 52 weeks were 35.6 (IQR 34.0–44.0) and 45.0 (IQR 20.0–57.0), respectively. Unlike the PCF group, NDI scores did not appear to improve from baseline in the ACD group.

For the NRS-NP and NRS-AP, there was an initial increase from baseline in neck pain score on day 1 post operation in both groups [median 5.5 (IQR 4.0–8.0) at baseline to 8.5 (IQR 6.0–10.0) at 1 day post operation in the PCF group; median 5.0 (IQR 4.0–7.0) at baseline to 7.0 (IQR 4.0–9.0) at 1 day post operation in the ACD group]. Neck pain decreased after day 1 in both treatment groups; at 52 weeks, the median scores were 4.0 (IQR 2.0–5.0) in the PCF group and 5.0 (IQR 3.0–7.0) in the ACD group. In both groups, arm pain improved on day 1 [median 3.0 (IQR 2.0–8.0) in the PCF group; median 4.0 (IQR 0.5–5.0) in the ACD group] and reached its lowest level 12 weeks post operation [median 3.0 (IQR 2.0–8.0) in the PCF group; median 2.5 (IQR 0.0–5.0) in the ACD group]. Thereafter, arm pain deteriorated (increased), but remained below baseline [median 5.0 (IQR 2.0–7.0) in the PCF group and median 5.0 (IQR 3.0–6.0) in the ACD group at 52 weeks].

PainDETECT category scores fluctuated over the postoperative period in the PCF group, but reduced over time in the ACD group, suggesting that in the ACD group a higher proportion of the participants had developed nociceptive, rather than neuropathic, pain. The ASIA score remained unchanged in both treatment groups over the 6-week assessment period.

For the EAT-10 and the VHI-10 outcomes, the ACD group had worse outcomes at day 1 [median EAT-10 scores of 0.0 (IQR 0.0–4.0) in the PCF group and 13.5 (IQR 3.5–16.0) in the ACD group, and median VHI-10 scores of 0.0 (IQR 0.0–2.0) in the PCF group and 2.0 (IQR 0.5–8.5) in the ACD group], after which the two groups are comparable. However, the median GETS score was worse in the ACD group postoperatively, although the IQRs in each treatment group overlap at all time points except day 1.

Five postoperative complications were reported in five participants throughout the trial, all occurring in the ACD group. Reported complications included two instances of dysphagia and three 'other' complications: 'wound infection', 'urinary retention' and 'wound redness stitches overnight'. No serious or unexpected serious complications, deaths or reoperations were reported.

The health economics and qualitative study

The revised aims of the cost-effectiveness analysis were to describe the costs of the surgical interventions, health-care service use and participant out-of-pocket expenditures, and the productivity costs of losses associated with the surgery and its consequences. Responses to the EQ-5D-3L questionnaire of generic health-related quality of life and the rate of data completion are summarised. All costs are based on 2019/20 prices and are presented without discounting, as the time horizon of the analysis is 52 weeks.

The costs of the intervention were heavily influenced by outliers in the PCF group, resulting in mean health-care costs of initial surgery, including devices, operation and hospital stay, of £2745 [95% confidence interval (CI) £2344 to £3147] for the PCF group (n = 12) and £4295 (95% CI £3436 to £5154) for the ACD group (n = 8). The corresponding median costs were £2622 (IQR £2402–2824) for participants undergoing PCF and £4423 (IQR £3849–4821) for participants undergoing ACD. These costs were driven by the time in theatre, which was a mean of 30 minutes (median 45 minutes) shorter for PCF (mean 61 minutes, median 52 minutes, IQR 49–60 minutes) than for ACD (mean 91 minutes, median 100 minutes, IQR 75–109 minutes).

Results aggregated up to week 6 are presented owing to high attrition thereafter. The mean costs from the NHS and Personal Social Services perspective were £2716 (95% CI £2345 to £3087) for the PCF group and £4133 (95% CI £3099 to £5167) for the ACD group; the median costs were £2634 (IQR £2444–2741) and £4214 (IQR £3602–4994) for the PCF and ACD groups, respectively. The mean per-patient costs to society were £4608 (95% CI £2514 to £6703) for the PCF group and £5015 (95% CI £2286 to £7743) for the ACD group; the median costs were £4097 (IQR £2448–6591) and £4143 (IQR £4126–4284) for the PCF and ACD groups, respectively.

At baseline, severe problems with anxiety and depression were more common, and pain and discomfort according to the EQ-5D-3L classification system was more severe in the PCF group than in the ACD group, resulting in mean utility scores of 0.291 (95% CI 0.07 to 0.51) and 0.595 (95% CI 0.40 to 0.78) for PCF and ACD, respectively. The corresponding median scores were 0.210 (IQR −0.01 to 0.60) and 0.689 (IQR 0.66–0.69). This is likely to have played a role in the larger observed gains from baseline in postoperative EuroQol-5 Dimensions (EQ-5D) scores for participants in the PCF group than in the ACD group [median change at 6 weeks of 0.10 (IQR 0.00–0.13) and 0.02 (IQR −0.03 to 0.06), respectively].

A rapid qualitative study was conducted during trial close-down to understand the experiences of health-care professionals and participants who participated in the FORVAD trial and why recruitment had been challenging, with the aim of informing future research in this area.

Semistructured interviews were conducted with 18 health-care professionals (research nurses and surgeons) and two participants who had participated in the FORVAD trial. Interviews explored participants' experiences of the FORVAD trial and their reasons for taking part, and staff experiences of recruiting to the FORVAD trial and neurosurgery trials in general. Interviews were audio-recorded and transcribed verbatim. Transcripts were analysed using rapid qualitative analysis.

There was no single key factor that limited recruitment, and several themes were identified as common to all sites. Surgeons at participating sites supported the trial, and recognised collective clinical equipoise; however, many had preferences for one or the other procedure, linked to their usual practice. Organisation of the trial recruitment pathway varied, with some sites choosing to direct potentially eligible patients to dedicated clinics and other sites taking a more ad hoc approach. In the FORVAD trial, the dedicated clinic approach appeared to contribute to more eligible patients being identified and recruited, although staff at other sites explained that dedicated clinics did not fit easily with their clinical pathways. Randomisation on the day of surgery presented ethical and organisational challenges, and, where possible, should be avoided in future surgical trials.

Organisation and implementation of a surgical trial in neurosurgery are complex and present many challenges. Future trials in neurosurgery should identify aspects of the protocol where it is possible to offer flexibility and ensure early multidisciplinary involvement at sites to maximise the effective integration of trial and clinical pathways.

Conclusions

The data suggest that PCF may be associated with better outcomes, fewer complications and lower cost, but the trial recruited slowly and was closed early. As a consequence, the trial is underpowered and definitive conclusions cannot be drawn.

Trial recruitment was impaired by the lack of individual equipoise and concern about randomising on the day of surgery. A large prospective multicentre trial comparing ACD and PCF in the treatment of cervical brachialgia is still required.

Trial registration

This trial is registered as ISRCTN10133661.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 27, No. 21. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.6

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 16/31/53. The contractual start date was in January 2018. The draft report began editorial review in July 2021 and was accepted for publication in March 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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