DiPALS: Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis – a randomised controlled trial

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Scientific summary

DiPALS

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Scientific summary

Background

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease resulting in death, usually from respiratory failure, within 2–3 years of symptom onset. Affected individuals experience increasing weakness affecting the limbs, speech and swallowing, and breathing. Management is largely aimed at easing symptoms and supporting patients to maximise their function through a multidisciplinary approach. One treatment, riluzole, can marginally slow down disease progression, prolonging survival, usually by around 3 months.

Non-invasive ventilation (NIV) is a treatment that, when given to patients in respiratory failure, leads to improved survival and quality of life (QoL). A randomised controlled trial (RCT) demonstrated an improvement in QoL and a median survival benefit of approximately 7 months ($p = 0.006$) in ALS patients using NIV who had good bulbar function. However, some individuals are unable to tolerate using the mask and there comes a point in the course of the disease when NIV is no longer effective.

The NeuRX® RA/4 diaphragm pacing system (DPS)™ (Synapse Biomedical, Oberlin, OH, USA) is a four-channel percutaneous neuromuscular stimulation system that may offer additional or alternative benefits to patients with ALS in respiratory failure. Stimulating electrodes are inserted into the undersurface of the diaphragm, using a minimally invasive laparoscopic technique. The leads (including an additional anode) are then tunnelled to an exit site on the abdomen and an external stimulator delivers the stimulus pulses.

Initial experience with the NeuRX RA/4 DPS in the spinal cord injury population suggested diaphragm pacing (DP) could reduce time spent on mechanical ventilation. The NeuRX RA/4 DPS is now licensed for use in spinal cord injury across many countries, including the USA, and within the European Union.

To date, the evidence base for DPS in the ALS population is limited to a case series and one uncontrolled, multicentre cohort study for which the full data have not been published. Their findings are consistent with those from the spinal cord patient population, and highlighted the apparent simplicity and operative safety of the NeuRX RA/4 DPS. The US Food and Drug Administration approved the NeuRX RA/4 DPS as a humanitarian-use device in ALS following the submission of a humanitarian device exemption application. Following the humanitarian-use device approval of the NeuRX RA/4 DPS for ALS there has been increasing use of this therapeutic option worldwide. The promising survival data, lack of apparent harm and absence of alternatives have made this an appealing option, especially among patients who are unable to tolerate NIV, who may account for up to 50% of patients with ALS. Moreover, pacing is expensive and it is not known if DPS would meet the National Institute for Health and Care Excellence threshold for cost-effective interventions for end-of-life care. Therefore, although the preliminary data are promising, DPS is unlikely to be widely introduced without robust, randomised evidence together with formal analysis of cost-effectiveness. This was our motivation for undertaking the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis (DiPALS) trial.

Objectives

The aim of this study was to perform a definitive RCT of the efficacy and long-term safety of the NeuRX RA/4 DPS when used in addition to NIV, compared with standard care of NIV alone in patients with ALS.

We planned to test the following specific hypothesis:

- The use of DPS in addition to NIV will improve overall patient survival.

We also planned to evaluate the effect of DP in addition to NIV on:

- QoL of participants
- QoL of the main carer
- safety [adverse events (AEs)] and tolerability (withdrawal from treatment)
- quality-adjusted life-years
- views and perceptions of patients and family carers regarding acceptability and impact on life.

Methods

The DiPALS trial was a multicentre, parallel-group, open-label RCT incorporating health economic analyses and a qualitative longitudinal substudy. Patients aged 18 years or above with a confirmed diagnosis of ALS (familial or sporadic ALS diagnosed as laboratory-supported probable, probable, or definite according to the World Federation of Neurology El Escorial criteria) were identified from seven participating UK hospitals. Patients were confirmed as eligible for the trial if they had been stabilised on riluzole therapy and had respiratory insufficiency and clinically acceptable bilateral phrenic nerve function.

Respiratory insufficiency was determined by one or more of:

1. forced vital capacity (FVC) < 75% predicted
2. supine vital capacity < 75% of sitting or standing vital capacity
3. sniff nasal inspiratory pressure (SNIP) < 65 cmH_2O for men or 55 cmH_2O for women in the presence of symptoms
4. SNIP < 40 cmH_2O in the absence of symptoms
5. partial pressure of carbon dioxide ($PaCO_2$) > 6 kPa (daytime) or $PaCO_2$ > 6.5 kPa (overnight)
6. significant overnight O_2 desaturation (> 5% of night with peripheral capillary oxygen saturation < 90%).

Phrenic nerve function defined as clinically acceptable by:

1. absence of paradoxical abdominal wall movement during a sniff manoeuvre (sharp inhalation through the nose) and recording < 10% decline of FVC when moving from sitting to supine position, or
2. on ultrasound: evidence of at least 1 cm of downward diaphragm movement independent of thoracic or abdominal wall movement during the patient performing a sniff manoeuvre.

Patients were not recruited to the trial if they met any of the exclusion criteria:

1. prior NIV prescription
2. pre-existing implanted electrical device such as pacemaker or cardiac defibrillator
3. underlying cardiac or pulmonary diseases, or other disorders that would affect pulmonary tests independently of ALS (increased risk of general anaesthesia or adverse effect on survival over the course of the study)
4. women who were pregnant or breastfeeding at the time of screening

5. significant decision-making incapacity (patient suffered from major depression, schizophrenia, dementia or similar disorder) preventing informed consent by the patient
6. marked obesity affecting surgical access to diaphragm or significant scoliosis/chest wall deformity
7. the involvement in any respiratory trial that could have influenced the safety or outcome measures of the study within 3 months of the planned implantation of the device or during the year of follow-up
8. pre-existing diaphragm abnormality such as a hiatus hernia or paraoesophageal hernia of abdominal contents ascending into the thoracic cavity
9. FVC $< 50\%$ predicted or SNIP $< 30\ cmH_2O$ in patients unable to perform FVC (bulbar patients) (because of potential anaesthetic risk).

Recruited patients were randomly allocated to treatment group using a centralised randomisation system. Patients were allocated their treatment (NIV alone or NIV plus DPS) by method of minimisation, using baseline bulbar function, baseline FVC, age and sex as the minimisation factors.

The primary outcome was overall survival. Secondary outcomes were quality-adjusted life-years [European Quality of Life-5 Dimensions, three levels (EQ-5D-3L)], QoL of the patient (EQ-5D-3L, Short Form questionnaire-36 items and Sleep Apnoea Quality of Life Index questionnaire); QoL of the main carer (EQ-5D-3L and Caregiver Burden Inventory); safety and tolerability of the device; health economic objectives and resource use; and perceptions of patients and carers regarding acceptability and impact of the device.

Follow-up visits were conducted at clinic (1 week, and at 2 months, 3 months, 6 months, 9 months and 12 months). Trial data were collected on the study case report form and patient diary and were entered into a validated bespoke web-based database system (Prospect) managed by the Sheffield Clinical Trials Research Unit (CTRU). Sheffield CTRU has developed Prospect in collaboration with epiGenesys (a software development company wholly owned by the University of Sheffield). Prospect's validation status reflects our approach of continuous development, so is not identified by a formal version number or release date. The source code version control system records all changes and associates these with a specific revision number. Prospect is hosted on servers operated by the University of Sheffield Corporate Information and Computing Services (CiCS) department.

We planned to recruit 108 patients (54 per group) to ensure a power of 85% using a two-sided type I error of 5%. The sample size was estimated based on log-rank test, using Simpson's rule, and estimated on a conservative (but clinically important) 1-year difference in survival of 45% versus 70%, which produced the estimated hazard ratio (HR) of 0.45.

Statistical analyses were by intention to treat, with preplanned secondary analyses of overall survival based on protocol adherence and NIV use. A significance level of 5% was used for significance testing, and all confidence intervals (CIs) were two-sided 95% intervals.

The primary end point was overall survival, defined as the time from randomisation to death from any cause. Overall survival was compared between the groups using the log-rank test and modelled using Cox proportional hazards regression, with the minimisation factors as covariates. QoL was analysed both longitudinally (i.e. over the duration of the trial rather than individual time points) and at the end of the study follow-up (12 months).

Average NIV use was defined as the average number of hours used from the date of NIV initiation onwards, and DPS usage was defined as the average daily use from the date of procedure onwards. The relationship between NIV and DPS usage by time point was also assessed. NIV use by participants was categorised as non-adherence (typical usage below 1 hour per day), low adherence (typical usage 1 to < 4 hours per day) or good adherence (typically ≥ 4 hours per day).

Adverse events and serious AEs were coded by the chief investigator blind to the participant's treatment group. AEs were summarised for each AE category and overall as the number and percentage of patients affected and the number of events in total (as the same AE may occur more than once in the same patient).

Sheffield Teaching Hospitals NHS Foundation Trust sponsored the trial (reference STH15625). Oversight committees were established to govern study conduct: a Trial Management Group, a Trial Steering Committee and a Data Monitoring and Ethics Committee (DMEC). The trial was conducted in accordance with CTRU standard operating procedures with committees convening at appropriate intervals as dictated by both study requirements and standard operating procedures.

Qualitative substudy

A qualitative longitudinal study formed a subelement of the trial design.

The aim of the qualitative component was to evaluate the acceptability and perceived impact of the intervention on patients with ALS and their family.

Methods

We purposively selected participants for the qualitative element of the study from those randomised to the pacing intervention arm of the trial. We intended that our sample would include diversity in terms of patient sex, age and ALS type and across the different ALS centres taking part in the trial.

Qualitative interviews with patients and carers were carried out at two time points: 1 month following initiation of the pacing intervention and, when possible, 6 months later.

Early stopping

The DMEC recommended early stopping of the trial on safety grounds following review of unblinded survival data. The DMEC advised initial suspension of recruitment (December 2013), and subsequent discontinuation of pacing in all patients (June 2014).

Results (research findings)

In total, 74 participants (37 per arm) were randomised between 5 December 2011 and 18 December 2013, when the DMEC recommended that recruitment cease. Study follow-up concluded in December 2014, by which time 47 patients had died; one patient was last followed up in August 2014, with the remaining 26 known to be alive in December 2014.

The median survival (interquartile range) was 22.5 months (lower quartile, 11.8 months' upper quartile not reached) months in the NIV arm and 11.0 months (6.7–17.0 months) in the NIV plus pacing arm, with an adjusted HR of 2.27 (95% CI 1.22 to 4.25; $p = 0.01$). Patient QoL during 12-month follow-up was lower in the NIV plus pacing arm when assessed by EQ-5D-3L, but was similar on other measures. Carer QoL was similar on all measures.

Non-invasive ventilation was initiated in 70 out of 74 patients. Overall, 57 patients were initiated within 2 weeks of randomisation, a further six within 1 month and the remaining seven between 3 and 11 months. NIV use was similar in the two groups; the median (interquartile range) in the NIV plus pacing arm was 3.2 hours (0.5–8.2 hours) and in the NIV arm was 4.6 hours (0.0–7.8 hours).

Five pacing group participants did not undergo surgery; the reasons were respiratory function below safety threshold ($n = 1$), patient choice ($n = 2$) and DMEC intervention ($n = 2$). A sixth patient stopped pacing within 1 month because of device technical issues.

Implantation was successful for all who underwent surgery. When used, the median daily usage was 4.6 hours (interquartile range 3.0–8.4 hours), with target pacing largely achieved by 15 days.

Fourteen patients took part in the qualitative substudy; nine were interviewed both immediately following initiation of DP and 6 months later. The device was described as being easy to operate, having little impact on life, and was often preferred to NIV. Tolerance of DP varied, with some patients experiencing significant levels of pain, whereas others reported only a noticeable but minor sensation. Patients described hope that the intervention would lead to benefits in the longer term; however, few perceived any direct gains.

Conclusions

Meaning of the study and implications for clinicians or policy-makers

Diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure. We cannot exclude that in subgroup of patients there is a benefit; however, this should not be assumed. Our findings demonstrate that insertion of the NeuRX RA/4 DPS is harmful when instigated at the point at which an individual with ALS develops respiratory failure. A study investigating whether or not implanting earlier in the ALS disease trajectory is of benefit has recently been suspended, and the full results from this study are awaited (NCT01583088). DPS has also been approved for use in the spinal cord injury population. Before widespread use of DPS in the spinal cord injury population, or indeed other populations, we suggest that the evidence base needs to be firmly established.

A poor prognosis and the absence of curative therapy understandably encourage a ‘nothing to lose’ approach among patients and some clinicians alike, with an attendant lowering of the standards of evidence required to adopt a new intervention. Our trial demonstrates the potential for harm that can arise from adopting this approach. We strongly recommend that all interventions be subjected to appropriate study, which will usually mean a RCT, before adoption into routine practice. This should apply to medical devices, particularly those that expected to have an impact on survival or necessitate invasive procedures.

Recommendations for future research

We cannot exclude that a subgroup of highly selected individuals might benefit from DP, for example those with predominantly upper motor neurone disease. Future work may focus on exploring such uncertainties. Any further studies should include measures to understand the mechanism by which harm or benefit occurs as a result of DP.

Trial registration

This trial is registered as ISRCTN53817913.

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