NICE guidance

Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease

Interventional procedures guidance
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www.nice.org.uk/guidance/ipg593

This guidance replaces IPG307.

1 Recommendations

1.1 Current evidence on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease suggests that there are serious long-term safety concerns. Evidence on efficacy is limited and therefore, this procedure should not be used to treat this condition.

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2 Indications and current treatments

2.1 Motor neurone disease is a neurodegenerative condition affecting the brain and spinal cord. The most common type of the disease is amyotrophic lateral sclerosis. Motor neurone disease is characterised by the degeneration of primarily motor neurones, leading to muscle weakness, limb weakness, problems with speech, swallowing and breathing, which ultimately leads to respiratory failure and death.

2.2 Current standard care for managing chronic respiratory failure in patients with motor neurone disease includes non-invasive forms of ventilation support (such as Bi-level positive airway pressure [BiPAP]). In advanced stages of respiratory failure mechanical ventilation is done through a permanent tracheostomy.

3 The procedure

3.1 The aim of intramuscular diaphragm stimulation is to make the diaphragm contract, strengthening it and allowing full or partial weaning from mechanical ventilation. This procedure needs intact phrenic nerve function, and avoids the need to access the phrenic nerve through the neck or thorax, as well as reducing the risk of phrenic nerve damage.

3.2 The procedure is done laparoscopically with the patient under general anaesthesia. A special probe is used to identify areas of the diaphragm where minimal electrical stimulation causes maximal diaphragm contraction (known as the 'motor points'). Two intramuscular electrodes are implanted on the abdominal surface of each hemi-diaphragm at the motor points. The electrode leads are tunnelled subcutaneously to an exit site in the chest where they are connected to an external battery-powered pulse generator. A reference electrode (anode) is also implanted and the leads tunnelled with the other electrodes. Intraoperative stimulation and voltage calibration tests are carried out to confirm adequate contraction of the diaphragm. After implantation the patient has a diaphragm conditioning programme, which involves progressive use of the system for increasing periods of time with gradual weaning from the ventilator.

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4 Efficacy

This section describes efficacy outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

4.1 In a multicentre randomised controlled trial (RCT) of 74 patients with respiratory failure caused by amyotrophic lateral sclerosis (ALS), non-invasive ventilation (NIV) plus diaphragm pacing (n=37) was compared with NIV alone (n=37). Overall survival (defined as the time from randomisation to death from any cause) was statistically significantly shorter in the NIV plus pacing group than in the NIV-alone group (median 11.0 months; 95% confidence interval [CI] 8.3 to 13.6, compared with 22.5 months; 95% CI 13.6 to not reached, adjusted hazard ratio 2.27; 95% CI 1.22 to 4.25, p=0.009). Tracheostomy-free survival (defined as the time to death or tracheostomy) was also statistically significantly shorter in the NIV plus pacing group than in the NIV-alone group (median 11.0 months; 95% CI 8.3 to 13.6, compared with 22.5 months; 95% CI 13.6 to not reached, adjusted hazard ratio 2.42; 95% CI 1.28 to 4.59, p=0.007). Median survival from symptom onset was 28 months (95% CI 22 to 45) for NIV plus pacing patients and 45 months (95% CI 32 to not reached) for those having NIV alone.

4.2 In another multicentre triple-blind RCT in 74 patients with probable or definite ALS, active stimulation (n=37) was compared with sham stimulation (n=37). The NIV-free survival in the intention-to-treat population was statistically significantly shorter in the active stimulation group than in the sham stimulation group (median 6.0 months; 95% CI 3.6 to 8.7, compared with 8.8 months; 95% CI 4.2 to not reached, adjusted hazard ratio 1.96; 95% CI 1.08 to 3.56, p=0.02). The cumulative incidence of NIV did not differ between the 2 groups (since randomisation: median 6; 95% CI 5.1 to 12, compared with 8.8; 95% CI 4.7 to not reached, p=0.42; since symptom onset: median 40; 95% CI 33.6 to 61.7, compared with 34.1; 95% CI 26.4 to not reached, p=0.81). A statistically significant difference in overall tracheostomy-free survival in favour of the sham survival group was seen in the final analysis (49% [18/37] of patients died in the active stimulation group compared with 19% [7/37] in the sham stimulation group; adjusted hazard ratio 3.14; 95% CI

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1.31 to 7.53). Overall survival from randomisation was statistically significantly shorter in the active stimulation group than in the sham stimulation group (median 15.6 months; 95% CI 9 to 27, compared with not reached [more than 33], p=0.007). This was also true for overall survival from symptom onset (median 51 months; 95% CI 39 to 74.1, compared with not reached [more than 133], p=0.03).

4.3 In the multicentre RCT of 74 patients with respiratory failure caused by ALS, there were no statistically significant differences between the NIV plus pacing group and the NIV-alone group in patient or carer pre-planned quality-of-life measures. These included the health questionnaires SF-36 (physical health score p=0.78, mental health score p=0.11), Sleep Apnoea Quality of Life (SAQLI, p=0.11) and Caregiver Burden Inventory (CBI, p=0.55). The patient health utility (measured using the EQ-5D-3L) was slightly lower in the NIV plus pacing group than in the NIV-alone group (p=0.056), and the differences were statistically significant when a score of 0 was assigned to the EQ-5D-3L following death. Differences between groups were modest at any individual time point (at 12 months the mean difference was −0.12; 95% CI −0.24 to −0.00, p=0.056), but longitudinal analysis demonstrated statistically and clinically significant differences on all patient EQ-5D-3L questionnaires (mean difference −0.14; 95% CI −0.24 to 0.04, p=0.001).

4.4 The specialist advisers listed key efficacy outcomes as reduction in dependency on external mechanical ventilation, survival and quality of life.

5 Safety

This section describes safety outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

5.1 In a multicentre randomised controlled trial (RCT) of 74 patients with respiratory failure caused by amyotrophic lateral sclerosis (ALS), non-invasive ventilation (NIV) plus diaphragm pacing (n=37) was compared with NIV alone (n=37). In the NIV plus pacing group 76% (26/37) of patients died and in the NIV-alone group 51% (19/37) of patients died.

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The causes of death were similar across the groups (mainly respiratory failure, chest infection, ALS and hypothermia). In another multicentre triple-blind RCT in 74 patients with probable or definite ALS, active stimulation (n=37) was compared with sham stimulation (n=37). More patients died in the active stimulation group than in the sham stimulation group (49% [18/37] compared with 19% [7/37]) as a result of chest infection, acute respiratory failure and terminal respiratory insufficiency. Six patients died before NIV in the active stimulation group because of acute respiratory failure in 5 and sudden cardiac death in 1. No deaths were related to treatment.

5.2 There were more adverse events reported in the NIV plus pacing group than in the NIV-alone group (162 events [5.9 events per person-year] in 78% [29/37] of patients compared with 81 events [2.5 events per person-year] in 62% [23/37] of patients) in the RCT of 74 patients with respiratory failure caused by ALS. More patients had serious adverse events in the NIV plus pacing group than in the NIV-alone group (73% [27/37] compared with 51% [19/37]; 46 events compared with 31 events). Respiratory events were the most common in both groups (68% [25/37] compared with 38% [14/37]) followed by gastrointestinal events (27% [10/37] compared with 24% [9/37]), symptoms of motor neurone disease (22% [8/37] compared with 8% [3/37]), gastrostomy (percutaneous endoscopic or per-oral image-guided insertion; 14% [5/37] compared with 24% [9/37]), genitourinary events (8% [3/37] in each group), cardiovascular events (11% [4/37] compared with 5% [2/37]) and dermatological problems (8% [3/37] compared with 11% [4/37]).

5.3 Serious adverse events (mainly capnothorax or pneumothorax, acute respiratory failure needing mechanical ventilation, venous thromboembolism and gastrostomy tube placement) were reported in 65% [24/37] of the active stimulation group and in 59% [22/37] of the sham stimulation group in the triple-blind RCT of 74 patients. Some patients had more than 1 adverse event. Other serious adverse events reported include dyspnoea (3 patients), loss of walking ability (3 patients), oesophagitis (1 patient), admission to hospital for any cause (3 patients), accidental removal of gastrostomy tube (1 patient), and reopening of the laparoscopy insertion point needing repair (1 patient). Capnothorax was reported in 13% (5/38) of patients with ALS in a case

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series of 88 patients. Capnothorax was managed successfully by aspiration, drainage or observation.

5.4 Suture granuloma causing infection at the superficial wire connection site (treated by externalising the electrodes) was reported in 1 patient with ALS in the case series of 88 patients. Infection at the stimulation cable entry point was noted in 22% (8/37) of patients in the active group (3 patients needed antibiotics) and 19% (7/37) of patients in the control group (5 patients needed antibiotics) in the triple-blind RCT of 74 patients. Respiratory infections (needing antibiotics) were reported in 5 patients in a case series of 16 ALS patients with respiratory insufficiency treated by diaphragm pacing. Superficial wound infection (treated with antibiotics) was reported in 1 patient in the same study. Urinary infection (needing admission to hospital) and severe pulmonary infection were reported in 1 patient each in a case series of 11 patients.

5.5 External electrode repairs were needed in 7 patients in the case series of 16 patients with ALS. Wire failure was reported in 14% (5/37) of patients in the NIV plus diaphragm pacing group in the RCT of 74 patients with respiratory failure caused by ALS.

5.6 Pain (needing analgesics) was commonly reported in the active stimulation and sham stimulation groups (92% [34/37] compared with 89% [33/37]) in the triple-blind RCT of 74 patients. Pain needing a reduction in the intensity of diaphragm pacing was noted on day 2 in 54% (20/37) of patients in the active stimulation group and none in the sham stimulation group in the same study.

5.7 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse event: excess mortality. They considered that the following were theoretical adverse events: decompensated respiratory failure, breathlessness related to diaphragm pacing and atrophy and progression of diaphragm weakness.

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6 Committee comments

6.1 Randomised controlled trials showed increased mortality in the treatment groups, although the reasons for this were unclear.

6.2 Despite apparent short-term procedural success there were serious concerns about the long-term outcomes.

7 Further information

7.1 For related NICE guidance, see the NICE website.

7.2 Patient commentary was sought but none was received.

Information for patients

NICE has produced information on this procedure for patients and carers (information for the public). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

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Accreditation

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