NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional procedure consultation document

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

Some patients with motor neurone disease (also called amyotrophic lateral sclerosis or ALS) need a mechanical ventilator to help them breathe. Intramuscular diaphragm stimulation involves keyhole abdominal surgery (laparoscopy) to implant electrodes into the diaphragm. Wires from the electrodes run under the skin to a battery-operated electrical stimulation system, which causes the diaphragm to contract as in normal breathing. The aim of the procedure is to allow patients to breathe without a ventilator and to improve their quality of life.

The National Institute for Health and Care Excellence (NICE) is examining intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease and will publish guidance on its safety and efficacy to the NHS. NICE's interventional procedures advisory committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The advisory committee has made draft recommendations about intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease.

This document summarises the procedure and sets out the draft recommendations made by the advisory committee. It has been prepared for public consultation. The advisory committee particularly welcomes:

- comments on the draft recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

Note that this document is not NICE's formal guidance on this procedure. The recommendations are provisional and may change after consultation.

The process that NICE will follow after the consultation period ends is as follows.

- The advisory committee will meet again to consider the original evidence and its draft recommendations in the light of the comments received during consultation.
- The advisory committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.

For further details, see the Interventional Procedures Programme process guide, which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 23 June 2017

Target date for publication of guidance: September 2017

1 Draft 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.

2 Indications and current treatments

2.1 Motor neurone disease (MND) is a neurodegenerative condition affecting the brain and spinal cord. The most common type of MND is amyotrophic lateral sclerosis. MND 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 MND 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. Phrenic nerve pacing, in which the diaphragm is stimulated to contract by electrodes placed on the phrenic nerve in the neck or thorax, is an alternative treatment for patients who have intact and functional phrenic nerves (the nerves that contract the diaphragm).

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 and are connected to an external battery-powered pulse generator. A reference electrode (anode) is also implanted and 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.

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 ***[add URL]***.

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 shorter in the NIV plus diaphragm 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 similar to overall survival (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 diaphragm 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 median NIV-free survival in the intention-to-treat population was 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 significant difference in overall tracheostomy-free survival was seen in the final analysis (49% [18/37] compared with 19% [7/37]); from randomisation: median 15.6 months; 95% CI 9 to 27, compared with not reached (more than 33), p=0.007; from symptom onset: median 51 months; 95% CI 39 to 74.1, compared with not reached (more than 133), p=0.03; adjusted hazard ratio 3.14; 95% CI 1.31 to 7.53.

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 diaphragm pacing group and the NIV alone group in patient or carer pre-planned quality-of-life measures. These included the health questionnaire SF-36 (physical health score p=0.78, mental health score p=0.11), Sleep Apnoea Quality of Life questionnaire (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 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 ***[add URL]***.

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 pacing group 76% (26/37) of patients died and in the NIV alone group 51% (19/37) of patients died. 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] compared with 81 events [2·5 events per person-year]; 78% [29/37] compared with 62% [23/37]) in the RCT of 74 patients with respiratory failure caused by ALS. More patients had serious adverse events in the pacing group than in the NIV alone group (73% [27/37] compared with 51% [19/37]; 46 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] compared with 8% [3/37]), 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 (in 3 patients), loss of

walking ability (in 3), oesophagitis (in 1), admission to hospital for any cause (in 3), accidental removal of gastrostomy tube (in 1), and reopening of the laparoscopy insertion point needing repair (in 1). Capnothorax secondary to carbon dioxide tracking above the diaphragm was reported in 13% (5/38) of patients with ALS in a case 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 a case series of 88 patients. Infection at the stimulation cable entry point was noted in 22% (8/37) of patients in the active group (antibiotics needed in 3 patients) and 19% (7/37) of patients in the control group (antibiotics needed in 5 patients) in the triple-blind RCT of 74 patients. Respiratory infections (needing antibiotics) were reported in 5 patients in the case series of 16 ALS patients with respiratory insufficiency treated with 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 the 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.

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.

7.3 This guidance is a review of NICE's interventional procedure guidance on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease.

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May 2017