Non-invasive ventilation and diaphragmatic pacing in ALS

Published Online
July 31, 2015
http://dx.doi.org/10.1016/S1474-4422(15)00185-4

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Nutritional and respiratory care are the most important symptomatic and supportive treatments for patients with amyotrophic lateral sclerosis (ALS). Non-invasive ventilation prolongs survival and maintains overall quality of life, and is now regarded as the standard of care for patients whose forced vital capacity is reduced to 50% or less.[1,2] However, this technique is not without its shortcomings: some patients simply cannot tolerate it and others have asynchronisation with their own breathing, causing poor sleep.[3] Ultimately, non-invasive ventilation may not be able to support patients' progressive hypoventilation fully, prompting the need for decision making regarding tracheostomy with invasive ventilation or palliative care.[1,2]

The NeuRx 4/4 Diaphragm Pacing System has been developed as an assistive medical device to improve respiratory failure caused by diaphragmatic weakness, mainly in patients with spinal-cord injuries.[4] Four stimulators on the lower diaphragmatic surface are endoscopically placed at or near the neuromuscular junction where the best contractile responses are observed. A multicentre study[5] was done in patients with ALS, showing prolongation of survival in patients treated with the Diaphragm Pacing System compared with published historical data for non-invasive ventilation as the control. On the basis of these results, in 2011, the device received Humanitarian Device Exemption approval from the US Food and Drug Administration (FDA).[6] At that time, a cautionary commentary urged for a scientific publication of that study and further randomised controlled trials.[7] Retrospectively, that no data from the original study were published in scientific papers that had undergone vigorous peer review was an early warning sign.

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To my knowledge, only three randomised controlled studies investigating diaphragm pacing in ALS have been independently initiated, and one of the studies is published in *The Lancet Neurology*.[8] In this study, done by the DiPALS Study Group collaborators, the combination of non-invasive ventilation and diaphragm pacing was worse than non-invasive ventilation alone for survival (median 11·0 months *vs* 22·5 months; adjusted hazard ratio 2·27, 95% CI 1·22–4·25; p=0·009). The investigators would not recommend the use of diaphragm pacing in patients with ALS who develop hypoventilation. The other two studies investigating application of diaphragm pacing are still pending (ClinicalTrials.gov, numbers NCT01938495 and NCT01583088).

This report[8] certainly triggers several important and intriguing questions. Why are the results from this study so different from those of the earlier study, which led to FDA humanitarian exemption? Whereas drug approval from the FDA usually requires two pivotal randomised trials to be done, approval for a medical device does not. Although it is our responsibility to bring either pharmacological or non-pharmacological treatment to patients with this devastating disease at the earliest opportunity, we also have a strong obligation to protect patients from uncertain treatment.

Because the makers of the pacing system and key investigators involved in the study that led to the humanitarian device exemption[5] have the scientific expertise and necessary resources, a randomised controlled trial should have expeditiously followed the initial promising results. Once a drug or device is approved by the FDA, a formal investigation examining efficacy becomes much harder to undertake, which might have contributed to the slow recruitment in the US diaphragm pacing study (NCT01938495; Katz J, California Pacific Medical Center, CA, USA, personal communication). Another important question is how useful and reliable the historical controls are when compared with the results of the previous diaphragm pacing study.[5] Historical controls were

used for the first time in ALS in a study investigating lithium carbonate,[9] in response to a report describing the potential benefits with lithium that triggered a frenzy of hope in the ALS community. The use of historical controls was well justified in the case of lithium because various randomised controlled trials with lithium were already on the horizon. Yet nearly everyone agrees that studies with historical controls are useful only for probing of possibilities, and that any possible efficacy shown should be followed by appropriate randomised controlled trials. Because the ALS community has already accumulated a large amount of data, meaningful historical control-based studies might become a viable option in the future,[10] but how to select historical controls in each trial is still an issue of fundamental importance.

Although the DiPALS investigators fully discuss possible reasons for poor outcomes with non-invasive ventilation and diaphragm pacing in their report,[8] the mechanisms of why this happened could have been investigated with use of periodical nocturnal pulse oximetry and, in selected patients, polysomnograms could have been obtained. This information would have helped us learn how to manage non-invasive ventilation in the future. Our experience with diaphragm pacing raises several important questions of how to undertake ALS clinical trials properly and from early stages. There is a strong need for new international guidelines for clinical trials of ALS, which would detail how to undertake more effective and efficient clinical trials in the future, especially because the current guidelines are already 16 years old.[11]

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I declare no competing interests.

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Constraint-induced movement therapy translated into practice

Constraint-induced movement therapy (CIMT) is the massed task practice of the affected limb with shaping techniques and constraint of the unaffected limb. CIMT and modified CIMT are the most empirically supported approaches to rehabilitation of the upper limbs after stroke. CIMT is a successful example[1] of translating findings from basic research (from animal studies),[2] to human clinical research (including phase 1–3 clinical trials)[3,4] and practice-based research (phase 3 randomised trials).[5–7] In one study[5] of 222 patients with stroke-related upper limb dysfunction, the effect of CIMT given before or after routine therapy was compared with standard care; however, without data from clinical practice, the assessment of CIMT or modified CIMT is arguably a conceptual investigation that will not benefit patients who receive regular therapy at clinics. In The *Lancet Neurology,* Anne Barzel and colleagues[7] now report

Published Online July 29, 2015 http://dx.doi.org/10.1016/S1474-4422(15)00183-0

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