Does home oxygen therapy (HOT) in addition to standard care reduce disease severity and improve symptoms in people with chronic heart failure? A randomised trial of home oxygen therapy for patients with chronic heart failure

Andrew L Clark,1* Miriam Johnson,2 Caroline Fairhurst,3 David Torgerson,3 Sarah Cockayne,3 Sara Rodgers,3 Susan Griffin,4 Victoria Allgar,5 Lesley Jones,6 Samantha Nabb,7 Ian Harvey,8 Iain Squire,9 Jerry Murphy10 and Michael Greenstone11

1Hull York Medical School, Castle Hill Hospital, Cottingham, UK
2Hull York Medical School, University of Hull, Hull, UK
3Department of Health Sciences, York Trials Unit, University of York, York, UK
4Centre for Health Economics, University of York, York, UK
5Hull York Medical School, University of York, York, UK
6School of Social Sciences, University of Hull, Hull, UK
7Department of Sport, Health and Exercise Science, University of Hull, Hull, UK
8Department of Academic Cardiology, Castle Hill Hospital, Cottingham, UK
9Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, UK
10Department of Cardiology, Darlington Memorial Hospital, Darlington, UK
11Medical Chest Unit, Castle Hill Hospital, Cottingham, UK

*Corresponding author

Declared competing interests of authors: Caroline Fairhurst, Sarah Cockayne, Sara Rodgers and David Torgerson all report other grants from the National Institute for Health Research Health Technology Assessment programme.

Published September 2015
DOI: 10.3310/hta19750
Scientific summary

The home oxygen therapy (HOT) trial
Health Technology Assessment 2015; Vol. 19: No. 75
DOI: 10.3310/hta19750

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Scientific summary

Background

Chronic heart failure (CHF) affects at least 1% of the population and is responsible for around 4% of all admissions to hospital in the UK. The prognosis of heart failure if it is not well treated is bleak. The clinical course for most patients with heart failure tends to be one of gradual decline, often punctuated with episodes of severe deterioration resulting in hospitalisation. Towards the end of their lives, many patients with CHF become very symptomatic, with limiting breathlessness on minimal exertion and even at rest. Although standard treatment may relieve symptoms, for many the last few months and even years of life can be miserable, with persisting severe breathlessness on minimal exertion and episodic hospitalisation.

Home oxygen therapy (HOT) is commonly prescribed to patients with severely symptomatic CHF in order to alleviate suffering. However, unlike the situation for patients with chronic obstructive airways disease and severe hypoxia, in whom oxygen prolongs survival, there is no evidence to support the use of HOT in patients with CHF.

Objectives

The HOT trial was designed to address the question of whether or not there is any effect of HOT on quality of life (QoL) in patients with severely symptomatic heart failure. Secondary end points were to assess the effects of HOT on breathlessness, 6-minute walk test distance, severity of left ventricular (LV) systolic dysfunction, N-terminal B-type natriuretic hormone (NT-proBNP) level and prognosis.

The study consisted of three parts. The main study was a randomised controlled trial (RCT) designed to measure the impact of HOT on QoL in severely symptomatic patients. A qualitative substudy assessed the burden on patients and their carers, and an acute oxygen substudy assessed whether or not there was any effect of oxygen given in the same concentration as used by concentrators at home on haemodynamics.

Methods

The main study was a pragmatic, two-arm RCT, recruiting patients with severe CHF. Patients were recruited from heart failure outpatient clinics in hospital or the community, in a range of urban and rural settings. Patients had to have heart failure of any aetiology, severe symptoms (breathlessness either at rest or on minimal exertion) and at least moderate LV systolic dysfunction, and be receiving maximally tolerated medical management. Patients were excluded if they had had a cardiac resynchronisation therapy device implanted in the past 3 months, chronic obstructive pulmonary disease fulfilling the criteria for long-term oxygen therapy (LTOT), interstitial lung disease or malignant disease that would impair survival or were using a device or medication that would impede their ability to use LTOT.

Patients received best medical therapy (BMT) and were randomised to open-label LTOT, prescribed for 15 hours per day including overnight hours, or no oxygen therapy. Home oxygen was delivered by concentrators in the patients' homes. The inspired oxygen was increased from 20.9% (normal room air) to approximately 28%. There were two substudies: a linked qualitative substudy to assess the view of 25 patients and a free-standing oxygen substudy to assess the haemodynamic effects of acute oxygen administration.
Results

The HOT trial was stopped early by the funders, the Health Technology Assessment programme, because of poor patient adherence to the oxygen prescription. Between April 2012 and February 2014, 114 patients were randomised to receive either LTOT or BMT. The mean age was 72.3 years [standard deviation (SD) 11.3 years] and 70% of patients were male. Ischaemic heart disease was the cause of heart failure in 84% of patients; 95% were in New York Heart Association class III; mean left ventricular ejection fraction (LVEF) was 27.8%; and median NT-proBNP was 2203 ng/l. Arterial oxygen saturation was normal at rest and there was no significant change in arterial oxygen saturation during exercise or during recovery from exercise. There was a low prevalence of sleep-disordered breathing.

The primary analysis used a covariance pattern mixed model which included patients only if they provided data for all baseline covariates adjusted for in the model and outcome data for at least one post-randomisation time point (n = 102: intervention, n = 51; control, n = 51). There was no difference in Minnesota Living with Heart Failure (MLwHF) questionnaire score at 6 months between the two arms [at baseline the mean score was 54.0 (SD 18.4) for LTOT and 54.0 (SD 17.9) for BMT; at 6 months the mean score was 48.1 (SD 18.5) for LTOT and 49.0 (SD 20.2) for BMT; adjusted mean difference −0.10, 95% confidence interval (CI) −6.88 to 6.69; p = 0.98]. At 3 months, the adjusted mean MLwHF questionnaire score was lower in the LTOT group (adjusted mean difference −5.47, 95% CI −10.54 to −0.41; p = 0.03), coinciding with improvements in breathlessness scores which did not persist to 6 months. There was no effect of LTOT on any secondary measure including 6-minute walk test distance, NT-proBNP level and LVEF. There was slightly greater survival in the oxygen-treated group (unadjusted hazard ratio 2.03, 95% CI 0.76 to 5.40, for BMT relative to LTOT), but the difference was not statistically significant (p = 0.16).

In the haemodynamic substudy there were no deleterious effects of 28% oxygen. There was a small increase in cardiac output and a small fall in pulmonary vascular resistance.

Adherence to HOT was poor, with only 11% of patients reporting using the oxygen as prescribed. Findings from the qualitative substudy suggested that participants viewed study participation in the trial both as an altruistic act and as a way of accessing optimal clinical care. Adherence was related not specifically to the context of a clinical trial but to a deep-seated belief that oxygen was a therapy for acute deterioration or for those with end-stage disease. Thus, participants felt that the use of LTOT was counterintuitive, despite clear explanation of the trial’s aim. This misunderstanding formed a poor basis for subsequent weighing up by the participants of the benefit–burden balance of the LTOT.

Conclusions

The prevalence of hypoxia in patients with severe heart failure at rest, following exercise and during an overnight sleep test is low. There is no evidence that LTOT, although safe, improves the symptoms, prognosis or severity of heart failure in patients with severe CHF at 6 months. There is no evidence to support the use of HOT in patients with heart failure.
Recommendations for future research

The trial was stopped early because of poor adherence to the prescription of 15 hours per day. However, the prescription was based on extrapolation from studies of patients with a different pathology, chronic airways disease, and who had severe hypoxia. It may be that shorter periods of exposure might have been effective, either in terms of symptom relief or in terms of preventing hospitalisation. We suggest that two further studies might be appropriate:

1. a trial of patients with severe heart failure randomised to have emergency oxygen supply in the house, supplied by cylinders rather than oxygen concentrator, powered to detect a reduction in admissions to hospital
2. a study of bed-bound patients with heart failure who are in the last few weeks of life, powered to detect changes in symptom severity.

Trial registration

This trial is registered as ISRCTN60260702.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.
Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/80/01. The contractual start date was in January 2010. The draft report began editorial review in November 2014 and was accepted for publication in May 2015. 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.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

© Queen’s Printer and Controller of HMSO 2015. This work was produced by Clark et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Editor-in-Chief of *Health Technology Assessment* and NIHR Journals Library

**Professor Tom Walley**  Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

**Professor Ken Stein**  Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

**Professor Andree Le May**  Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

**Dr Martin Ashton-Key**  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

**Professor Matthias Beck**  Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

**Professor Aileen Clarke**  Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

**Dr Tessa Crilly**  Director, Crystal Blue Consulting Ltd, UK

**Dr Peter Davidson**  Director of NETSCC, HTA, UK

**Ms Tara Lamont**  Scientific Advisor, NETSCC, UK

**Professor Elaine McColl**  Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

**Professor William McGuire**  Professor of Child Health, Hull York Medical School, University of York, UK

**Professor Geoffrey Meads**  Professor of Health Sciences Research, Faculty of Education, University of Winchester, UK

**Professor John Norrie**  Health Services Research Unit, University of Aberdeen, UK

**Professor John Powell**  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

**Professor James Raftery**  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

**Dr Rob Riemsma**  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

**Professor Helen Roberts**  Professor of Child Health Research, UCL Institute of Child Health, UK

**Professor Helen Snooks**  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

**Professor Jim Thornton**  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

**Editorial contact:** nihredit@southampton.ac.uk