An integrated palliative and respiratory care for patients with advanced disease and refractory breathlessness: a randomised controlled trial

Higginson, I.J.; Bausewein, C.; Reilly, C.C.; Gao, W.; Gysels, M.H.; Dzingina, M.; McCrone, P.; Booth, S.; Jolley, C.J.; Moxham, J.

Published in:
The Lancet Respiratory Medicine

DOI:
10.1016/S2213-2600(14)70226-7

Citation for published version (APA):
An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial

Irene J Higginson, Claudia Bausewein, Charles C Reilly, Wei Gao, Marjolein Gysels, Mendwas Dzingina, Paul McCrone, Sara Booth, Caroline J Jolley, John Moxham

Summary

Background Breathlessness is a common and distressing symptom, which increases in many diseases as they progress and is difficult to manage. We assessed the effectiveness of early palliative care integrated with respiratory services for patients with advanced disease and refractory breathlessness.

Methods In this single-blind randomised trial, we enrolled consecutive adults with refractory breathlessness and advanced disease from three large teaching hospitals and via general practitioners in South London. We randomly allocated (1:1) patients to receive either a breathlessness support service or usual care. Randomisation was computer generated centrally by the independent Clinical Trials Unit in a 1:1 ratio, by minimisation to balance four potential confounders: cancer versus non-cancer, breathlessness severity, presence of an informal caregiver, and ethnicity. The breathlessness support service was a short-term, single point of access service integrating palliative care, respiratory medicine, physiotherapy, and occupational therapy. Research interviewers were masked as to which patients were in the treatment group. Our primary outcome was patient-reported breathlessness mastery, a quality of life domain in the Chronic Respiratory Disease Questionnaire, at 6 weeks. All analyses were by intention to treat. Survival was a safety endpoint. This trial is registered with ClinicalTrials.gov, number NCT01165034.

Findings Between Oct 22, 2010 and Sept 28, 2012, 105 consenting patients were randomly assigned (53 to breathlessness support service and 52 to usual care). 83 of 105 (78%) patients completed the assessment at week 6. Mastery in the breathlessness support service group improved compared with the control (mean difference 0·58, 95% CI 0·01–1·15, p=0·048; effect size 0·44). Sensitivity analysis found similar results. Survival rate from randomisation to 6 months was better in the breathlessness support service group than in the control group (50 of 53 [94%] vs 39 of 52 [75%]) and in overall survival (generalised Wilcoxon 3·90, p=0·048). Survival differences were significant for patients with chronic obstructive pulmonary disease and interstitial lung disease but not cancer.

Interpretation The breathlessness support service improved breathlessness mastery. Our findings provide robust evidence to support the early integration of palliative care for patients with diseases other than cancer and breathlessness as well as those with cancer. The improvement in survival requires further investigation.

Funding UK National Institute for Health Research (NIHR) and Cicely Saunders International.

Introduction

Breathlessness is a common and distressing symptom in many advanced chronic diseases, causing considerable disability, anxiety, and social isolation. Worldwide, more than 75 million people have breathlessness every year, including more than 90% of the 65 million people with severe lung disease, more than 50% of the 10 million with incurable cancer, and 50% of the 23 million with heart failure. Breathlessness increases as the disease progresses; is frightening for patients and families, and often results in emergency hospital admission because it is accompanied by feelings of loss of mastery over breathing and panic. Once treatment of the underlying disease is optimised, breathlessness that continues is deemed refractory. Patients with refractory breathlessness in advanced disease have many symptoms and concerns that are complex and interact; consequently palliative care has been recommended. In this study, we developed and assessed a new short-term breathlessness support service. This provided one point of access for patients, brought together palliative care and respiratory medicine, and responded to the call for shared care at an earlier stage in disease than usual. We hypothesised that patients attending the breathlessness support service, compared with those receiving standard care, would have better mastery of breathlessness at 6 weeks.

Methods

Study design and participants

This trial was a randomised controlled, parallel group, pragmatic, single-blind fast-track trial in South London,
UK, recruiting patients between Oct 22, 2010 and Sept 28, 2012. We screened for potential patients across three large teaching hospitals and via general practitioners.

Patients were included according to a standard proforma completed by the identifying clinician. Patients had to meet all criteria: refractory breathlessness on exertion or rest (MRC dyspnoea scale score ≥2), despite optimum treatment of the underlying disease, as deemed by the identifying clinician; advanced disease such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease; willing to engage with short-term home physiotherapy and occupational therapy; and able to provide informed consent. Patients were excluded for any of the following: breathlessness of unknown cause; a primary diagnosis of chronic hyperventilation syndrome; completely house (or hospital or nursing home) bound, despite offer of free transport to clinic; or within 2 weeks of treatment for an acute exacerbation. Such patients were reapproached after 2 weeks.

Protocol, procedures, information sheets, consent forms, and questionnaires were approved through the independent UK Integrated Research Approval System via the ethics committee at King’s College Hospital (Ref. 10/H0808/17). We then applied for and were granted NHS Research and Development approval in all recruiting sites. Patients gave written informed consent before enrolment. Our protocol[12] followed CONSORT recommendations. There were no protocol deviations.

Panel 1: Outcome, quality of life and health-care use assessments

- Chronic Respiratory Disease Questionnaire, a 20-item validated health-related quality of life questionnaire in which experiences are rated on seven-point scales ranging 1 (maximum impairment) to 7 (no impairment)[9,10]
- Severity of breathlessness in the previous 24 h on a 0–10 numerical rating scale (NRS), average, at rest, and on exertion[12]
- London Chest Activity of Daily Living, a questionnaire of the level of disability induced by breathlessness for 15 activities (in four areas: personal care, domestic, physical, and social); each activity is scored 0–5 (0=I wouldn’t do it anyway, 5=someone else needs to carry out the activity)[12]
- EQ-5D and EQ-VAS which assess mobility, self-care, usual activities, pain or discomfort, anxiety or depression according to three levels of severity (1=no problems, 2=some or moderate problems, and 3=extreme problems), plus a Visual Analogue Scale (VAS) of present health-related quality of life, scored 0–100[12]
- Palliative care Outcome Scale, a ten-item measure for advanced disease widely validated in cancer and non-cancer; each item is rated 0 (no problem) to 4 (overwhelming problem)[13]
- Hospital Anxiety and Depression Scale (HADS), a 14-item measure of psychological distress with separate anxiety and depression subscales[12]
- Client Services Receipt Inventory (CSRI)[12] in which patients reported the health, voluntary, and social care services received over the past 3 months, or if follow-up since the last research interview[12]

Randomisation and masking

Using data from the baseline interview, the King’s Clinical Trials Unit’s Online randomisation system, independent of research and clinical teams, randomly assigned (1:1) patients to the intervention (immediate access to breathlessness support service in addition to standard care) or control group (standard best practice; offered breathlessness support service after 6 weeks). Allocation was done by minimisation[12] to balance four potential confounders: cancer versus non-cancer, breathlessness severity (numerical rating scale >3 or not), presence (or not) of an informal caregiver, and ethnic origin (white or other). After randomisation, the clinical trials unit team informed the breathlessness support service clinic administrator of the patient’s study group via secure email, who then arranged clinic appointments accordingly. Research nurses and interviewers were masked to treatment allocation. Patients were aware of treatment allocation, and were asked not to disclose this information to interviewers or research nurses. The trial coordinator and the trial administrator were aware of treatment allocation; the coordinator informed the research nurses when, and with whom, they had to do interviews.

Procedures

The breathlessness support service is an additional service to usual UK National Health Service (NHS) care. It is a multi-professional integrated service that combines respiratory, physiotherapy, occupational therapy, and palliative care assessment and management. It brings together assessment and treatment of physical, emotional, psychological, and spiritual concerns, through one point of access. The service comprises (appendix pp 1–2) a first outpatient clinic appointment with respiratory medicine and palliative care clinicians assessing present treatment and concerns. The patient (and family if present) is given a breathlessness pack including information, management, and pacing guidance, a hand-held fan or water spray, and a poem (a short mantra to help breathing and relaxation during crises) and helped to agree a crisis plan. A home assessment is done 2–3 weeks after the clinic visit by a physiotherapist and/or occupational therapist to assess the need for walking and home aids and adaptations, reinforcement of self-management, and further guidance on pacing and exercises, including a DVD when appropriate. 4 weeks after the first clinic visit, a second and final clinic appointment with a palliative care specialist is arranged to agree further actions and a discharge plan.

Service modelling for the breathlessness support service is built on the nurse-led clinic, developed by Bredin and colleagues[8] and the palliative care and physiotherapy approach developed by Booth and colleagues,[9] and systematic reviews,[8] qualitative interviews,[7] cross-sectional[10,11] and longitudinal studies,[8] and consultation with local stakeholders.[7] These data suggested that breathlessness support services should provide one point of access, integrate palliative care with existing services,
offer outpatient and home contact, and focus on improving patient self-management.

Patients randomly assigned to the control group continued with optimum management as provided by their usual services in accordance with relevant UK guidance to ensure best practice (appendix pp 3–5). After the 6 week (primary endpoint) research interview, these patients were offered the breathlessness support service.

Study measurements included the Chronic Respiratory Disease Questionnaire, severity of breathlessness in the previous 24 h, the London Chest Activity of Daily Living questionnaire, EQ-5D and EQ-VAS, the Palliative care Outcome Scale, the Hospital Anxiety and Depression Scale (HADS), and the Client Services Receipt Inventory (panel 1). These measurements were collected in a standard questionnaire booklet consisting of demographic, clinical, outcome assessments, and use of health-care services. Research data were collected in face to face interviews with patients, usually in their own homes, at baseline and 6 weeks follow-up (the primary endpoint). In addition face to face qualitative interviews were conducted after the trial was completed.

At baseline and 6 weeks follow-up, interviewers measured pulmonary function and oxygen saturation with a portable spirometer and finger pulse oximeter.

**Outcomes**

The primary outcome was breathlessness mastery at 6 weeks as recorded in the 6 week face to face interview, determined according to one domain of the quality of life measure, the Chronic Respiratory Disease Questionnaire (panel 1). Mastery is the average of four questions about the feeling of control over the disease and its effects on quality of life and function (range=1 [maximum impairment] to 7 [no impairment]). Secondary outcomes included: severity of breathlessness on exertion in the previous 24 h, activity (assessed by London Chest Activity of Daily Living questionnaire), other domains of the Chronic Respiratory Disease Questionnaire (breathlessness, fatigue, and emotional function), quality of life (EQ-5D), palliative needs (assessed by Palliative care Outcome Scale), depression and anxiety (measured by the Hospital Anxiety and Depression Scale [HADS]), and spirometry. Patient survival (since randomisation) was planned to be measured pulmonary function and oxygen saturation with a portable spirometer and finger pulse oximeter.

**Interviews**

Patient interviews were semi-structured and followed a topic guide on patients’ expectations, experiences, and views about the content, format, and effect of the breathlessness support service. Questions were open-ended and not based on pre-existing theory. Interviews were tape-recorded and transcribed verbatim.

**Statistical analysis**

On the basis of our primary outcome, the Chronic Respiratory Disease Questionnaire mastery domain, we estimated that more than 34 patients per group would detect a mean difference of 0–70 (SD 1), a p value of less than 0.05 at power 80%. To allow for a conservative estimated attrition of 40% we planned to recruit at least 110 patients into the study.

All randomly assigned participants were included in the intention-to-treat analysis. Missing data were explored according to cause. Continuous variables, expressed as means and standard deviations, were compared with the Student’s t test. Categorical variables were compared with χ² test or Fisher’s exact test, as appropriate.

---

**Figure 1: Trial profile**

*Our biggest loss before consent was the 47 individuals (21.8% of 216 referred to the trial, and 42.3% of those not consented and randomly assigned) whom we were unable to contact. Appendix p 9 shows the efforts made to contact people.
Quality of life measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall (n=105)</th>
<th>Breathlessness support service group (n=53)</th>
<th>Control group (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS breathlessness average 24 h (0-10)‡</td>
<td>5·9 (2·0)</td>
<td>6·2 (2·0)</td>
<td>5·7 (1·9)</td>
</tr>
<tr>
<td>NRS breathlessness worst at rest (0-10)‡</td>
<td>4·9 (2·6)</td>
<td>5·1 (2·7)</td>
<td>4·8 (2·6)</td>
</tr>
<tr>
<td>NRS breathlessness on exertion 24 hours (0-10)‡</td>
<td>8·3 (1·4)</td>
<td>8·4 (1·5)</td>
<td>8·3 (1·4)</td>
</tr>
<tr>
<td>CRQ HROQ (score range 20-140)‡</td>
<td>60·9 (19·1)</td>
<td>59·3 (18·7)</td>
<td>62·7 (19·6)</td>
</tr>
<tr>
<td>CRQ dyspnoea (score range 1-7)†</td>
<td>2·2 (0·80)</td>
<td>2·1 (0·7)</td>
<td>2·3 (0·9)</td>
</tr>
<tr>
<td>CRQ emotion (score range 1-7)†</td>
<td>3·6 (1·3)</td>
<td>3·6 (1·3)</td>
<td>3·7 (1·3)</td>
</tr>
<tr>
<td>CRQ fatigue (score range 1-7)†</td>
<td>2·9 (1·3)</td>
<td>2·7 (1·2)</td>
<td>3·0 (1·3)</td>
</tr>
<tr>
<td>CRQ mastery (score range 1-7)†</td>
<td>3·4 (1·5)</td>
<td>3·5 (1·4)</td>
<td>3·3 (1·5)</td>
</tr>
<tr>
<td>EQ-SD index**</td>
<td>0·35 (0·33)</td>
<td>0·37 (0·32)</td>
<td>0·34 (0·34)</td>
</tr>
<tr>
<td>EQ-SD-HROQ-VAS (score range 0-100)‡</td>
<td>51 (20)</td>
<td>52 (18)</td>
<td>50 (22)</td>
</tr>
<tr>
<td>LCADL total score (score range 0-75)‡</td>
<td>44·6 (12·9)</td>
<td>45·1 (12·9)</td>
<td>44·2 (12·2)</td>
</tr>
<tr>
<td>POS total score (score range 0-40‡)</td>
<td>15·1 (6·5)</td>
<td>15·4 (6·0)</td>
<td>14·8 (6·9)</td>
</tr>
<tr>
<td>HADS anxiety (score range 0-21‡)</td>
<td>9·2 (2·7)</td>
<td>9·5 (3·0)</td>
<td>9·0 (2·2)</td>
</tr>
<tr>
<td>HADS depression (score range 0-21‡)</td>
<td>9·3 (2·2)</td>
<td>10·0 (2·0)</td>
<td>9·9 (2·3)</td>
</tr>
</tbody>
</table>

Costs and health-care use

- Hospital inpatient days in previous 3 months: 4·5 (7·2), 4·5 (6·8), 4·6 (7·6)
- Cost of formal care in the previous 3 months: £3390 (3749), £2911 (2729), £3709 (4484)

Data are absolute numbers or mean (SD) unless otherwise stated. FEV1=forced expiratory volume in 1 s. PEF=peak expiratory flow. VC=vital capacity. POS=Palliative care Outcome Scale. POS-S=Palliative care Outcome Scale-Symptom Score. CRQ=Chronic Respiratory Questionnaire. HROQ=health-related quality of life. HRQL=health-related quality of life visual analogue scale. LCADL=London Chest Activity of Daily Living scale. HADS=Hospital Anxiety and Depression Scale. SaO2 %=oxygen saturation. NRS=numerical rating scale. *Appendix p 6 shows breakdown of primary cancer type. †Other diagnoses were: left lower lobe collapse of unknown aetiology associated with severe symptoms; lupus, shrinking lung syndrome, and rheumatoid arthritis; severe asthma and gastro-oesophageal reflux disease. §Scale interpretation: high score better. ¶Measured for 13 patients (three in breathlessness support service group and ten in control group) while on supplemental oxygen (mean [SD] SaO2, 91·8 [5·1] and the remainder on room air (mean [SD] 90·8 [5·6]). ‡Scale interpretation: high score worse. [CRQ] subscores averaged on the 1-7 scale to give comparability across subscales. *EQ-SD index scores based on the standard UK population-based preference weights with the standard scoring algorithm; 0=death and 1=perfect health.

Table 2: Baseline characteristics
problems or hospital admissions. Table 1 shows the baseline characteristics. Patients had severe disease: forced expiratory volume in 1 s (FEV1) was 46% predicted, vital capacity 58% predicted, oxygen saturation (SaO2, %) at rest 93%, average breathlessness 5.9/10, on exertion 8.3/10. Their average Chronic Respiratory Questionnaire breathlessness mastery was 3.4. Their average total Palliative care Outcome Score was 15/40, indicating important unmet palliative care concerns; for the HADS, the mean scores were 9 for anxiety and 10 for depression, both above the cutoff for clinical significance.

At week 6, 82 of 105 (78%) patients completed assessments. The main reasons for attrition were illness or death (figure 1). Attrition to the primary outcome was slightly lower than estimated (22% not 40%); therefore, we agreed to stop recruitment after 105 patients had consented. Missing data, death, and dropout were not important unmet palliative care concerns; for the HADS, the mean scores were 9 for anxiety and 10 for depression, both above the cutoff for clinical significance.

We recorded a significant improvement in the primary outcome, the mastery domain of the Chronic Respiratory Disease Questionnaire, in the breathlessness support service group compared with the control group at 6 weeks (table 2). Patients receiving the breathlessness support service had on average a 16% improvement for breathlessness mastery over the control group (mean difference 0.58, effect size 0.44, control group mean score 3.57). Results were similar to those from our sensitivity analysis of the primary outcome: ANCOVA adjusted for diagnosis, p=0.037; ANCOVA adjusted for diagnosis and baseline score, p=0.05; multiple imputation (number of imputations 45) based on baseline score of the measure of interest, p=0.07; adjusted for baseline score, diagnosis, FEV1, SaO2, %, p=0.072; control and intervention groups were imputed separately. In further post-hoc sensitivity analyses, first excluding patients referred or identified via palliative care services, and second excluding those with cancer (because of potential bias of palliative care effect), we noted 6 week mean mastery scores of, respectively, 4.18 and 3.52 (1.3) in the control group (p=0.033).

We noted no significant differences in patient-reported secondary outcomes between study groups at 6 weeks (table 2). For all items, except anxiety, the breathlessness support service group had better scores than the control group; this was largest, but not significant, for the London Chest Activity of Daily Living questionnaire and breathlessness on exertion. Findings of pre-post analysis within groups (appendix p 8) showed significant improvements in the breathlessness support service group between baseline and 6 weeks for seven outcomes: mastery, total quality of life score, dyspnoea, and emotion, assessed by Chronic Respiratory Disease Questionnaire, average breathlessness per 24 h, on exertion breathlessness per 24 h, and Palliative care Outcome Scale total score. No outcome showed deterioration. The control group had a significant improvement between baseline and 6 weeks for only Palliative care Outcome Scale total score, and significant deteriorations for London Chest Activity of Daily Living questionnaire and HADS.

We noted a significant difference in survival for the whole sample that appeared early after randomisation (generalised Wilcoxon 3:90, p=0.048). Survival was similar between the study arms for patients with cancer, but significantly different for patients without cancer: all 42 patients without cancer in the breathlessness support service group were alive through to 6 months (180 days), of the 42 control patients without cancer at baseline, 38 were alive at 90 days, and 32 at 180 days (table 3 and figure 2). The standard care group received the breathlessness support service by 120 days.

<table>
<thead>
<tr>
<th>Table 2: Comparison of patient mastery (primary outcome) and secondary outcomes measured at week 6 of study, by trial group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breathlessness support service group (n=42)</strong></td>
</tr>
<tr>
<td>Primary outcome (CRQ mastery)*†</td>
</tr>
<tr>
<td>Secondary outcomes</td>
</tr>
<tr>
<td>NRS breathlessness average 24 h‡</td>
</tr>
<tr>
<td>NRS breathlessness worst at rest 24 h‡</td>
</tr>
<tr>
<td>NRS breathlessness on exertion 24 h‡</td>
</tr>
<tr>
<td>CRQ HRQL*†</td>
</tr>
<tr>
<td>CRQ dyspnoea*†</td>
</tr>
<tr>
<td>CRQ emotion*†</td>
</tr>
<tr>
<td>CRQ fatigue*†</td>
</tr>
<tr>
<td>EQ-5D index*</td>
</tr>
<tr>
<td>EQ-5D HROQL, VAS*†</td>
</tr>
<tr>
<td>LCADL total score*†</td>
</tr>
<tr>
<td>POS total score*</td>
</tr>
<tr>
<td>HADS anxiety*</td>
</tr>
<tr>
<td>HADS depression*</td>
</tr>
<tr>
<td>Days in hospital, since randomisation*</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated. p values were calculated with two-sided Student’s t test for independent samples. CRQ-Clinical Respiratory Disease Questionnaire. NRS=nuricating rating scale. HROQL=Health-related Quality of Life. EQ-5D=quality of life. LCADL=London Chest Activity of Daily Living survey. POS=Palliative care Outcome Scale. HADS=Hospital Anxiety and Depression Scale. FEV1=forced expiratory volume in 1 s. PEF=peak expiratory flow. SaO2=oxygent saturation. *Scale interpretation; high score better. †CRQ sub-domains averaged on the 1–7 scale to give comparability across subscales. ‡Scale interpretation: high score worse.
Improved knowledge, confidence, and insight into how to function despite breathlessness were identified as potential mechanisms in the qualitative analysis through which the breathlessness support service improved patient mastery (appendix pp 10–11).

Discussion

This is the first randomised trial of a breathlessness support service integrating palliative care and respiratory medicine, and the first powered trial to test early integrated palliative care including patients without cancer (panel 2). The breathlessness support service integrated respiratory medicine, palliative care, physiotherapy, and occupational therapy for patients with advanced conditions and refractory breathlessness. The service responds to calls for earlier integration of palliative care including for patients without cancer. At 6 weeks, the primary outcome, breathlessness mastery, improved more in the breathlessness support service group than in the standard care group. Qualitative data provided evidence of the breathlessness support service improving confidence, function, and control over breathlessness. No secondary patient-reported outcomes were significantly different between groups, although there was evidence in the pre-post analysis that the breathlessness support service group had improved activities of daily living and reduced breathlessness on exertion and depression. We recorded no harms of the breathlessness support service. The number of inpatient bed days and total formal care costs, on the basis of patient-reported total service use, were similar between groups.

Refactory breathlessness is a difficult clinical problem, usually the second most common symptom after pain in patients with advanced chronic disease, with high costs for society. Oxygen has a role for individuals with severe hypoxaemia at rest or exercise desaturation, but is of little symptomatic value when patients are not hypoxic. Low-dose, sustained-release opioids safely reduce breathlessness without respiratory depression, but no other effective drugs exist. Non-pharmacological treatments (eg, rollator devices, fan therapy, breathing control, and muscle strengthening) can provide benefits as can multidisciplinary rehabilitation programmes, but in advanced disease, many patients are unable to attend or benefit. In this context, palliative care can have a role (panel 2), but robust trials are scarce.

Although the finding of improved mastery in patients in the breathlessness support service group might not be surprising, this service (integrated palliative and respiratory care) is not standard, and usual care did not achieve the same result. All patients had advanced and deteriorating disease, in the palliative phase of a progressive illness, in which breathlessness progressively increases up to death. Therefore, the finding of little change in our secondary outcomes is not surprising, especially ones such as spirometry. These data suggest that we included an appropriate group of patients.

At 6 weeks, we noted no significant differences between total formal care costs in the two groups. 6 week mean costs were £1422 in the breathlessness support service group (bootstrapped 95% CI 897–2101) and £1408 in the control group (899–2023). Costs varied greatly between individuals.
The American Thoracic Society defines breathlessness as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”. Like pain, breathlessness is a subjective experience resulting from complex interactions between pathological, physiological, and emotional elements. Therefore, it is difficult to choose the correct outcome to measure in breathlessness trials. We chose a well-established quality of life measure's mastery domain, rather than levels of breathlessness, for several reasons. First, ratings of breathlessness levels are very variable and patients can have breathlessness attacks several times a day without constant breathlessness. Therefore, helping these patients to master their attacks might be more important than reducing the severity of one attack. Second, breathlessness is a limited endpoint because people perform activity to the highest level of breathlessness they can bear, but hope to do more before they reach that point. Breathlessness support services aimed to support and provide patients with coping strategies and interventions to help them master their breathlessness, while accepting that the disease cannot be cured and its natural history changed. Thus, the amount of perceived breathlessness mastery is probably a more important component of quality of life than is amount of breathlessness. As the qualitative results suggest, patients found this point important.

We found a difference in survival between study groups; patients in the control group had poorer survival in the early period of the study compared with patients in the breathlessness support service group. This difference was not found for patients with cancer, but was significant for patients with diseases other than cancer, mostly those with COPD and interstitial lung disease. We do not have reliable data for the longevity of the disease or prognosis before randomisation, which limits interpretation of this finding. However, our results support another trial of early palliative care, although we are the first to find a survival difference for patients with diseases other than cancer. Therefore, these results need further exploration and testing in future trials, as does the optimum timing of the breathlessness support service.

The breathlessness support service had some similar components to the breathlessness intervention service developed in Cambridge, UK in the late 2000s, including one point of entry, integration of palliative care with physiotherapy, some specific interventions, and education. However, there are differences between the services; we included assessment by respiratory medicine (a component valued by patients in the qualitative interviews), asked patients to attend outpatient clinics (the breathlessness intervention service is home based), and used the poem for crisis management.

Our study has limitations. We were only able to single mask the groups. Our primary outcome measure was subjective; patients who knew their study group could...
have been subject to the placebo effect. However, participants were unaware that mastery was an endpoint because it was not emphasised in interviews and relevant questions were dispersed within the questionnaire. Additionally, the research nurse could have seen breathlessness support service equipment (eg, hand-held fan and information sheets) in the home, which could have biased their interviews. Our inclusion and exclusion criteria prevented extrapolation of study results to patients in the last month of life. Further, our outcome follow-up was short because of the fast-track nature of the trial. Although this short follow-up gave us acceptability from referrers and patients, it restricted our assessments, especially of care costs and long-term survival; the trial was not designed specifically to test for survival. We recruited from a small number of sites in urban areas where usual care at specialist centres was probably of an unusually good standard, with expert staff who were motivated to take part in this research. We were unable to contact more than a fifth of patients screened and eligible for the study, and could not pursue this further because of data protection and ethics approval requirements. Therefore, we do not know how our recorded effects translate to other routine scenarios and settings. Some patients were identified via palliative care services, which might have affected our results; however, the difference in our primary outcome remained when these effects were excluded.

Our primary outcome had an effect size of 0·44, smaller than that proposed in our sample size calculation. Puhan and colleagues recommended an effect size of smaller than that proposed in our sample size calculation. This study was funded mainly by a National Institute for Health Research (NIHR) grant from Research for Patient Benefit (RPB-PG-0808-17311). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. Additional support for the work and interviews was from an NIHR senior investigator award and the Cicely Saunders International breathlessness programme. The UKCRC-registered King’s Clinical Trials Unit at King’s Health Partners is part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King’s College London and the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC). The funders of the study had no role in protocol design, collection or analysis of the data, or interpretation or writing of the results. We thank all the patients who participated in this research; everybody who identified and screened patients for this study, especially the Palliative Care, Respiratory Medicine and Physiotherapy Departments at King’s College Hospital (London, UK), and the Community Palliative Care teams across Guy’s and St Thomas’ Hospitals (London, UK); H Bellas (physiotherapist), E Brink (social worker), J Kelly (clinical nurse specialist), and the occupational therapists for their input in the delivery of breathlessness support service, and C Pannell and S de Wolf-Linder (research nurses) for their interviews with patients; members of our project advisory group for their advice during the course of the study and in particular J Taylor of St Christopher’s Hospice (London, UK) for allowing us to use the Breathlessness poem; C Murphy and colleagues at the Clinical Trials Unit at King’s Health Partners for their support in the randomisation, D Yi for support of the economic analysis, and M Costantini for comments on an earlier draft of this paper; and J Fuller and J Davies for providing administrative support during this project.

References

1 Currow DC, Abernethy AP, Ko DN. The active identification and management of chronic refractory breathlessness is a human right. Thorax 2014; 69: 191–94.


8 Barbera L, Taylor C, Dudgeon D. Why do patients with cancer visit the emergency department near the end of life? CMAJ 2010; 182: 563–68.


Contributors

IJH, CB, CJJ, WG, PMC, and JM conceived the idea of the study and secured funding. IJH, CB, CJJ, CCR, and JM set up the study. JM, CCR, CJJ, and IJH provided the intervention. CB and CCR oversaw the study. CCR checked and cleaned the data. CCR, WG, and IJH analysed the quantitative data. MG the qualitative data, and MD and PMC the economic data. SB provided critical comment and advice on the protocol, set up, intervention modelling, and analysis stages. IJH, CB, and CCR produced the first draft of the paper. All authors commented on and contributed to the final draft. IJH is the guarantor. All authors had full access to all of the data of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded mainly by a National Institute for Health Research (NIHR) grant from Research for Patient Benefit (RPB-PG-0808-17311).


