Randomised placebo-controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis

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ONLINE DATA SUPPLEMENT

METHODS

Subjects

Subjects were recruited from the Alfred Hospital Adult CF Service between August 2003 and September 2005, as a follow on from a cross-sectional study which has been reported elsewhere.[1] Exclusion criteria (any of the following): previous home treatment with O_2 therapy or NIV, current sedative medication, significant cardiac or neurological disease, obstructive sleep apnoea (apneoa-hypopnoea index > 15 events per hour with predominance obstructive events), colonisation with Burkholderia cepacia.

Study Design

The trial design was randomised, controlled crossover. Each subject received 6 weeks of nocturnal air (placebo), O_2 and NIV in random order separated by a 2 week washout. A computer-generated Latin square design was used to randomly assign treatment order for each patient. The treatment schedules were sealed in sequentially numbered opaque envelopes by a person not involved in the trial and opened as each patient was enrolled. Subjects were clinically stable at baseline and at the commencement of each intervention (no hospitalisation or new antibiotics 2 weeks prior). Data was collected at baseline and at the end of each treatment period.

Interventions

Patients were encouraged to use all treatments for the entire time in bed. Phone contact was made at days 2, 7, 14 and 28 for all treatment arms. Any reported machine or compliance difficulties were discussed by phone and assessed in clinic if required.

Outcome Measures

Sleep monitoring and lung function

Overnight in-laboratory polysomnography (Compumedics E-series, Abbottsford, Australia) was performed and included four-lead (C3-A2, C4-A1, O1-A2, O2-A1) electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, oronasal flow with thermistor (Pro-Tech Services, Washington USA) and nasal pressure cannula (Salter Labs,California, USA), ribcage and abdominal movements with piezo-electric sensors, SpO_2 (Oxypleth, Novametrix, Connecticut USA), transcutaneous CO_2 (TCM3, Radiometer, Copenhagen, Denmark) calibrated against evening and morning arterial blood gases (ABG), snoring and body position sensors. Sleep staging, arousals, respiratory events and periodic limb movements were scored manually using standard criteria [2, 3] by two experienced sleep technologists blinded to the treatment arm. Randomly selected trial studies were used to test inter-observer variability and a kappa value of > 0.8 was found for all parameters. Spirometry and lung volumes (Profiler and Elite Series, Medgraphics, MN, USA) meeting American Thoracic Society criteria were performed.[4]

Quality of life

Quality of life was assessed using two CF-specific questionnaires (Cystic Fibrosis Quality of Life Questionnaire, Cystic Fibrosis Subjective Sleep Disturbance Questionnaire- developed in house)[1, 5], two sleep questionnaires (Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index)[6, 7] and two dyspnoea questionnaires (Medical Research Council Dyspnoea scale, Baseline and Transitional

Dyspnoea Index).[8, 9] At study end patients were asked ‘which treatment was most comfortable?’ and ‘which treatment would you prefer to continue?’

The Cystic Fibrosis Quality of Life Questionnaire (CFQoL) is a validated disease-specific measure which assesses nine functional domains.[5] A score from 0 (worst) to 100 (best) is obtained for each domain. A change in score of 5 points for a domain appears to indicate a small meaningful change to the patient although larger studies are needed to confirm this (personal correspondence author). A priori, four domains were selected (physical functioning, treatment issues, chest symptoms, emotional responses) which, from clinical experience, might be expected to improve with nocturnal NIV. A Cystic Fibrosis Subjective Sleep Disturbance Questionnaire (CSQ) was developed in house as a disease-specific questionnaire which assesses subjective symptoms of sleep disturbance using 6 questions graded on a Likert-type scale to produce a score 0 (worst) to 100 (best). We have previously reported an association between lower CSQ scores and nocturnal hypoxia.[1] The Epworth Sleepiness Scale (ESS) is a validated and extensively used tool for assessing daytime sleepiness with a score > 10 providing evidence of subjective daytime sleepiness.[6] The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire assessing sleep quality and disturbances over a 1 month period.[7] Seven component scores combine to give a global score 0-21. A score > 5 is a sensitive and specific measure of poor sleep quality. The Medical Research Council (MRC) Dyspnoea scale is a widely used and validated measure of dyspnoea in COPD. It grades the effect of breathlessness on daily activities to produce 5 categories of perceived respiratory disability from 0 (none) to 4 (very severe).[9, 10] The Baseline Dyspnoea Index (BDI) is a rating scale validated in COPD, which assesses dyspnoea at baseline in 3 categories: functional

impairment, magnitude of task and magnitude of effort.[8] Each category is rated from 0 (severe) to 4 (unimpaired) to give a baseline focal score (range, 0 to 12). Changes from baseline are measured using the Transitional Dyspnoea Index (TDI). Scores range from -3 (major deterioration), to 0 (unchanged) to +3 (major improvement). The three categories are added to produce a transition focal score (range, -9 to +9). A one unit change represents the minimally important clinical difference.[11]

Modified shuttle test

The modified shuttle test is a 15 level externally paced incremental exercise test. It has been adapted from the validated shuttle walking test in COPD with the addition of 3 levels and permission for subjects to run, to elicit a maximal response in adult patients with CF. Patients are asked to run/ walk at increasing speeds back and forth on a 10 metre course with audible pacing beeps. It is a validated objective measure of exercise capacity in adults with CF. The distance achieved on the shuttle test correlates strongly with peak O2 consumption measured on a treadmill test.[12] The minimally important clinical difference for this test is 40 metres.[13]

RESULTS

There were no significant change in neurocognitive function with any treatment (Table 1).

Table 1 Neurocognitive function

	Baseline	Air	Oxygen	NIV
PVT mean (secs)	273 (39)	256 (46)	257 (62)	288 (129)
PVT errors (no.)	0.6 (0.5)	1.3 (2.2)	0.9 (1.4)	1.7 (2.1)

PVT lapses (no.)	2.4 (3)	1.9 (3.8)	2.4 (5.6)	7.1 (18)
Stroop color words in 45 secs (no.)	50 (7)	54 (10)	57 (8)	59 (10)
Trails A (secs)	25 (7)	19 (4)	21 (8)	22 (6)
Trails B (secs)	58 (15)	43 (9)	45 (14)	44 (15)
COWAT (total words)	42 (11)	46 (10)	47 (11)	40 (18)
Digits backwards memory (% correct)	76 (14)	77 (14)	78 (16)	73 (20)

Values are mean (SD).

* $p < 0.02$

PVT, Psychomotor vigilance task; COWAT, Controlled oral word association test.

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