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Long-term benefits in self-reported health status of nasal continuous positive airway pressure therapy for obstructive sleep apnoea

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Summary

Doubt has been expressed about the efficacy of nasal continuous positive airways pressure (NCPAP) therapy for sleep apnoea. Recent evidence from a randomized controlled trial of 1 month duration, suggested that NCPAP therapy can have a substantial impact on subjective and clinical outcomes in the short term, but data was not available to determine whether these effects were sustained over the long term. This study, an extension of the original trial, examined whether the beneficial impacts of NCPAP continued over the longer term. Patients were followed-up 1 month after being placed on active or sub-therapeutic NCPAP. They completed health status measures and a clinical test of sleepiness. After this period, all patients were placed on NCPAP and followed up 5 months later. The beneficial impact of NCPAP on sleep apnoea was sustained on all measures at follow-up. Furthermore, those who had initially been in the sub-therapeutic arm gained scores after 5 months of NCPAP similar to those of the active group. The impact of NCPAP appears sustained in the longer term. Subjective health status instruments have been advocated as important outcome points in randomized trials. This study would support such a use, and shows the important role of patient report in the evaluation of health care.

Introduction

Obstructive sleep apnoea is the most common condition investigated and treated in specialist sleep clinics. It is an ailment in which the clinical presentation is characterized by grossly fragmented sleep, snoring and daytime sleepiness.[1] Treatment for OSA can be provided by nasal continuous airways pressure therapy (NCPAP), in which splinting open the upper airway during sleep with continuous positive airway pressure (about 10 cmH_2O) via a nasal mask prevents the recurrent pharyngeal collapse. This reduces sleep fragmentation and improves sleep quality. Despite the widespread use of NCPAP, doubt has been expressed as to the efficacy of this treatment.[2] Recently, however, results from a double-blind randomized controlled parallel trial of NCPAP therapy indicated that NCPAP can have substantial and beneficial effects.[3] One month follow-up of patients receiving either active treatment or 'sham' treatment indicated that active treatment led to substantial improvements in subjective health outcomes, as measured on the SF-36. However, evidence was not available to determine whether such improvements were sustained beyond the initial month, which is clearly important in a chronic treatment. Consequently, this paper provides data on the same endpoints from the original trial at follow-up at 6 months, in order to (i) establish if the large changes seen on active

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therapy at 1 month are sustained in the longer term, and (ii) to confirm these results in the control group when they too were subsequently placed on active therapy.

Methods

The study took the form of a randomized controlled trial in which patients were placed on either active NCPAP or sham NCPAP for a period of 1 month. Assessments (detailed below) were made at baseline and follow-up at 1 month. After the 1-month follow-up, all patients were placed on active treatment and assessed again at 6 months. The results reported here are based upon the 88 patients who completed all measures at all three time points.

The trial methodology, sample size calculations, and outcome measurements have been described in full elsewhere.[3] Briefly, a sleep study was undertaken to determine the presence of OSA. The severity of OSA was quantified from the number of $>4\%$ falls in SaO_2 per hour of study. This predicts the severity of OSA symptoms and its response to treatment at least as well as any other index. If patients demonstrated excessive sleepiness (as defined on a standardized sleep score, the Epworth Sleepiness Score[4] (ESS), as >9) and sleep apnoea (defined by >10 episodes/h $>4\%$ falls in arterial oxygen, with additional evidence these were caused by pharyngeal collapse) they were asked if they would take part in the trial. Those who agreed were then randomized to CPAP active treatment or sub-therapeutic (control) CPAP. The randomization was achieved from sealed envelopes which were prepared in advance of the trial by CJ, who was not involved in the treatment allocation. Those on active treatment received NCPAP at a therapeutic pressure estimated using the DeVilbiss Horizon autotitrating NCPAP machine (Sunrise Medical). Sub-therapeutic NCPAP was produced by providing a system for the patient identical in every way to therapeutic NCPAP, except that the pressure at the mask was unlikely to be adequate to splint open the pharynx. The sub-therapeutic pressure was achieved by using a NCPAP machine set to the lowest pressure possible (~ 3 cmH_2O), partially restricting airflow within the machine and providing extra blow-off holes at the mask which lowered the pressure further to about 1 cmH_2O. Since they had never experienced NCPAP before, there was no reason for them to realize that the lower pressure might prove to be sub-therapeutic. Therefore, combined with the parallel design, it was extremely unlikely that the subjects would behave differently towards the two pressures in a way that would invalidate the masking.

Self-reported health status was assessed using the SF-36.[5–7] The SF-36 is a 36 item questionnaire which measures eight multi-item dimensions on which item scores are coded, summed and transformed on to a scale from 0 (worst possible health) to 100 (best possible health). Furthermore, two summary scores can be calculated; the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[8] The PCS and MCS are 'standardized' such that a mean score of 50 and a standard deviation of 10 reflect the mean score of the 'general' population, which in this instance was gained from a large scale community survey.[9] Changes in the individual dimensions and the two component summaries can be quantified using effect-size statistics.[10] An effect size of one is equivalent to a shift in the mean of the group by 1 SD from the baseline mean. Using this approach, an effect size of 0.2 is considered small, 0.5 medium and 0.8 large. Excessive subjective daytime sleepiness was measured on the ESS.[11] Scores range from 0 (no sleepiness) to 24 (extremely sleepy) with 9 being generally regarded as the upper limit of normal.

Clinical assessments of sleepiness were made using a modified maintenance of wakefulness test (MWT), one of the standard ways to quantify this symptom.[12] This is the average ability, as measured in minutes, to resist sleep onset over four challenges. Subjects lie semi-recumbent in a darkened room tapping a finger every 3 s in response to a dim flashing light: sleep onset being defined as failure to respond for >20 s.

Statistical comparisons were made between the two groups. Due to multiple comparisons, significance was set at $p<0.01$.

Results

During the recruitment period for the trial (January 1997–August 1998), 172 patients were eligible for the study. Sixty-five people were excluded (34 refused to take part; seven were unable to give informed consent due to mental impairments; 14 chose an alternative therapy; eight required immediate treatment and two were recruited into another study). One hundred and seven were randomized, 53 receiving sub-therapeutic CPAP and 54 active treatment. Six patients did not return for follow-up at one month (four sub-therapeutic and two therapeutic). Eighty-eight of these patients returned at 6 months. After the 1-month follow-up, a further seven patients from the original active treatment group and six from the original sub-therapeutic group did not return for the final 6-month follow-up. Thus, at 6 months, 88 patients

returned: 43 (49%) of these patients had originally been allocated to the sub-therapeutic group at baseline and 45 (51%) to active treatment. After the 1-month follow-up, all patients were placed on active treatment. The mean age of patients initially in the treatment group was 51.8 years (SD 10.6; min = 33, max = 73) and for those initially in the sub-therapeutic group it was 50.0 years (SD 9.6; min = 33, max = 68).

Table 1 shows the baseline, 1- and 6-month data for ESS, MWT and nCPAP compliance, with statistical assessment of the differences between the treatment groups. All outcome measures at 6 months were highly statistically different from baseline values in both groups (all $p < 0.0001$). Compared to the 1-month figures, in the original therapeutic group there were further significant improvements in sleepiness at 6 months (ESS, $p = 0.002$; MWT, $p < 0.0001$): as would be expected, there were considerable improvements for all endpoints in the sub-therapeutic group (all $p < 0.0001$), following receiving active therapy for the first time.

Table 2 shows baseline, 1- and 6-month data for the eight dimensions of the SF-36, as well as the Mental Component Summary Score and the Physical Component Summary Score. At baseline, no statistically significant differences were found between therapeutic and sub-therapeutic groups on any of the SF-36 scores. At 1-month follow-up, significant and substantial improvements were found on a number of scores on the SF-36 with those receiving active treatment improving substantially over those in the sub-therapeutic group. These results are normalized by effect sizes and reported in Table 3. There are slight but insignificant reductions in mean scores at the 6-month follow-up compared to 1 month in the group who had received active treatment since baseline.

Discussion

Evidence-based medicine demands that proof is provided for the efficacy of treatment regimens if they are to continue to be provided. In the case of NCPAP, there was considerable controversy over the value of the treatment in the absence of rigorously conducted randomized controlled trials. Previous work has suggested that CPAP is beneficial, using patients randomized to active therapy vs. an oral placebo.[13,14] However, controversy over the value of CPAP has continued, in part because the placebo was so unlike real therapy. In the Oxford NCPAP trial, patients in the placebo arm were provided with treatment which was indistinguishable from active therapy. The trial has

Table 1 ESS, MWT and compliance data for sub-therapeutic and therapeutic groups at baseline, and at 1 month and 6 month follow-up

Subjects completing to 6 months: subtherapeutic $n = 43$ therapeutic $n = 45$	Baseline			1 month			6 months		
	Sub-therapeutic	Therapeutic	p	Sub-therapeutic	Therapeutic	p	Originally sub-therapeutic	Originally therapeutic	p
Epworth Sleepiness Score (0 = no sleepiness, 24 = maximum sleepiness)	15.0 (9.0–22.0)	16.0 (10.0–23.0)	NS	14.0 (4.0–19.0)	7.0 (0.3–16.4)	<0.0001	5.0 (1.0–14.8)	5.0 (1.0–10.0)	NS
Multiple maintenance of wakefulness test (minutes, maximum 40)	20.1 (5.0–40.0)	22.4 (7.3–40.0)	NS	25.2 (7.2–40.0)	33.5 (11.2–40.0)	<0.0001	38.0 (9.8–40.0)	40.0 (19.1–40.0)	NS
NCPAP compliance (h/night)	NA	NA	NA	4.6 (0.9–8.4)	5.9 (2.7–7.5)	NS	5.5 (0.9–7.6)	6.3 (2.1–8.4)	NS

Data are medians (5^{th}–95^{th} centiles). NA, not applicable.

Table 2 SF-36 mean (SD) scores at baseline, 1 month and 6 months follow-up for therapeutic group (CPAP) and those initially in the sub-therapeutic group (SHAM)

	Baseline	1 month	6 months
CPAP—General Health Perception	59.78 (17.83)	71.86 (20.97)	68.49 (18.99)
SHAM—General Health Perception	59.28 (20.94)	63.07 (22.73)	68.00 (23.53)
CPAP—Physical Functioning	82.78 (18.54)	88.44 (18.15)	86.22 (20.59)
SHAM—Physical Functioning	79.42 (20.24)	79.88 (22.45)	83.02 (22.84)
CPAP—Social Functioning	74.32 (18.54)	93.33 (14.29)	92.59 (12.53)
SHAM—Social Functioning	74.68 (24.88)	83.46 (22.66)	91.47 (17.29)
CPAP—Role—Physical	65.00 (35.91)	92.78 (20.38)*	90.00 (24.07)
SHAM—Role—Physical	60.47 (35.87)	72.09 (38.66)*	90.70 (24.41)
CPAP—Role—Emotional	71.11 (33.78)	94.81 (15.82)**	93.33 (16.82)
SHAM—Role—Emotional	68.99 (37.37)	72.86 (36.56)**	88.37 (29.89)
CPAP—Pain	83.95 (22.54)	90.86 (17.29)	82.72 (18.43)
SHAM—Pain	76.23 (25.50)	85.53 (21.63)	81.65 (23.49)
CPAP—Mental Health	72.53 (17.34)	86.31 (12.89)	82.13 (16.19)
SHAM—Mental Health	69.58 (17.91)	76.93 (17.21)	79.63 (18.14)
CPAP—Energy/Vitality	35.56 (21.77)	74.89 (15.68)**	70.44 (18.97)
SHAM—Energy/Vitality	33.14 (17.08)	50.70 (20.83)**	67.33 (18.40)
CPAP—Physical Component Summary	45.17 (10.02)	50.15 (9.25)	48.08 (9.52)
SHAM—Physical Component Summary	42.94 (9.89)	45.99 (10.17)	47.96 (11.03)
CPAP—Mental Component Summary	43.93 (10.67)	55.92 (6.62)**	54.90 (7.14)
SHAM—Mental Component Summary	43.61 (10.76)	47.88 (10.03)**	53.34 (9.66)

Significant differences found between groups at one month follow-up only, (*$p<0.01$; **$p<0.001$).

Table 3 Effect sizes (ES) from time one (t1) to time two (t2) and t1 to time three (t3) for treatment (CPAP) group and those initially in the sub-therapeutic group (SHAM)

	ES. t1 to t2	ES. t1 to t3
CPAP—General Health Perception	0.68	0.49
SHAM—General Health Perception	0.18	0.42
CPAP—Physical Functioning	0.31	0.18
SHAM—Physical Functioning	0.02	0.18
CPAP—Social Functioning	1.03	0.99
SHAM—Social Functioning	0.35	0.67
CPAP—Role—Physical	0.77	0.70
SHAM—Role—Physical	0.32	0.84
CPAP—Role—Emotional	0.70	0.65
SHAM—Role—Emotional	0.11	0.52
CPAP—Pain	0.31	−0.05
SHAM—Pain	0.36	0.21
CPAP—Mental Health	0.79	0.55
SHAM—Mental Health	0.41	0.57
CPAP—Energy/Vitality	1.81	1.60
SHAM—Energy/Vitality	1.03	1.92
CPAP—Physical Component Summary	0.50	0.29
SHAM—Physical Component Summary	0.31	0.51
CPAP—Mental Component Summary	1.12	1.10
SHAM—Mental Component Summary	0.40	1.01

provided evidence that active treatment has substantial beneficial effects over placebo in the treatment of OSA.[3] However, the possibility existed that such effects may only be short term, and, given that most patients remain on NCPAP for considerable periods of time, it was important that evidence could be gained to support longer-term use. The results of the 6-month follow-up reported here seem to confirm the efficacy of this form of treatment in the longer term.

Following 5 months of active treatment, the original sub-therapeutic (control) group achieved the same improvement in symptoms as the group originally randomized to active therapy. At 6 months, there was no further improvement in the self-reported health status (SF-36) of the original therapeutic treatment group, although there were continued improvements in sleepiness scores as measured on the MWT and ESS. On all measures of outcome at 6 months, the original sub-therapeutic group improved to similar values to the therapeutic group. Furthermore, the drop-out rates across the whole study were very similar between the groups.

Results on the SF-36 show that NCPAP has a beneficial impact on patients' well-being and functioning in the longer term. Much has been written of the potential benefits of subjective health status instruments as primary outcome points in randomized trials.[15] This study would support such a use, and shows the important role of patient report in the evaluation of health care.

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References

1. Stradling J. *Handbook of Sleep Related Breathing Disorders*. Oxford, Oxford University Press, 1993.
2. Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *Br Med J* 1997; **314**:851–60.
3. Jenkinson C, Davies R, Mullins R, Stradling J. Comparison of therapeutic and sub-therapeutic nasal continuos positive airways pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet* 1999; **353**:2100–5.
4. Johns M. Daytime sleepiness, snoring, and obstructive sleep apnoea: the Epworth Sleepiness Scale. *Chest* 1993; **103**:30–6.
5. Ware J, Sherbourne C. The MOS 36-Item Short-Form Health Survey 1: conceptual framework and item selection. *Med Care* 1992; **30**:473–83.
6. Jenkinson C, Stradling J, Petersen S. How should we evaluate health status? A comparison of three methods in patients presenting with obstructive sleep apnoea. *Quality Life Res* 1998; **7**:95–100.
7. Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. *J Sleep Res* 1997; **6**:199–204.
8. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Scales: A User Manual*. Boston MA, The Health Institute, New England Medical Center, 1994.
9. Jenkinson C, Layte R, Lawrence K. Development and testing of the SF-36 summary scale scores in the United Kingdom: Results from a large scale survey and clinical trial. *Med Care* 1997; **35**:410–16.
10. Kazis L, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care* 1989; **27**:S179–89.
11. Johns M. Daytime sleepiness, snoring, and obstructive sleep apnoea: the Epworth Sleepiness Scale. *Chest* 1993; **103**:30–6.
12. Doghramji K, Mitler MM, Sangal RB, *et al*. A normative study of the Maintenance of Wakefulness Test (MWT). *Electroencephalogr Clin Neurophysiol* 1997; **103**:554–62.
13. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. *Am J Resp Crit Care Med* 1999; **159**:461–7.
14. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas-NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. *Thorax* 1998; **53**:341–5.
15. Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia, Lippincott-Raven, 1996.