Nutrition and Exercise Rehabilitation in Obesity Hypoventilation Syndrome (NERO): A Pilot Randomised Controlled Trial (Online Supplement)

METHOD

Blood pressure

Blood pressure was measured after a minimum rest period of 20 minutes with a standard blood pressure monitor (Vital Signs Monitor, Mindray Bio-Medical Electronics Co Ltd, Shenxhen, China) according to international guidance (1).

Motivational interviewing

Motivational interviewing (MI) has been used effectively in the field of substance abuse. It is a patient-centred approach that involves preparing the subject for change in behaviour (e.g. weight-loss) so that the decision for change is internally patient-driven, rather than prescribed by the clinician, using specific techniques (2). Studies have shown that using this technique is superior to other modes of weight loss (3). The sessions of MI were based on moving the subject through the cycle of change and ranged from 30-60mins. Details of the MI session delivered during the intervention period are summarised in *Table E1* below.

Table E1: Aims of the motivational interviewing sessions

	Participants	
Session 1	Patient Dietician Physiotherapist ± Physician Researcher	• Explore reasons for change • Advantages vs. disadvantages of weight loss • Development of personalised diet and exercise programme
Session 2	Patient Dietician Physiotherapist	• Review progress • Affirm positive changes leading to weight loss • If weight loss has been successful, modify diet and exercise programme • If there is evidence of relapsing, exploration of difficulties
Session 3	Patient Dietician Physiotherapist ± Physician Researcher	• Review progress • Affirm positive changes leading to weight loss • If weight loss has been successful, modify diet and exercise programme • If there is evidence of relapsing, exploration of difficulties • Development of independent home programme

Session 1 was a joint session with the patient, physiotherapist and dietician and lasted up to 1 hour. The aim was to explore the patients' reasons for wanting to change their behaviour, disadvantages of not changing and preparing for behavioural change. If a patient was resistant to change, MI techniques were used to understand reasons for this, with questioning directed towards the patient to exploring their perception of the potential health and other benefits of weight-loss and increased physical activity. This was to promote an independent decision such that a change would be perceived as beneficial. When it was established that the patient was ready for change, the physiotherapist and dietician would develop a personalised home exercise and diet programme and discuss this in detail with the patient.

Sessions 2 and 3 were again joint sessions with the patient, dietician and physiotherapist. These sessions reviewed the subjective and objective changes made and reaffirmed any new positive behaviours. If change was demonstrated, the diet and exercise programme was altered to enhance further weight loss through modification of either, or both, the diet and exercise programme. If the patients had relapsed or the patient was still considering the change then any new positive behaviours were reinforced and existing and new negative behaviours explored with the aim of encouraging the patient to enter the circle of change again. At session 3, there was a focus on preparing the individual to continue the programme independently at home. These sessions were of 30-45 minutes duration.

Prior to initiation of the trial an expert group consisting of physiotherapists with an interest in rehabilitation and those involved in the trial was held. An exercise booklet was developed with exercises that could be performed at home such as marching on the spot and seated rowing. Each participant was given a target number of each of these exercises to do. If the participant was able to achieve the target number a secondary target was also set. For participants that were able to perform the exercises in the booklet easily a programme of exercise in a gym was developed for them. Additionally the dieticians involved with the trial prescribed a calorie restricted diet to each participant, who was asked to keep a food diary.

RESULTS

Gas exchange

Table E2: Change in gas exchange from baseline (prior to starting treatment)

	Control		Intervention		Mean difference	95% CI	p-value
	Baseline (n=18)	Δ 3 Month (n=15)	Baseline (n=17)	Δ 3 Month (n=15)			
pH	7.39 (7.37 to 7.41)	-0.002 (-0.02 to 0.01)	7.39 (7.38 to 7.41)	-0.004 (-0.02 to 0.01)	0.003	-0.01 to 0.02	0.66
PaO_2 (kPa)	8.08 (7.44 to 9.11)	0.94# (-0.22 to 1.8)	8.33 (7.52 to 9.27)	0.74 (-0.5 to 2.14)	-0.05	-1.00 to 0.90	0.91

$PaCO_2$ (kPa)	7.11 (6.55 to 7.47)	-0.73# (-0.92 to -0.2)	6.85 (6.51 to 7.39)	-0.91# (-1.65 to -0.14)	-0.26	-0.70 to 0.16	0.21
HCO^{3-} (mmol.l^{-1})	32.2 (28.6 to 34.2)	-2.6# (-4.9 to -1.5)	31.1 (30.0 to 32.3)	-4.5# (-5.9 to -1.1)	-0.88	-2.71 to 0.95	0.33
Mean nocturnal SpO_2 (%)	87 (81 to 91)	6.7# (3.9 to 11.7)	87 (76 to 93)	8.1# (3.5 to 20.6)	0.7	-1.49 to 2.89	0.51
Mean nocturnal $TcCO_2$ (kpa)	7.14 (6.69 to 7.89)	-1.6# (-2.28 to 0.95)	8.01 (7.22 to 8.27)	-3.1# (-4.6 to -1.2)	-0.13	-0.73 to 0.48	0.67
4% ODI (events/hr)	75 (42 to 95)	-54.6# (-71.3 to -12.6)	74 (45 to 128)	-53.6# (-110 to -24)	-1.69	-15.3 to 11.93	0.80
%Time spent with $TcCO_2$ >7kPa	76 (14 to 97)	-51.8# (-89.9 to -6.0)	94 (70 to 99)	-78.3 (-91.6 to -1.5)	11.8	-11.11 to 34.77	0.30
% time spent with SpO_2 <90	48 (28 to 85)	-39.5# (-70.0 to -17.1)	56 (17 to 89)	-35.9# (-72.3 to -12.1)	3.64	-6.85 to 14.14	0.48

Abbreviations: PaO2 = arterial partial pressure of oxygen; PaCO2 = arterial partial pressure of carbon dioxide; HCO3- = arterial bicarbonate concentration; SpO2 = oxygen saturation; TcCo2 = transcutaneous CO2; ODI = oxygen desaturation index;

#denotes significant intragroup difference from baseline p<0.05

Physical activity

11 patients in the control group and 9 in the intervention group wore a physical activity monitor, for at least 5 consecutive days at baseline and at the 3 month follow up study (*Table E3*). There was a trend to increase in physical activity including average daytime activity counts and a reduction in the immobile time in the intervention group compared with the control group between baseline and 3 months follow up, albeit there was no difference between the groups.

Table E3 Changes in physical activity from baseline to 3 months: exploratory secondary outcome

	Control		**Intervention**		**Mean Difference**	**p-value**
	Baseline	**3 months**	**Baseline**	**3 months**		
	n=11	**n=11**	**n=9**	**n=9**		
Average	169	153	124	182	13.1	0.63

activity/min (AU)	(114-191)	(81-176)	(107-220)	(82-228)		
Immobile time (minutes)	170 (212-287)	193 (133-294)	231 (160-320)	128 (117-344)	0.41	0.07

Missing data: Control n=3, Intervention n=2

Changes in muscle mass

Table E4 demonstrates changes in measures of peripheral muscle size and strength with and without correction for weight and body mass index. There were significant improvements in measures of muscle size and strength when corrected for weight in the intervention group.

Table E4: Changes in muscle strength from baseline to 3 months: exploratory secondary outcome

	Control		**Intervention**				
	Baseline n=17	**3 Month n=15**	**Baseline n=14**	**3 Month n=13**	**Mean difference**	**95% CI**	**p-value**
RFcsa (mm^2)	913 (722-1177)	850# (692-1024)	760 (664-1084)	829 (714-1173)	167*	25 to 309	0.02*
RFcsa/weight (AU)	11.3 (6.72-17.5)	6.9# (5.04-7.24)	16.1 (14.3-20.2)	19.1# (16.5-25.7)	1.56*	0.4 to 2.7	0.01*
QMVC (kg)	24.5 (16.5-34.3)	25.5 (18.8-35.4)	26.5 (16.7-29.4)	28.1 (17.3-31.2)	-0.08	-5.56 to 5.41	0.98
QMVC/weight (AU)	0.16 (0.13-0.24)	0.18 (0.15-0.28)	0.18 (0.15-0.23)	0.21# (0.17-0.25)	0.01	-0.03 to 0.52	0.52
QMVC/BMI (AU)	0.40 (0.34-0.70)	0.50 (0.38-0.82)	0.44 (0.37-0.69)	0.59 (0.42-0.73)	0.03	-0.08 to 0.14	0.58
Mean hand grip (kg)	21 (16-46)	27 (18-33)	20 (19-41)	29 (20-40)	6.3	-3.18 to 15.8	0.18
Mean hand grip/weight (AU)	0.17 (0.10-0.36)	0.19 (0.18-0.25)	0.16 (0.12-0.31)	0.23# (0.15-0.36)	0.06	-0.01 to 0.13	0.09
Mean hand grip/BMI (AU)	0.46 (0.31-0.97)	0.55 (0.38-0.71)	0.39 (0.32-0.89)	0.67# (0.37-0.93)	0.19	-0.04 to 0.42	0.10

Missing data: Control n=2, Intervention n=2 at 2/3, control n=3, intervention n=2 at 3/5; for MVC data control n=1, intervention n=0

Abbreviation: RF_{CSA}=rectus femoris cross sectional area QMVC = quadriceps maximal voluntary contraction; AU= arbitrary units; BMI = body mass index

#denotes significant within group difference from baseline p<0.05;

**denotes parameters with significant difference between groups from baseline to 3 months in p-value column, p<0.05.*

Health economics

There was a trend towards significance in the EQ5 visual analogue score (VAS) between the two groups (p=0.053) at 3 months with greater improvements observed in the intervention group. The utility score was significantly improved in the intervention group, indicating an improvement in health status, and decreased in the control group, indicating deterioration in health. Within group analyses demonstrated improvements in the VAS (p=0.02) and utility score (p=0.05) from baseline to 3 months in the intervention group but there were no changes in the control group (*Table E5*).

Table E5: Changes in Euro-QoL indices

	Control		**Intervention**		**p-value ANCOVA**
	Baseline n=18	**3 months n=15**	**Baseline n=17**	**3 months n=15**	
EQ5 VAS	45 (35-63)	50 (45-65)	50 (40-68)	63[#] (59-76)	0.053
Utility score	0.54 (0.21-0.65)	0.39 (0.17-0.69)	0.57 (0.32-0.74)	0.71[#] (0.48-0.77)	0.086

Abbreviations: EQ5=Euroqol 5D; VAS=visual analogue scale
[#]denotes significant intragroup difference from baseline p<0.05;

The Markov chain Monte Carlo (MCMC) multiple imputation algorithm was performed for imputing missing data, the number of imputed datasets used were set to 50. Analysis of cost effectiveness demonstrated that rehabilitation is more cost effective than standard care (*Table E6*). There was a significant difference in cost between the two groups (£385.63, 95%CI £343.59 to £425.93), with the intervention group, as expected, having greater cost. There was, however, a difference in quality adjusted life years (QALY) in favour of the intervention group (0.018, 95%CI 0.011 to 0.026). Incremental cost effectiveness ratio (ICER) based on EQ-5D was on average 21730 £/QALY, 95%CI (14353.0 to 35238.7) per additional QALY gained and is cost-effective for the intervention group at a threshold of £30,000 per QALY gained. When the ICER was based on the weight loss at 3 months outcome as health status, the intervention

demonstrated also superiority over the control, on average by -49 (95%CI -73.2 to -33.4) for each kilogram of weight lost.

Table E6: Differences in cost and QALYs between control and intervention groups

	Control	Intervention	Difference (95%CI)
Total cost (£)	2488.03 (124.05)	2872.33 (143.79)	385.63 (343.59 to 425.93)
QALYs	0.10 (0.08)	0.15 (0.05)	0.018 (0.011 to0.026)
Outcome	138.76 (34.63)	127.41 (25.26)	-8.24 (-11.48 to -5.05)

Data are presented as mean (SD)

*Abbreviations: QALY=Quality adjusted life years *95%CI was estimated by bootstrap*

Uncertainty around the incremental cost per QALY gained is assessed by a cost-effectiveness acceptability curve after bootstrapping 1000 replications (*Figure 2*). The curve shows there is a 93.6% chance that intervention treatment would remain cost-effective, on the basis of a willing-to-pay threshold of >£30,000 and will be reduce to 45% if we use a threshold of £20,000 per QALY gained.

Blood pressure

There was an improvement in diastolic blood pressure in the intervention group compared to the control group at 3months (*Table E7*).

Table E7: Change in blood pressure from baseline to 3 months: exploratory secondary outcome

	Control		Intervention		Mean difference	95% CI	p-value
	Baseline n=17	Δ 3 Month n=15	Baseline n=16	Δ 3 Month n=15			
Systolic BP (mmHg)	126 (110-142)	-1 (-13 to 19)	124 (111-138)	-10 (-13 to 5)	-11.2	-24.06 to 1.59	0.08
Diastolic	74	6	70	-3	-10.5*	-19.34 to -	0.02*

BP (mmHg)	(61-82)	(-1 to 15)	(65-86)	(-22 to 4)		1.59	

Missing data at 3 months: Control n=2, Intervention n=6

**denotes significant difference in parameters between groups from baseline to 3 months (p<0.05)*

Respiratory function testing

Table E8: Differences in spirometry and respiratory muscle strength from baseline to 3 months: exploratory secondary outcome

	Control		Intervention		Mean difference	95% CI	p-value
	Baseline (n=20)	**Δ 3 month (n=15)**	**Baseline (n=17)**	**Δ 3 month (n=15)**			
FEV_1 (L)	1.44 (1.02 to 1.70)	0.14 (-0.09 to 0.39)	1.23 (0.96 to 2.01)	0.16 (-0.11 to 0.67)	0.101	-0.25 to 0.45	0.56
FVC (L)	1.70 (1.24 to 1.99)	0.16 (-0.07 to 0.43)	1.57 (1.19 to 2.42)	0.36# (0.02 to 0.51)	0.122	-0.22 to 0.46	0.47
MIP (cmH_2O)	33 (18 to 48)	12.0 (-4.0 to 16.0)	45 (35 to 61)	9.5# (-1.3 to 13.0)	3.20	-3.75 to 10.14	0.35
MEP (cmH_2O)	68 (57 to 95)	0 (-14.0 to 20.0)	83 (67 to 125)	19.0 (-1.3 to 26.5)	12.5	-3.83 to 28.9	0.13
SNIP (cmH_2O)	30 (22 to 38)	5.0 (0 to 14.0)	37 (26 to 52)	7.0 (-4.0 to 17.0)	0.30	-10.09 to 10.68	0.95

Missing data: Control n=3, Intervention n=2

Abbreviation: FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MIP = mouth inspiratory pressure; MEP = mouth expiratory pressure and SNIP = sniff nasal inspiratory pressure;

#denotes significant intragroup difference from baseline p<0.05;

DATA ANALYSIS

Sensitivity analysis

A simulation based on Monte-Carlo analysis was performed with an n of 33 (3 months) for the data monitoring committee (DMC) report as the trial had reached completion of the funding.At this time, the intervention group demonstrated an 8.5kg greater weight reduction (95% CI 3.6

to 13.4) than the control group (p=0.001). This is equivalent to a 7% (95% CI 2.8 to 10.6) difference in weight loss between the control group and intervention group. Given this improvement was highly significant, simulations were conducted using the same sample size (n=33) at 3 months with different random sub-sampling with replacement and different seeds using bootstrapping. Bootstrap analyses were performed with 1000 replications. All results were consistent with our finding, demonstrating the same estimate of difference in weight loss (8.5Kg) with only slight variations in confidence intervals but with p values which were all highly significant. Using the same simulation methodology, we have studied the benefit of recruiting the additional 27 patients required to reach the target sample size of 60. The estimated mean reduction was also 8.5kg (95%CI [4.5 to 12.5]) more on average in the intervention group compared to the control group (p=0.001).

DISCUSSION

Recruitment

Two additional sites were added to aid recruitment (Royal Brompton Hospital, London, UK and St James' Hospital, Leeds, UK). In addition to the excess clinical work pressures that limited these centres admitting and initiating NIV, there were further limitations of the research infrastructure. In particular, the lack of a dedicated research team with experience in motivational interviewing and nutritional support of the obese patient were major factors resulting in these two centres failing to both screen and recruit patients, which is in keeping with the data reported by Jordan et al (4). A multi-centre randomised controlled trial would have to accommodate for this and ensure each centre had adequate resource and training.

Blood pressure changes

As a secondary outcome measure, the cardiovascular effects of a targeted weight loss programme were investigated. There were clinically significant improvements in blood pressure with 11mmHg difference between the interventional and control group in both the systolic and diastolic blood pressure. The reduction in blood pressure was not attributable to change in medications or the control of sleep disordered breathing as this was similar in both

groups. This observation is supported by the report that weight loss in eucapnic OSA patients augments blood pressure control and cardiovascular health status when combined with CPAP therapy (5).

References

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