Online supplement

Title

Positive airway pressure for sleep disordered breathing in acute quadriplegia; a randomised controlled trial.

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* Professors Pierce and Kennedy died in 2009 and 2016 respectively.

Additional detailed methods

Study design and governance

The Institute for Breathing and Sleep at Austin Health in Melbourne, Australia oversaw the trial, managed the study database, trained data collection staff at each site, conducted annual site audits, and staged, scored and reported all sleep studies using standard criteria.[1] An independent data and safety monitoring board reviewed safety and trial data.

Sleep studies

All consented participants underwent a full, unattended, portable sleep study in their hospital beds (Compumedics™ SomtePSG, Abbottsford, Australia). Sleep study measures included a light sensor,[2] central (C4/A1, C3/A2) electroencephalography, bilateral electro-oculography, electromyography (chin, diaphragmatic), electrocardiography, blood oxygen saturation, nasal pressure (airflow), leg movements, body position and respiratory movements of the chest and abdomen. All studies were sleep staged and respiratory scored by an independent, trained sleep scientist. Sleep was staged in 30 second epochs, arousals marked and respiratory events scored according to international standard criteria (American Academy of Sleep Medicine, AASM).[1] All sleep staging, scoring and reporting was performed centrally at the Institute for Breathing and Sleep.

At trial conclusion, the sleep study was repeated. Those randomized to control had a repeat diagnostic sleep study performed to determine the presence and severity of any sleep disordered breathing (SDB). Those randomised to CPAP had a sleep study performed on their auto-titrating CPAP. If CPAP was not tolerated for the full night

on the final study, summary indices were generated for the proportion of the night when the pressure trace was visible. Participants who declined to have the final study on CPAP underwent a repeat diagnostic.

Heart rate variability (HRV) indices were calculated from a five minute portion of each PSG electroencephalogram trace taken during quiet resting (prior to sleep onset). The data were selected in the Compumedics PSG (analysis) software, exported as an European data format (EDF) file, imported into the Compumedics Somte analysis software and the automated HRV analyses applied. Studies where it was not possible to sample five minutes of quiet resting electroencephalogram trace data free from movement artefact were excluded from further analyses. Only those with complete data from the baseline and final sleep studies were analysed. Student t-tests assessed between group differences in change in SDANN (standard deviation of the average normal-to-normal sinus intervals) and HF/LF ratio (high frequency to low frequency ratio). These two summary variables summarize aspects of HRV in the time (SDANN) and frequency (LF/HF ratio) domains.

Pre-randomisation procedure

All subjects who fulfilled the inclusion, exclusion criteria, consented to participate and who were classified as positive SDB cases, were trialled on auto titrating CPAP (S8 and S9. Resmed Autoset, San Diego USA) for up to three nights. When the study commenced, the S8 device was in use commercially. This was replaced by the S9 in July 2012.

Subjects who were able to use the CPAP for at least four hours on any night, were randomised into either the treatment or usual care group. If four hours were tolerated on the first night, they were randomised at this time. Those who did not use the CPAP for four hours on any of the three nights ceased trial participation. The four-hour cut off was derived from the feasibility trial where those who were unable to achieve this time were not likely to be adherent in an ongoing way.[3]

The decision to only randomize those who were likely to be adherent with CPAP was the most significant study design modification to arise from the feasibility study. A rate of non-adherence of 50%, as was observed in the feasibility study, would render this study unfeasible. Pre-randomization selection potentially limits the study generalisability to those who are tolerant of CPAP, although it accurately reflects clinical practice (you would never "force" a patient to use a therapy they did not accept). This approach was strongly supported by the Australasian Sleep Trials Network, is a similar protocol to that employed in the multi-national The Sleep Apnoea Cardiovascular Endpoints (SAVE) study[4] and significantly increased the project feasibility by reducing the numbers of subjects, the timeframe and the associated staff cost.

Site training and CPAP equipment

As detailed in the protocol paper,[5] participants were fitted with masks as per local practice at each site. All sites were large, specialised spinal cord management centres and as such all had previous clinical experience with the application of non-invasive positive pressure for sleep apnoea or respiratory support in the study population. Sites were thus were well aware of and had strategies to address the "spinal-specific"

useability issues such as limited hand function that could potentially add to the burden of CPAP use. To ensure a consistent approach to therapy throughout the trial, all sites received extensive face-to-face training prior to participant enrolment from the central coordinating team. Site coordinator teleconferences occurred approximately three monthly throughout the study and site visits were undertaken at least annually by the coordinating centre. ResMed nasal pillows, face and oro-nasal masks were all available at each site and masking choice individualised to ensure fit, comfort and to minimise leak. The local treating team could transition participants from CPAP to bi-level support if indicated.

Sample size estimation

The specific neurocognitive test best characterized in both the spinal population and obstructive sleep apnoea (OSA) is the PASAT. Lower (worse) PASAT scores correlate with sleep fragmentation severity in the able-bodied[6] and OSA severity in quadriplegia.[7] Lower PASAT scores are associated with diminished frontal lobe function[8] and a mean difference in PASAT scores of seven discriminates between those with and without cognitive impairment in multiple sclerosis.[9] In the able-bodied with OSA, those adherent to CPAP over three months have an 18 unit (standard deviation of 33) higher PASAT score than those who are not.[10]

Analyses

Previous research which examined the relationship between the OSA severity and neurocognitive dysfunction in acute quadriplegia controlled for age, sex, medications (baclofen, opiates, benzodiazepines and other potentially sedating medications), days since injury, body mass index (BMI), pre-morbid intelligence (NAART) and pre-

injury apnoea symptom frequency.[11] Only age and pre-morbid intelligence consistently contributed and as such were controlled for at baseline in the linear regression modelling of the effect of CPAP on change in neuropsychological function.

Results

Exclusions and withdrawals

A total of 1,810 people with incident tetraplegia were assessed for trial inclusion between July 2009 and October 2015. At the screening stage of the study, 1190 people were excluded from further trial participation; 63 were too young and 116 were too old (before the upper age limit was removed on 30th June 2011), 81 had an AIS E lesion (no neurological deficit), 166 had a contraindication to CPAP use such as a facial fracture, 99 had a significant head injury (a Glascow Coma Scale of less than 8 at first assessment), 8 had hypercapnia, 454 were assessed as unlikely to be followed for the three month trial (typically expected inpatient stay of less than three months from randomisation, transfer out of unit, etc), 53 were not proficient in English, 24 had successfully used CPAP for OSA previously and 126 were unable to provide initial informed consent.

Alterations to trial protocol

The age of people experiencing a SCI has rapidly increased alongside an ageing population and an associated increase in injurious falls.[12] The initial exclusion of those over 70 years of age was considered to be compromising trial generalizability and completion, and therefore removed on 30th June 2011. No other protocol alterations were made.

Age distribution

The average participant age was 46.7(15). As illustrated in Figure E1, the distribution was bimodal with a median age of 48 years, an inter-quartile range of 33 to 59. Two peak incidence ranges can be observed; from 20 to the mid-30s and another from 40 to the mid-50s.

Respiratory function

The vital capacity in both the CPAP and usual care groups improved over time, but no difference attributable to group allocation was observed (ANOVA group*time interaction effect, p=0.37). Average (standard deviation) vital capacity at baseline, one, two and three months were: CPAP 2.83(0.86), 3.07(0.85), 3.04(0.84), 3.07(0.87) and usual care 2.91(1.04), 3.07(0.93), 2.96(1.04), 3.03(1.05). A per-protocol with respect to CPAP adherence analysis also found no significant group*time interaction (p=0.89). Similarly FEV_1 improved over time without any change attributable to group allocation (ANOVA group*time interaction effect, p=0.87). FEV_1 at baseline, one, two and three months were: CPAP 2.24(0.68), 2.34(0.76), 2.33(0.70) and 2.36(0.80) and usual care 2.27(0.88), 2.38(0.84), 2.33(0.87) and 2.43(0.83).

CPAP adherence

The pattern of use across all those randomized to auto-titrating CPAP is illustrated in Figure E2 and overall CPAP adherence averaged 2.9 (SD=2.3) hours per night. Figure E2 illustrates that in contrast with the non-disabled, adherence in the first week was not always predictive of continued use and that a number of participants fell in and

out of the “adherent” group as classified by five out of seven nights of at least four hours of use over the trial duration. Despite tolerating therapeutic CPAP for at least four hours during the run-in phase, many participants had less than 4 hours per night on 5 nights per week after randomization. Adherence, leak and pressure information (95^{th} centile, etc.) was downloaded weekly and available to clinical research staff to assist with CPAP troubleshooting and optimisation.

Adverse events

No differences were observed in the frequency of autonomic dysreflexia events per week between those randomised to auto-titrating CPAP (mean=0.39, SD=0.75) and usual care (0.57, 1.48; p=0.37). No significant differences were observed between randomisation groups on any serious adverse events. With respect to minor adverse events, participants in the usual care group had a significantly higher prevalence of pressure injuries (81.8% versus 64.2%; p=0.01), ear or sinus discomfort (10.4% versus 2.5%; p=0.04) and chest pain (13% versus 3.7%; p=0.03). Participants in the CPAP group experienced a significantly higher prevalence of skin breakdown over the face or head (18.5% versus 1.3%; p<0.01), nasal stuffiness (18.5% versus 5.2%; p=0.01) and device-related issues; CPAP pressure complaints (23.5% versus 5.2%; p<0.01), mask discomfort (30.9% versus 10.4%; p<0.01), refusal of CPAP (55.6% versus 11.7%; p<0.01), condensation (4.9% versus 0.0%; p=0.048) and equipment malfunction (8.6% versus 0.0%; p<0.01).

Heart rate variability

No between group differences in change in SDANN (n=69) and LF/HF ratio (n=55) were found between those randomised to CPAP (SDNN mean=-0.29, SD=26.64;

LF/HF ratio mean=0.08, SD=2.89) and usual care (SDNN mean=7.99, SD=31.69, p=0.24; LF/HF ratio mean=-1.64, SD=4.47 p=0.09).

Auto-titrating CPAP use and change on SDB over time

As illustrated in Table E1, 31 people randomised to CPAP did not have a final sleep study performed on CPAP. In 21 of these cases, the studies were repeat diagnostic PSG. In these participants, the baseline AHI was 45.07(30.34), the final AHI was 37.19(25.36), a similar reduction as observed in the usual care cases in Table E1.

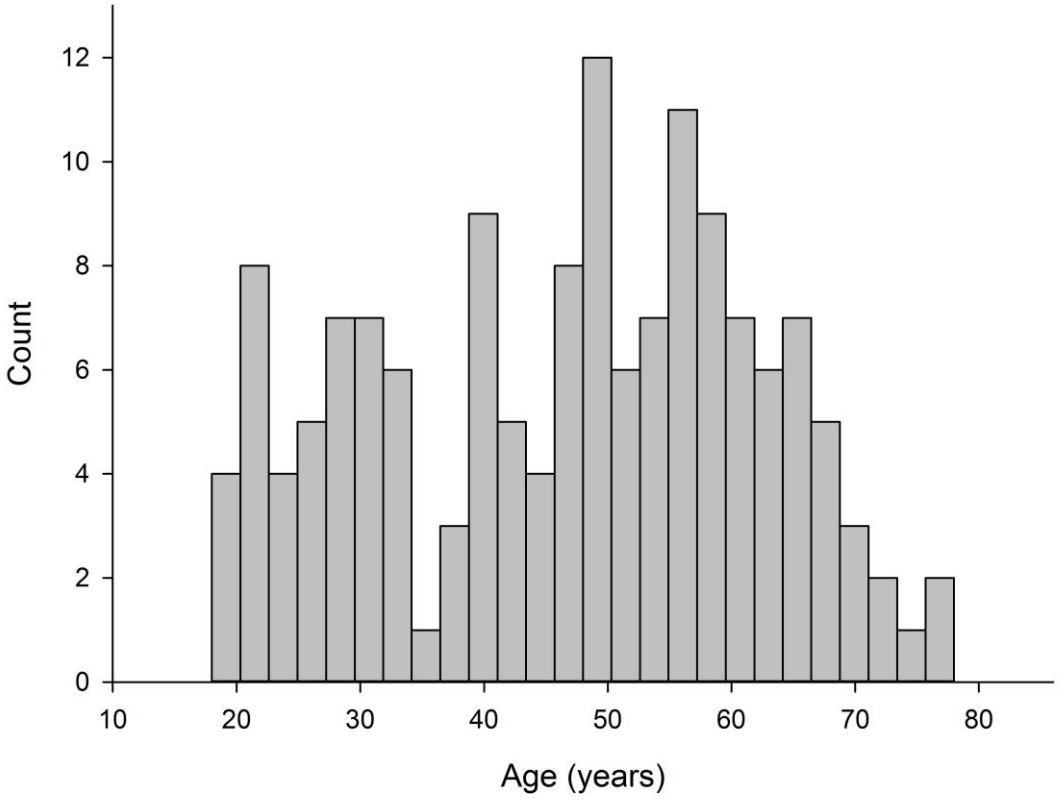

Figure E1. Age distribution of participants

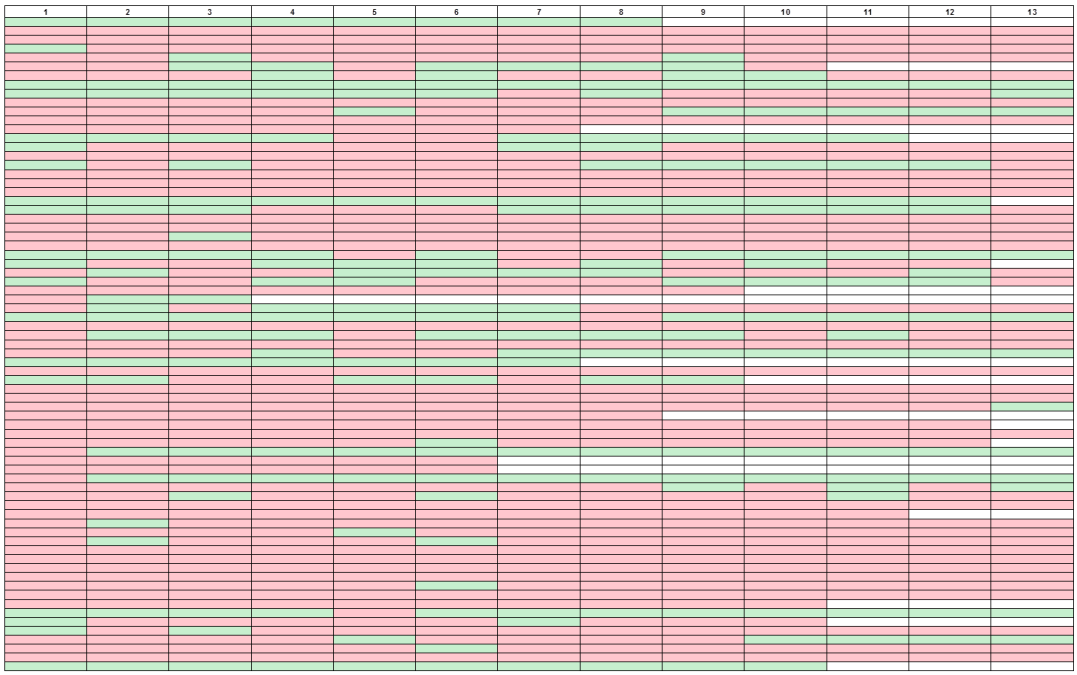

Figure E2. Pattern of weekly adherence in those randomized to CPAP

Green = adherent (more than four hours per night on at least five of seven nights in the week), Red = non-adherent, White = discharge from treating unit prior to 13 weeks.

Summary variables	CPAP baseline	CPAP final	P value	Usual Care baseline	Usual Care final	P value
N	42	42		68	68	--
Apnoea hypopnoea index, AHI	41.1(21.1-69.3)	NA	NA	40.8(24.4-56.5)	33.9(16.1-50.7)	**0.04**
Central apnoea index	0.5(0.0-2.1)	NA	NA	0.4(0-1.2)	0.3(0-1.1)	0.93
Obstructive apnoea index	11.0(1.2-37.4)	NA	NA	9.0(1.5-20.0)	8.7(1.4-18.8)	0.72
Arousal index (AI)	25.5(15.8-37.8)	17.8 (8.2-27.0)	**<0.01**	24.4(13-40.4)	17.8(10.7-33.8)	0.05
Oxygen desaturation index, ODI	13.0(1.8-44.5)	0.0 (0.0-0.7)	**<0.01**	9.7(3.4-30.4)	10.2(3.0-26.5)	0.39

4%						
Total sleep time*	350.91(87.89)	306.37(103.95)	0.01	339.53(115.60)	341.67(115.12)	0.90
Stage 1%*	0.10(0.08)	0.08(0.07)	0.13	0.12(0.11)	0.13(0.17)	0.65
Stage 2%*	0.50(0.13)	0.46(0.11))	0.14	0.50(0.12)	0.48(0.14)	0.33
Stage 3%*	0.14(0.08)	0.14(0.08))	0.99	0.14(0.09)	0.12(0.08)	0.32
Stage 4%*	0.08(0.09)	0.14(0.10)	**<0.01**	0.07(0.08)	0.08(0.08)	0.17
REM%*	0.18(0.08)	0.17(0.09)	0.95	0.17(0.08)	0.18(0.08)	0.61
Sleep efficiency, SE*	67.10(16.35)	69.71(18.65)	0.38	65.78(19.00)	67.86(19.41)	0.48
% total sleep time with SpO_2 < 90%	4.4(0.5-16.8)	0.1(0.0-0.7)	**0.01**	1.75(0.3-11.0)	2.2(0.4-11.8)	0.88
Periodic leg movements, PLM	7.7(1.2-50.7)	24.3(63.7-117.3)	0.27	5.9(0.3-45.3)	13.0(2.2-62.0)	0.16

PLM episodes	0.9(0.0-3.2)	1.6 (0.1-4.0)	0.09	0.7(0-2.5)	1.1(0.3-2.8)	0.22

Table E1. Baseline and end-study (3 month) sleep study summary data for those with complete data PSG at both baseline and follow-up. Values are mean (SD)* or median (IQR). P values are paired t-test comparisons between the baseline and final sleep study values for the two allocated groups. Statistically significant measures are highlighted in **bold** text. NA = not applicable.

	Age		NAART		SDB severity (AHI≥30)		Allocated group	
Outcome measure	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
PASAT*	**-0.41**	**-0.76, -0.07**	**0.42**	**0.03, 0.80**	10.30	-0.13, 20.73	-1.15	-10.0, 7.73
KSS^	0.00	-0.02, 0.02	0.00	-0.02, 0.03	0.18	-0.55, 0.90	**-0.65**	**-1.3, -0.01**
RAVLT Immediate Recall*	-0.02	-0.05, 0.00	**0.03**	**0.00, 0.06**	-0.65	-1.37, 0.07	-0.40	-1.04, 0.23
RAVLT Total Recall*	-0.08	-0.20, 0.03	**0.17**	**0.05, 0.29**	-1.58	-4.73, 1.57	-0.79	-3.58, 1.99
RAVLT Learning*	-0.01	-0.04, 0.02	0.02	-0.01, 0.05	0.66	-0.19, 1.52	0.20	-0.56, 0.96
RAVLT Short Term Memory*	-0.03	-0.06, 0.01	0.03	-0.00, 0.07	-0.11	-1.10, 0.87	0.37	-0.49, 1.24
RAVLT Delayed Recall*	**-0.04**	**-0.07, -0.01**	**0.05**	**0.02, 0.09**	-0.54	-1.47, 0.40	0.11	-0.72, 0.93
RAVLT Forgetting^	**0.03**	**0.00, 0.05**	0.00	-0.03, 0.02	0.67	-0.08, 1.42	-0.45	-1.12, 0.22
RAVLT Recognition*	-0.01	-0.03, 0.01	0.02	-0.01, 0.04	-0.15	-0.75, 0.45	-0.19	-0.73, 0.35
Digit span forwards*	-0.02	-0.04, 0.00	**0.03**	**0.00, 0.06**	-0.26	-0.95, 0.44	-0.40	-1.02, 0.21
Digit span backwards*	-0.02	-0.04, 0.01	0.03	-0.004, 0.05	-0.55	-1.30, 0.21	-0.36	-1.03, 0.30

SDMT*	**-0.39**	**-0.50, -0.28**	**0.17**	**0.05, 0.28**	0.72	-2.28, 3.73	-2.34	-5.00, 0.32
HADS anxiety^	-0.02	-0.05, 0.01	-0.03	-0.07, 0.00	0.85	-0.16, 1.87	0.83	-0.07, 1.73
HADS depression^	-0.01	-0.04, 0.03	-0.03	-0.07, 0.01	0.74	-0.35, 1.83	0.36	-0.61, 1.33
POMS total^	-0.02	-0.34, 0.29	-0.24	-0.59, 0.11	4.91	-4.68, 14.50	-2.58	-11.13, 5.98
BNSQ total score^	0.06	-0.07, 0.18	**-0.16**	**-0.30, -0.03**	3.05	-0.71, 6.82	**-3.42**	**-6.67, -0.16**
AQOL health utility*	-0.00	-0.00, 0.00	0.00	-0.00, 0.00	0.02	-0.05, 0.09	-0.03	-0.98, 0.03

Table E2. Linear regression model factor coefficients for outcome measures

Statistically significant measures are highlighted in **bold**. *Higher test scores represent better and ^lower scores represent better functioning.

These data represent the regression model coefficients for each of the study outcome measures. The total model was controlled for the baseline value for each outcome measure to account for baseline differences between participants. The selection of other variables included in the model was informed by previously published data.[11] Age in years, NAART = North American adult reading test, OSA severity is dichotomised at mild (10-30) versus moderate to severe (>30), Allocated group is coded as 0 = usual care and 1 = CPAP, PASAT = paced auditory serial addition task, KSS = Karolinska sleepiness scale, RAVLT = Rey auditory verbal learning task, Digit span sub-test of the Wechsler Adult Intelligence Scale

Revised, SDMT = Symbol digit modality test, HADS = Hospital anxiety and depression scale, POMS = Profile of mood states, BNSQ = Basic Nordic sleep questionnaire, AQoL = Assessment of quality of life.

	CPAP adherent (n = 18)	Usual Care & CPAP non-adherent (n = 131)	*p*
PASAT*	22.5 (8.69, 36.31)	16.2 (11.18, 21.22)	.38
KSS^	-1.89 (-3.13, -0.65)	-0.55 (-1.07, -0.03)	.07
RAVLT Immediate Recall*	1.33 (0.16, 2.50)	0.92 (0.57, 1.28)	.44
RAVLT Total Recall*	5.56 (1.44, 9.67)	2.59 (0.99, 4.20)	.20
RAVLT Learning*	0.06(-1.35, 1.46)	-0.99 (-1.47, -0.51)	.14
RAVLT Short Term Memory*	1.61 (0.44, 2.78)	0.64 (0.10, 1.17)	.20
RAVLT Delayed Recall*	1.61 (0.25, 2.98)	0.93 (0.42, 1.44)	.35
RAVLT Forgetting^	-0.22 (-1.84, 1.39)	-1.00 (-1.44, -0.55)	.24
RAVLT Recognition*	0.94 (-0.76, 2.64)	0.15 (-0.64, 0.94)	.50
SDMT*	2.94 (-2.72, 8.59)	2.50 (0.79, 4.21)	.87
Digit Span Forwards*	0.39 (-0.91, 1.69)	0.27 (-0.07, 0.61)	.81
Digit Span Backwards*	0.72(-0.33, 1.77)	0.31 (-0.06, 0.67)	.43
HADS Anxiety^	-0.67 (-2.66, 1.32)	-0.69 (-1.29, -0.09)	.98
HADS Depression^	-0.89 (-2.83, 1.06)	-0.85 (-1.47, -0.22)	.96
POMS Tension / Anxiety^	-0.72 (-4.38, 2.94)	-1.53 (-2.40, -0.65)	.55
POMS Depression^	-0.56 (-6.42, 5.31)	-2.79 (-4.39, -1.20)	.35
POMS Anger^	0.83 (-3.37, 5.04)	0.07 (-0.89, 1.03)	.61

POMS Vigour*	0.83 (-2.95, 4.61)	1.02(-0.09, 2.12)	.91
POMS Fatigue^	-1.83 (-5.39, 1.73)	-1.30 (-2.26, -0.35)	.71
POMS Confusion^	-1.28 (-4.85, 2.29)	-0.72 (-1.47, 0.03)	.64
POMS Total^	-4.39 (-24.76, 15.98)	-7.29 (-11.92, -2.65)	.69
AQoL Illness^	0.16 (0.03, 0.30)	0.20 (0.15, 0.25)	.63
AQoL Relationships^	0.09 (-0.03, 0.22)	0.05 (-0.0001, 0.09)	.48
AQoL Sensory^	-0.01 (-0.05, 0.04)	0.00 (-0.02, 0.01)	.92
AQoL Mental Health^	0.09 (-0.07, 0.24)	0.02 (-0.01, 0.04)	.12
AQoL Total Health Utility*	0.14 (0.02, 0.25)	0.13 (0.09, 0.16)	.90
BNSQ Total^	-12.94 (-19.15, -6.72)	-3.85 (-5.90, -1.80)	**<.01**
Mean autonomic dysreflexia events per person-week^	0.58(0.10)	0.47(1.20)	.71

Table E3. *Per protocol* change scores and comparisons between participants for usual care or CPAP.

PASAT = paced auditory serial addition task, KSS = Karolinska sleepiness scale, RAVLT = Rey auditory verbal learning task, Digit span sub-test of the Wechsler Adult Intelligence Scale Revised, SDMT = Symbol digit modality test, HADS = Hospital anxiety and depression scale, POMS = Profile of mood states, AQoL = Assessment of quality of life, BNSQ = Basic Nordic sleep questionnaire. Statistically significant measures are highlighted in **bold** text. *Higher test scores represent better and ^lower scores represent better functioning.

Group PASAT score	Mean or reported range of means (% correct)
Able-bodied control data	56-74
Chronic fatigue syndrome	62
Mild traumatic brain injury	39-57
Multiple sclerosis	45-54
Baseline COSAQ	41
Final COSAQ	49
Moderate to severe traumatic brain injury	19-51

Table E4. Paced Auditory Serial Addition Task (PASAT) percent correct values for non-disabled, clinical populations, baseline and final scores in the current study.

Data are expressed as the percentage correct from a total possible score of 240. Comparison data are taken from Tombaugh[13] and Schembri[11]

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