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Positive Airway Pressure for Obstructive Sleep Apnoea: Systematic Evaluation Versus Clinical and Technological Drift

A thesis presented in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY
in
PUBLIC HEALTH

At Massey University, Wellington Campus,
New Zealand

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2005
ABSTRACT

The practice of sleep medicine is expanding and evolving rapidly, often ahead of the evidence base to support clinical practice. Obstructive Sleep Disordered Breathing (SDB) is a condition characterised by repetitive airway collapse causing harmful intermittent blood oxygen desaturations and fragmented sleep. When combined with daytime sleepiness it is known as Obstructive Sleep Apnoea Syndrome (OSAS). Continuous Positive Airway Pressure (CPAP) eliminates SDB by pneumatically splinting open the airway with positive air pressure applied through the nose and/or mouth. CPAP effectively reduces daytime sleepiness in patients with severe OSAS. However, doubt remains as to the effectiveness of CPAP in the majority of patients with mild-moderate OSAS.

The effects of CPAP were compared to a placebo CPAP during a three week crossover Randomised Controlled Trial (RCT) that included 31 mild-moderate OSAS patients. CPAP effectively eliminated SDB (when worn) and moderately improved subjective sleepiness. But, it did not improve objective wakefulness, mood, psychomotor function, or quality of life. Patients who were extremely sleepy at baseline tended to gain the most placebo adjusted benefit from treatment.

A systematic review and meta-analysis aimed to gather and objectively combine all relevant RCT studies to find out whether CPAP reduced sleepiness in patients with mild-moderate OSAS. Seven trials were combined and showed that both subjective sleepiness and objective wakefulness were slightly improved by CPAP therapy.
Objective sleepiness was not improved by CPAP. It is not clear from these two studies that treating mild-moderate OSAS with CPAP is an effective use of resources.

CPAP effectiveness might be limited by sub-optimal compliance. C-Flex aims to improve compliance by modulating pressure during exhalation. C-Flex was compared to CPAP during a pilot RCT that included 19 patients with severe OSAS. C-Flex was associated with a non-significant increase in compliance of 1.7 hours/night compared to CPAP. However, this increase in compliance was not associated with better daytime patient outcomes. Further experiments are proposed as a result of our pilot RCT.

This thesis helps expand evidence-based sleep medicine. Practitioners need to be vigilant, ensuring that treatments are effective in the patients groups in which they are being used (clinical drift), and that new treatments are not adopted without superiority over existing treatments (technological drift).
ACKNOWLEDGMENTS

I have tried to be very clear in the text of this thesis when I’m reporting the products of collaborators’ work exactly who they are and what I am grateful to them for providing. But I think it’s important to be clear at the start that these studies are the work of a number of people over a number of years and that these contributions require specific acknowledgement.

For the study reported in Chapter 2 I owe a great deal of thanks to my co-authors Deidre Sheppard, Dr Angela Campbell and Dr Alister Neill from WellSleep, Wellington School of Medicine and Health Sciences. Funding for this study was provided by the Health Research Council of New Zealand to Dr Neill. The study conception and design was originally his and has also aided me greatly in being my second supervisor and as a Sleep Physician the prime example of who this information is primarily aimed at. Deidre Sheppard was responsible for the day-to-day running of the study. Gordon Purdie from the Department of Public Health at the Wellington School of Medicine and Health Sciences provided statistical advice regarding mixed models. All polysomnography was collected and scored by Dr Angela Campbell and the technicians at WellSleep, Karyn O’Keeffe, Margo van den Berg, and Michinobu Imazu. The later stages of this project were also supported by a PhD stipend from the office of the Assistant Vice-Chancellor (Research), Professor Nigel Long. Thirty-one patients gave up their time to help us and were subjected to the PVT and MWT in return. We remain amazed at how much people will put up with to help us. Thank you.

The study reported in Chapter 3 and 4 was also supported by the funding of a PhD stipend from Professor Nigel Long’s office and from Professor Philippa Gander
through the Sleep Wake Research Centre. Dr Maree Barnes from the Institute for
Breathing and Sleep at the Austin Hospital in Melbourne has been half of the joint effort
to produce the systematic review and extract data. Noemie Travier ran the meta-
analyses based on the data I had extracted from the manuscripts. This chapter has been
submitted to a peer reviewed journal, I am the first author, Dr Barnes the second and
Mdme Travier the third. Other authors are Drs Angela Campbell and Alister Neill from
the Wellington School of Medicine, Professor Robert Pierce of the University of
Melbourne, Professor Doug McEvoy of the Adelaide Institute of Sleep Health and
Professor Philippa Gander of the Sleep/Wake Research Centre.

The study reported in Chapter 4 was made possible by the loan of six C-Flex
machines from Care Medical, the New Zealand suppliers of Respironics CPAP
machines. All polysomnography was collected and scored by Dr Angela Campbell and
the technicians at Wellsleep, Karyn O’Keeffe, Deidre Sheppard, Michinobu Imazu, Sue
Garret, and Helen Morgan. CPAP compliance was also monitored and collected by
WellSleep staff as I was blinded throughout the trial. Twenty-six patients were
subjected to the PVT and MWT. Co-authors on the paper under review describing these
results are Drs Angela Campbell and Alister Neill.

All of my writings now owe part of their character to my supervisor, Professor
Philippa Gander, who has improved significantly all my attempts at communication.
Writing about science to her has fundamentally changed the way I think about things
and the depth that I think about things. Beneficially this has also made me realize the
depths of my own ignorance about almost everything. It’s difficult to imagine a better
supervisor and I am deeply grateful.
About a year and a half ago at the Sleep/Wake Research centre I got the palpable feeling that we, all, were really getting somewhere. Projects were being finished and new ideas for future projects were being discussed. It has felt good to work with people who know what they don’t know (and more importantly know what nobody knows) and are actively working to alleviate that condition. Allison Clark, Riz Firestone, Jesse Gale, Dr Sandy Garden, Dr John Matthewson, Dr Kara Mihaere, Sarah-Jane Paine, Heather Purnell, Dr Leigh Signal, Denise Ratieta, Noemi Travier, and Margo van den Berg: everybody has helped in some way and they have been very good people to be around. Even when they are stressed they seem to remain unflappable. If only all work environments were this good. Dr Kara Mihaere has additionally been extremely helpful in the final stages of preparation in navigating me past the potential formatting minefield of documents this size. Thank you.

To my family: My Mother and Father, Gered and Ray, have always supported my brother and I in whatever we decided to do. As long as we did something and we enjoyed it. They also stopped me from starving during the first year of my PhD before the shift to Massey University (and a stipend!) saved them from having the son that wouldn’t leave home. Dr Delwyn Bartlett, my aunt, introduced me to the interesting world of sleep research about 7 years ago, while she was completing her PhD. After that, accountancy didn’t seem quite so appealing. Thank you.

My partner, Georgia Foster has caught me on numerous occasions talking about statistics in my sleep. Poor woman. Really don’t know how she puts up with me. I’ll cook dinner all of next week.
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GLOSSARY & ABBREVIATIONS

AHI  Apnoea/Hypopnoea Index- The most common measure of Obstructive Sleep Apnoea severity.
0-5 /hr Sub Clinical Severity
5-15 /hr Mild
15-30 /hr Moderate
30+ Severe

AutoPAP  Automatically self-titrating continuous positive airway pressure device. CPAP devices that are designed to change pressure in response to the presence or absence of apnoeas, hypopnoeas and/or upper airway resistance. May not be as effective as marketed.

BMI  Body Mass Index- Standard measure of Body Density
Weight(kg)/Height²(m²).
< 20 Underweight
20-25 Normal
25-30 Overweight
30+ Obese

BP  Blood Pressure

COPD  Chronic Obstructive Pulmonary Disease. Also known as chronic obstructive respiratory disease (CORD)

EBM  Evidence based medicine. Application of rationality and scientific methodologies to the provision of healthcare

ECG  Electrocardiogram measurement of electrical output of heart.

EEG  Electroencephalogram measurement of electrical output from brain.

EMG  Electromyogram measurement of electrical output of muscles.

EOG  Electrooculogram: Electrophysiological measurement of eye movements. Standard Measure during polysomnography and during the MWT.

ES  Effect Size. The size of the effect on a given measure divided by the background standard deviation of that measure. Gives the magnitude of the effect which can then be compared between different measures.
<0.2 Insignificant
0.2-0.5 Small
0.5-0.8 Moderate
>0.8 Large

ESS  Epworth Sleepiness Scale- Most commonly used measure of chronic subjective sleepiness in clinical settings.

CPAP  Continuous Positive Airway Pressure, common treatment for OSAS.
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<tr>
<td>CT</td>
<td>Conservative medical treatment of OSAS.</td>
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<td>EDS</td>
<td>Excessive Daytime Sleepiness.</td>
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<td>FOSQ</td>
<td>Functional Outcomes Sleep Questionnaire: Sleepiness Related Quality of Life Measure.</td>
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<td>GHQ</td>
<td>General Health Questionnaire.</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Score.</td>
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<td>LTSA</td>
<td>Land Transport Safety Authority.</td>
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<tr>
<td>ModMWT</td>
<td>Modified version of the Maintenance of Wakefulness Test. See MWT</td>
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<td>mmHG</td>
<td>Millimetres of Mercury. Standard unit measure of blood pressure.</td>
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<td>MSLT</td>
<td>Multiple Sleep Latency Test, EEG test of daytime sleepiness. Measures time to fall asleep in a soporific environment when the patient is attempting to fall asleep.</td>
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<tr>
<td>MWT</td>
<td>Maintenance of Wakefulness Test, EEG test of daytime wakefulness. Measures time to fall asleep in a soporific environment when the patient is attempting to stay awake.</td>
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<td>MVA</td>
<td>Motor Vehicle Accident</td>
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<td>NHP</td>
<td>Nottingham Health Profile.</td>
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<tr>
<td>OA or OD</td>
<td>Oral Appliance or Oral Device. Mandibular advancement splints or tongue stabilisers aimed at increasing airway calibre to treat SDB.</td>
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<td>OSAS</td>
<td>Obstructive Sleep Apnoea Syndrome.</td>
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<td>OSLER</td>
<td>Oxford Sleep Resistance test. A non EEG alternative to the Maintenance of wakefulness test. Has been shown to be sensitive to treatment for OSAS</td>
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<td>PSG</td>
<td>Polysomnography- literally many measurements of sleep. electrophysiological measurements of sleep include EEG, EOG, EMG, ECG. Respiratory channels are also included in the diagnosis and treatment of sleep disordered breathing</td>
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<td>RCT</td>
<td>Randomised Controlled Trial.</td>
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<td>RDI</td>
<td>Respiratory Disturbance Index: Common alternative but similar measurement to the AHI.</td>
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| REM          | Rapid Eye Movement Sleep also known as Paradoxical Sleep. The EEG is relatively active during REM, the eyes exhibit regular large
movements but the EMG amplitude is much reduced compared to sleep. Outwardly the person appears very still, but may twitch at the extremities. Respiration and heart rate become more variable than during normal sleep.

**SaO₂**
Percentage of oxygen saturation in blood.

**SD**
Standard Deviation, statistical measure of spread.

**SDB**
Obstructive Sleep Disordered Breathing: In this thesis SDB refers to frank apnoeas and hypopnoeas and not to the milder manifestations of obstructive SDB such as upper airway resistance syndrome or snoring.

**SE or SEM**
Standard Error of the Mean: Statistical measure of precision of an average value.

**SF-36**
Medical Outcome Survey Short Form 36. Common pencil and paper measure of health related quality of life.

**SHHS**
Sleep Heart Health Study: Group of longitudinal cohorts that represent best ongoing investigation into the effects of SDB.

**SWS**
Slow Wave, or Deep Sleep. Stages 3 and 4 of sleep marked by emergence and then predominance of delta waves in the EEG (0-2 cycles per second). Excludes lighter stages of sleep (stages 1 and 2) and also the qualitatively different REM stage.

**UK**
United Kingdom.

**UPPP**
Uvulopalatopharyngoplasty - an operation designed to treat OSAS by ablation of soft tissue in the back of the mouth.