SUCCESS IN BLINDING TO GROUP ASSIGNMENT WITH SHAM-CPAP

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Abstract

This study evaluated the success of sham-continuous positive airway pressure as a placebo in a 4-week clinical trial of adults with sleep apnea. Participants (n=23) were previously undiagnosed for obstructive sleep apnea, had no one in their household on sleep apnea therapy, and were willing to be randomized to either active or sham-continuous positive airway pressure. Before final debriefing, participants were asked to "guess" their group assignment. When questioned, 10 of the 23 participants (44%) were incorrect in their guess of group assignment; 2 of these participants stated that their guess was "random". The active continuous positive airway pressure group's average usage was significantly longer when compared to participants on the sham device (293 ± 117 minutes/day vs. 188 ± 110 minutes/day, $p = .046$). The results suggest that participants remained blinded to group assignment and that sham-continuous positive airway pressure is an appropriate placebo control device. Participants' lower adherence to the sham device may be a potential problem that requires attention in the use of sham-continuous positive airway pressure as a placebo during clinical trials.

Keywords

sleep apnea; methodological; clinical trial; continuous positive airway pressure; placebos; adherence

1. INTRODUCTION

Continuous positive airway pressure (CPAP), considered the most effective treatment for obstructive sleep apnea (OSA), reduces or eliminates apneas and hypopneas during sleep, improves sleep architecture and continuity, and improves self-reported daytime functioning (Gay, Weaver, Loube, & Iber, 2006). A randomized clinical trial, considered scientifically the most rigorous study approach to determine treatment efficacy, requires an appropriate control group. Blinding to treatment group assignment is used in clinical trials to prevent potential problems where either the investigator or participant becomes biased because of knowing the assigned intervention (Friedman, Furberg, & DeMets, 2010). However, in order

to successfully blind participants to treatment group assignment, a comparable placebo must be utilized. In addition, attention must be given to ethical issues at all stages of a clinical trial, especially one that involves the delay of treatment and the use of an elaborate placebo control device (Friedman, et al., 2010).

Early clinical trials that evaluated the efficacy of CPAP treatment were criticized because of the use of non-comparable control groups that utilized oral placebo tablets (Barnes et al., 2002; Barnes et al., 2004; Engleman et al., 1999; Engleman, Martin, Deary, & Douglas, 1997; Faccenda, Mackay, Boon, & Douglas, 2001) or conservative treatment (instruction not to sleep supine and nasal strips) (Ballester et al., 1999; Monasterio et al., 2001; Redline et al., 1998). Karlawish and Pack (2001) explain that these methods fail to evaluate the impact of positive pressure or the effect of the technological interface on CPAP efficacy. An additional problem with the use of oral placebo tablets was that blindness could be maintained only if participants were told that the placebo tablet may have efficacy, which presents an ethical dilemma because of the lack of veracity toward participants (Karlawish & Pack, 2001).

Farré (1999) first described the development of sham-CPAP in 1999; a refinement of this device has become the placebo of choice in clinical trials. While evaluating the success of the sham-CPAP device as a placebo, the conduct of a clinical trial provided a unique opportunity to assess the treatment efficacy of CPAP among patients with OSA. The purpose of this paper is to evaluate whether sham-CPAP was an appropriate placebo to blind participants to treatment group assignment in a 4-week clinical trial.

2. METHODS

2.1 Participants

Data from 23 community-dwelling adults (active CPAP n = 12, sham-CPAP n = 11) were used in this secondary analysis. Inclusion criteria include: no prior diagnosis of OSA, an apnea + hypopnea index (AHI) 10, CPAP naïve, no one in household on CPAP therapy, and willingness to be randomized. Potential participants were excluded if they had a safety sensitive occupation, history of a sleepiness related "near miss" or automobile accident, cardiovascular disturbances/prolonged hypoxia during their diagnostic sleep study, or unstable medical or psychiatric conditions. Participants identified with OSA were randomized to either the CPAP group or to the sham-CPAP control group. The PI, project manager, and participants were blinded to group assignment.

The majority of the sample was male (60%, n=14), Caucasian (52%), well-educated (mean years of school = 14 ± 3), and subjectively sleepy at baseline (mean Epworth Sleepiness Score (Johns, 1991, 1992) = 11 ± 4). The typical participant was middle-aged (mean age = 55.61 years $\pm$ 10.64), over-weight or obese (mean BMI = 35.50 $\pm$ 6.18), and with moderate-to-severe sleep apnea (mean AHI =39 ± 26).

2.2 CPAP and sham-CPAP placebo devices

Both the CPAP units and sham-CPAP devices were provided to the study without charge (Philips Respironics, Murrysville, PA). A sham circuit, used to create a CPAP placebo device, was similar in design to ones used in previous studies of CPAP efficacy (Kushida et al., 2006; Rodway et al., 2010). As shown in photos in the article by Rodway, a hidden leak and a restrictor in the connector between the mask and CPAP tubing allowed air to escape and prevented the rebreathing of carbon dioxide. The pressure was set to 0.5–1 cm H_2O at the mask to generate sufficient airflow and create a blower noise to simulate treatment. The sham-CPAP device does not deliver therapeutic pressure or produce clinically meaningful

alterations in pre-treatment AHI, nadir of oxygen desaturation, arousal index, and sleep efficiency (Kushida, et al., 2006).

2.3 Informed consent

Informed consent was obtained from all participants prior to proceeding with any study activity to determine eligibility. During the informed consent process, potential participants were informed that CPAP is the treatment for OSA used in clinical practice. CPAP treatment was described as a mask that is fitted over the nose and a machine that delivers air at positive pressure to act as a pneumatic "splint" to prevent breath holding or decreased breathing while sleeping. Sham-CPAP was described as appearing very similar, but not treating their OSA. Participants were advised that their being assigned CPAP or sham-CPAP was by random assignment "like flipping a coin" where a computer placed them into either active or sham-CPAP. All subjects were advised that they may continue to be sleepy and, if so, should not drive or operate dangerous equipment, even if they were in the active CPAP group. Approval for this study was obtained from the institutional review board at the University of Pittsburgh.

2.4 Diagnostic Sleep Study

Potential participants underwent an overnight in-laboratory diagnostic polysomnogram (PSG) sleep study performed at the Neuroscience Clinical and Translational Research Center (N-CTRC) at the University of Pittsburgh Medical Center. To determine the presence and severity of OSA, the PSG detected episodes of collapse of the upper airway that result in a cessation of airflow for >10 seconds (apnea) or reduction in airflow (hypopnea) of at least 30% associated with a drop of at least 4% in oxygen saturation. The following signals were recorded: electroencephalogram, electrooculograms (right and left outer canthi), electromyograms (bipolar submental and bilateral tibialis anterior), thoracic and abdominal expansion, nasal and oral airflow, pulse oximetry, and electrocardiogram. The sleep study was staged according to the recommendations of the American Academy of Sleep Medicine (American Academy of Sleep Medicine Task Force, 1999). Initial scoring was done by the trained polysomnography technicians at the N-CTRC; quality assurance is maintained within the center with routine inter-rater reliability evaluations. The studies were then evaluated by an AASM board certified physician.

2.5 Titration of CPAP or sham-CPAP

Participants who meet all of the inclusion/exclusion criteria were randomized to either the active CPAP or sham-CPAP groups. The participants were titrated to either active or Sham-CPAP during overnight, in-laboratory sleep studies, identical except for the titration of positive pressure to active-CPAP. All participants were educated about the diagnosis of OSA and how to use their device at home. They were then loaned either a CPAP or a sham-CPAP machine to take home for 4-weeks. Participants were encouraged to use their CPAP/sham-CPAP device for their entire sleep period every night. Adherence to wearing the CPAP/sham-CPAP device was monitored with a SmartCard® that measured the time the device was worn. The SmarCard® was mailed to the project manager once a week to monitor adherence. Participants were called the morning after their first night of CPAP/sham-CPAP use at home and then weekly to help problem-solve any difficulty and improve adherence.

2.6 Debriefing

Prior to revealing group status, all participants were asked to "guess" to which group they were assigned. Debriefing participants was done with the investigator and project manager talking with the participant one-on-one. All participants were provided with copies of their

sleep studies and encouraged to communicate with their health care providers about continuing on CPAP therapy.

2.7 Statistical analysis

Summary statistics were presented as mean (SD), range for continuous variables (age, BMI, AHI), and as frequencies for the categorical data (sex, race). Independent-sample t-test was used to examine differences in demographic variables, and adherence between active and sham-CPAP participants. Data analysis was conducted using IBM SPSS 19 software. An "intent-to-treat" (ITT) approach was used when exploring treatment efficacy: all participants were included in the data analysis based on their randomized assignment.

3. RESULTS

The sham-CPAP and the active CPAP groups were similar in age, sex distribution, BMI, number of years of education, and subjective sleepiness. (See Table 1 for profile of the sample by treatment group). As shown in Table 2, participants at baseline in the active CPAP group had significantly higher mean AHI and oxygen desaturations indexes than those in the sham-CPAP group (p<.05). As expected, active CPAP demonstrated treatment efficacy with a significant reduction in mean AHI while sham-CPAP did not (p=.001). Participants on sham-CPAP had no significant difference in sleep latency, total sleep time, AHI, oxygen desaturation index and nadir, or arousal index between their diagnostic sleep study and their sham-CPAP titration sleep study.

No significant difference was observed in age, sex, number of years of education, or AHI between those participants who were correct, and those who were incorrect, in their appraisal of treatment group assignment. When questioned, 10 of the 23 participants (44%) were incorrect in their guess of group assignment; of these, 2 participants stated that their guess was "random". There was a 95% retention rate of participants in the study. The one participant who chose to quit the study "guessed" he was on active CPAP but "it wasn't helping any"; this participant was actually on sham-CPAP. He stated that he understood the concept of being randomized to either active or sham CPAP.

Participants on both active and sham-CPAP were incorrect in their appraisal of group assignment (active CPAP + correct guess: n=7 [30%]; sham-CPAP + correct guess: n = 6 [26%], active CPAP + incorrect guess; n = 5 [22%], and sham-CPAP + incorrect guess: n =5 [22%]). Compared to participants on the sham, there was no statistical difference in the active CPAP group's average minutes per day of device usage or in the percentage of days when they used their devices 4 or more hours a night (CPAP 269 ± 140/minutes day, 65% of nights vs. sham-CPAP 170 ± 118/minutes day, 41% of nights. Table 3 presents the descriptive statistics of the minutes of adherence to either CPAP or sham-CPAP and the percentage of days with 4 or more hours of device usage according to treatment group assignment and by the participants' perception whether they were on active treatment.

4. DISCUSSION

This study examined sham-CPAP as a placebo in clinical trials to test the efficacy of CPAP treatment. Results of the study suggest that participants were blinded to whether they were in the control group when randomized to active or sham-CPAP. Although 56% of the subjects were correct in their "guess" of the correct assignment, the result is only slightly higher than what one could expect by chance. The use of sham-CPAP more closely approximates the experience of actual CPAP than early methods that used an oral placebo tablet (Barnes, et al., 2002; Engleman, et al., 1999). The results of this study, demonstrate that sham-CPAP has a minimal effect on OSA severity, and agrees with previous findings

by Rodway and colleagues (2010). When appropriate safeguards are incorporated in the study design, the results strengthen the evidence that participants can remain blinded to group assignment and that sham-CPAP can be used as an effective placebo control device in studies evaluating the effect of CPAP. Studies utilizing sham-CPAP need to be attentive to monitoring adherence and encourage all subjects to be fully adherent to wearing their device.

Weaver (1997) described the use of CPAP with a bimodal distribution of "adherent" patients who average 6 hours use, and "non-adherent" patients who routinely "skip" using their CPAP, or average less than 4 hours a night. Data from several studies suggest that patients decide during the first week of CPAP initiation on whether or not to be adherent (Aloia, Arnedt, Stanchina, & Millman, 2007; Weaver, et al., 1997). Data from our study suggests that the perception of not being in the active treatment group was associated with lower adherence both in the total device usage and in the percentage of days worn. An implication for future study is exploration of the association between perceived benefit of treatment and adherence to treatment.

The current study was careful in attending to potential ethical issues. According to Brown et al. (2011), clinical trials in OSA have specific ethical issues that must be addressed: these include clinical equipoise, uncertainty about the benefit of the treatment, and protection of subjects from potential harm. Full disclosure must be done in the informed consent by emphasizing that the study was for research, not clinical care, and the right of the subject to withdraw their consent at any time. In addition, studies utilizing sham-CPAP require close monitoring for potential problems and involvement by the safety officer and data safety monitoring board.

A limitation of this study is that it presents data from a pilot/feasibility study that had a small sample size which increases the risk for a type II error. Because of this the validity of measurement of outcomes associated with the primary variable, assignment to either active or sham-CPAP, may be affected. In addition, exclusion of subjects that may be inappropriate for sham-CPAP may limit ability of generalizing the results of the study to these individuals.

In summary, CPAP naïve participants with OSA can remain blinded to group assignment despite being assigned to a sham-CPAP device. The results from this study strengthen the evidence that sham-CPAP can be an appropriate placebo control device in studies evaluating the effect of treatment of OSA with CPAP. Further study is needed to reconcile whether a well-designed observational study can yield results that are comparable to randomized clinical trials in clarifying treatment effects of CPAP in patients with OSA.

Acknowledgments

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Table 1

Demographics of the Sample by Group

Variables Mean (SD)	Active CPAP n=12	Sham-CPAP n=11	p-value
Age	57.58 (10.98)	53.45 (10.33)	.365
Gender			
Male	7 (58%)	7 (64%)	.794
Female	5 (42%)	4 (36%)	
BMI	36.15 (6.85)	34.79 (5.60)	.610
Education (years)	13.9 (3.47)	14.36 (2.87)	.742
Epworth (baseline)	11.42 (4.62)	10.55 (4.72)	.626

Table 2

Comparison of Polysomnogram Values by Group and Time

Variables Mean (SD)	Active CPAP n=12	Sham-CPAP n=11	p-value
Baseline Polysomnogram			
Sleep latency (minutes)	16.92 (29.6)	15.91 (14.1)	.919
Total sleep time (minutes)	436 (58)	494 (58)	.026
Sleep efficiency (%)	76.9 (15.5)	80.7 (8.3)	.484
Wake after sleep onset (minutes)	88.50 (60.8)	82.55 (39.1)	.785
AHI (all body positions)	50.17 (31)	26.64 (11)	.027
Oxygen Desaturation Index (decrease 4%)	42 (30)	19 (9)	.024
Periodic Leg Movement Index	1.25 (2.3)	2.36 (3.6)	.381
CPAP Titration vs. sham-CPAP Titration Polysomnogram			
Sleep latency (minutes)	14.58 (13.9)	23.64 (24.8)	.287
Total sleep time (minutes)	444 (68)	458 (53)	.587
Sleep efficiency (%)	79.4 (11.6)	69.18 (12.8)	.058
Wake after sleep onset (minutes)	80.50 (48.3)	126.18 (54.1)	.044
AHI (all body positions)	6.92 (6.2)	21.27 (14.5)	.005
Oxygen Desaturation Index (decrease 4%)	4.67 (5.5)	14.73 (8.5)	.004
Periodic Leg Movement Index	1.25 (1.4)	4.45 (5.0)	.064

Table 3

Description of average adherence to CPAP/sham-CPAP according to actual group assignment and perception of group assignment

Assigned to active CPAP, guessed they were in "active CPAP" group (n=7)	
Average CPAP usage all days (minutes)	275 ±134
Percent of days with usage > 4 hrs	68%
Assigned to active CPAP, guessed they were in "sham- CPAP" group (n =5)	
Average CPAP usage all days (minutes)	260 ± 163
Percent of days with usage > 4 hrs	60%
Assigned to sham-CPAP, guessed they were in "sham- CPAP" group (n=6)	
Average sham-CPAP usage all days (minutes)	165 ± 122
Percent of days with usage > 4 hrs	41%
Assigned to sham-CPAP, guessed they were in "active- CPAP" group (n=5)	
Average sham-CPAP usage all days (minutes)	176 ± 127
Percent of days with usage > 4 hrs	41%