Epilepsy & Behavior 37 (2014) 270–275

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Effect of positive airway pressure therapy on seizure control in patients with epilepsy and obstructive sleep apnea

Darakul Pornsriniyom [a,b], Hu won Kim [a,c], James Bena [d], Noah D. Andrews [a], Douglas Moul [a], Nancy Foldvary-Schaefer [a,*]

[a] Cleveland Clinic Neurological Institute, Sleep Disorders and Epilepsy Centers, Cleveland, OH, USA
[b] Sleep Disorders Center, Department of Neurology, Bangkok Hospital Pattaya, Bangkok Hospital Group, Thailand
[c] Department of Neurology, Chosun University Hospital, Gwangju, Republic of Korea
[d] Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA

ARTICLE INFO

Article history:
Received 15 March 2014
Revised 18 June 2014
Accepted 7 July 2014
Available online 12 August 2014

Keywords:
Obstructive sleep apnea
Positive airway pressure therapy
Polysomnography
Seizure outcome
Epilepsy
Comorbidities

ABSTRACT

Previous studies suggest that treatment for obstructive sleep apnea (OSA) in patients with epilepsy can improve seizure control. We investigated the effect of positive airway pressure (PAP) therapy on seizures in adults with epilepsy referred to the Cleveland Clinic for polysomnography (PSG) from 1997 to 2010. Seizure outcome at baseline and 1 year later was compared in patients with no OSA (apnea–hypopnea index [AHI] <5), patients with PAP-treated OSA, and patients with untreated OSA. One hundred thirty-two subjects (age: 40.2 ± 13 (18–76) years, 65.4% female) were included. Seventy-six (57.6%) subjects had OSA; of these, 43 (56.6%) were on PAP therapy, and 33 (43.4%) were not on PAP therapy (either PAP-intolerant or refused therapy). Of the group with PAP-treated OSA, 83.7% were adherent (use ≥4 h/night at least 5 nights/week). The percentage of subjects with ≥50% seizure reduction and the mean percentage of seizure reduction were significantly greater in the group with PAP-treated OSA (73.9%; 58.5%) than in subjects with untreated OSA (14.3%; 17.0%). There were significantly more subjects with successful outcomes (with ≥50% seizure reduction or seizure-free at both baseline and follow-up) in the group with PAP-treated OSA (83.7%) than in the groups with no OSA (53.6%) and untreated OSA (39.4%). After adjusting for age, gender, body mass index, AHI, and epilepsy duration, we found that the odds of successful outcomes in subjects in the group with PAP-treated OSA were 9.9 and 3.91 times those of the groups with untreated OSA and no OSA, respectively. The group with PAP-treated OSA had 32.3 times the odds of having a ≥50% seizure reduction compared with the group with untreated OSA and 6.13 times compared with the group with no OSA. Positive airway pressure therapy appears to produce beneficial effects on seizures in adult patients with epilepsy and OSA.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder, affecting 24% of men and 9% of women in the U.S. based on studies published in the 1990s when obesity rates were lower than current estimates [1]. The prevalence of OSA was 33% among 39 adults with pharmacoresistant focal epilepsy [2] and 30% among 130 adults with epilepsy unselected for sleep disorder complaints, including 16% with moderate-to-severe disease [3], rates that markedly exceed general population estimates. Previously, most retrospective case series have shown that treatment for OSA with positive airway pressure (PAP) therapy or upper airway surgery improved seizure control in some patients with OSA and epilepsy [4–12]. We aimed to investigate the effect of PAP therapy on seizure control by comparing seizure outcomes in adults with epilepsy with PAP-treated OSA, patients with untreated OSA, and patients with no OSA.

2. Methods

This study was approved by the Cleveland Clinic Institutional Review Board, and subjects provided written informed consent prior to the completion of study procedures. We undertook a retrospective review of clinical and polysomnographic data of adults with epilepsy who underwent polysomnography (PSG) at the Cleveland Clinic from 1997 to 2010 either as part of a research study or for the clinical evaluation of OSA. Research subjects provided written informed consent prior to the completion of study procedures. Inclusion criteria included the following: 1) age ≥ 18 years, 2) confirmed epilepsy based on clinical history and EEG or MRI, and 3) seizure frequency data documented in a standardized manner (per month for each seizure type) in the electronic medical record (EMR) over the 6 months prior to PSG and at a clinical visit 6–12 months later.

* Corresponding author at: Cleveland Clinic Neurological Institute, 9500 Euclid Avenue, FA20, Cleveland, OH 44195, USA. Fax: +1 216 636 0090.
E-mail address: foldvan@ccf.org (N. Foldvary-Schaefer).

http://dx.doi.org/10.1016/j.yebeh.2014.07.005
1525-5050/

2.1. Study procedures

2.1.1. Clinical data collection

Clinical data including demographics (age, gender, and body mass index [BMI]) and epilepsy characteristics (epilepsy classification, seizure frequency, and type and dosage of antiepileptic drug [AED] therapy) were obtained through EMR review. Epilepsy was classified as focal, generalized (presumed genetic and symptomatic), or undetermined. Seizures were classified as generalized motor (tonic, clonic, myoclonic, or tonic–clonic) or nonconvulsive (focal or absence/dialeptic), excluding auras. Mean monthly seizure frequency was determined over 6 months prior to baseline and at follow-up 6–12 months after PSG. Type and total daily dose of AEDs were obtained at baseline and follow-up, excluding those taken as needed for prolonged seizures or seizure clusters. A standardized variable of the amount of AED taken daily was determined using the defined daily dose (DDD), a measure based on the assumed average daily dose in its main indication for adults assigned by the World Health Organization [13,14]. The prescribed daily dose (PDD)/DDD ratio was calculated and summed over all drugs for each subject. Standardized AED values >1 indicate dose regimens higher than the average.

2.1.2. Polysomnography

Subjects underwent PSG with 6- to 18-channel EEG recording, right and left electrooculogram, submental and bilateral tibialis anterior electromyography, airflow using nasal pressure transducer and naso-oral thermistor, effort using thoracoabdominal piezoelectric belts, snoring, body position, pulse oximetry, and electrocardiogram. Sleep staging and event scoring were performed according to published guidelines [15]. Apnea was defined as a ≥90% decrement in airflow for ≥10 s. Hypopnea was defined as a ≥50% reduction in the nasal pressure transducer signal lasting ≥10 s resulting in an arousal or ≥3% desaturation (alternate definition) as was customary in our laboratory. Obstructive sleep apnea was diagnosed by an AHI ≥ 5; subjects with AHI < 5 were classified as having no OSA. At the time of PSG, subjects completed the Epworth Sleepiness Scale (ESS), an 8-item questionnaire that measures one's propensity to fall asleep in 8 everyday situations [16]. An ESS score ≥10 is considered indicative of excessive daytime sleepiness.

2.1.3. PAP titration and adherence

Subjects with OSA had an overnight PAP titration to identify optimal pressure with the exception of three subjects who underwent autotitration (AutoPAP) in the home. The quality of titrations was graded as optimal (AHI < 5 for at least 15 min including supine REM sleep), adequate (AHI not normalized but reduced by 75% from baseline or absence of supine REM sleep at effective pressure), or suboptimal (not meeting other criteria) based on published criteria [17]. Subjects with OSA were educated about the adverse consequences of OSA and treatment options and then offered PAP therapy. Subjects with OSA were subdivided into PAP-treated OSA and untreated OSA (PAP-intolerant or refused treatment) for analysis. Positive airway pressure adherence was ascertained at the follow-up visit and defined as full (≥4 h/night ≥70% of nights) or partial (lesser amounts of use) based on self-report and adherent (≥4 h/night on average) or nonadherent (<4 h/night on average) based on machine download when available.

2.1.4. Seizure outcome assessment

Mean and median monthly seizure frequency were determined over the 6-month period prior to PSG and at a clinical visit 6–12 months later. The primary seizure outcome was percent of subjects with ≥50% seizure reduction (responder rate) for subjects not seizure-free at baseline. Responder rate, percent change from baseline to follow-up (for all subjects), and percent of subjects with successful outcomes (≥50% total seizure reduction in patients not seizure-free at baseline or continued seizure freedom in those seizure-free at baseline) were calculated.

2.2. Statistical analysis

The data were presented as mean, standard deviation (SD), and percentiles of interest for continuous variables and frequencies and percentages for categorical variables. Median rather than mean data were used for seizure outcome tests, given that the data were not normally distributed. We compared demographics, epilepsy-related variables, ESS scores, PSG variables, and seizure outcome between the groups with PAP-treated OSA, untreated OSA, and no OSA. Pearson's Chi-squared test and Fisher's exact test were used to compare categorical factors, while Kruskal–Wallis tests were used for continuous measures. For comparisons of the three study groups, when significant overall tests were observed, Bonferroni-adjusted Wilcoxon rank sum tests were used to identify differences among the 3 groups for each measure while controlling the overall significance level at 0.05. In these comparisons, a p-value < 0.017 (0.05/3) was considered statistically significant. While we used this criterion, we also chose to present all p-values unadjusted, which allows the reader to use their preferred significance level. Logistic regression models were used to compare groups on successful outcome and responder rate, adjusting for age, gender, BMI, AHI, and epilepsy duration. Nonparametric restricted cubic splines were used to flexibly fit the relationship between continuous measures and the response. In all cases, diagnostic tests indicated that the nonlinear fits of these covariates were unnecessary, so linear fits were used. The Hosmer–Lemeshow test was used to evaluate goodness of fit for the logistic models. Analyses were performed using R software (version 2.15; Vienna, Austria).

3. Results

One hundred thirty-two subjects including 85 (65.4%) females having a mean age of 40.2 ± 13 years (18–76) were included. Seventy-six (57.6%) subjects had OSA. Of these, 43 (56.6%) were on PAP therapy (40 CPAP and 3 AutoPAP) and 33 (43.4%) were not on PAP therapy. With the exclusion of subjects seizure-free at baseline, our sample included 23 subjects with PAP-treated OSA, 21 subjects with untreated OSA, and 37 subjects with no OSA.

Overall demographic and epilepsy-related variables by group are summarized in Table 1 and for the subset of subjects not seizure-free at baseline in Supplemental Table 1. Overall results and among subjects not seizure-free at baseline were similar with the exception that a difference in epilepsy duration was observed in the overall sample, while no difference between groups was found among the subset not seizure-free at baseline. In addition, among seizure-free patients, a significant difference in baseline generalized motor seizures was observed. The majority of subjects (71.2%) had focal epilepsy. Mean monthly seizure frequency for total, focal/dialeptic, and generalized motor seizures was 3.9, 2.5, and 1.4, respectively, and did not differ between groups in the overall sample. Antiepileptic drug type or dosage change between baseline and follow-up was made in 26.5% of the subjects. However, the standardized AED dose change was minimal and not significantly different between groups. No subjects underwent epilepsy surgery during the follow-up period. Subjects without OSA were significantly younger, more likely to be female, and had lower BMIs compared with the two groups with OSA. Age, gender, and BMI did not differ between the groups with PAP-treated OSA and untreated OSA.

Polysomnographic data are shown in Table 2. The mean AHI for all subjects was 13.0 ± 16.6 events/h. As expected, subjects without OSA had lower overall supine and REM AHI and higher SpO_2 nadir compared with the group with OSA. The median [P25, P75] AHI in the PAP-treated OSA group was significantly higher than that in the group with untreated OSA. Positive airway pressure data for the 43 subjects with PAP-treated OSA are shown in Table 3. The majority of subjects with PAP-treated OSA were fully adherent to PAP therapy based on self-report. In the subset of fourteen subjects with PAP-treated OSA with available objective adherence data, all those reporting full adherence met the objective