

**The Effect of Zolpidem on CPAP Acclimatization in Patients with OSA: A
Crossover, Randomized, Double-blinded, Placebo-controlled Trial**

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Abstract

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Introduction

Obstructive sleep apnea (OSA) is a sleep disorder characterized by a cessation or significant decrease in airflow during sleep.¹ According to a recent study, OSA may impact over 1 billion individuals worldwide.² In Thailand, the prevalence of snoring in children is 6.9-8.5%, while the prevalence of OSA in children is 0.7-1.3%.³ Moreover, OSA affects 15.4% of Thai male adults and 6.3% of Thai females.⁴ Untreated OSA can lead to daytime sleepiness, decreased productivity, increased motor vehicle accidents, and worsening hypertension, atrial fibrillation, and stroke. Oral appliances, upper airway surgery, and continuous positive airway pressure (CPAP) devices are available as treatment alternatives.

CPAP is the preferred therapy and has high effectiveness at all levels of OSA severity. It acts as a pneumatic splint to maintain upper airway patency during sleep, preventing the soft tissues from collapsing. Through this mechanism, it effectively eliminates the apneas and/or hypopneas, decreases the arousals, and normalizes the oxygen saturation.⁵ However, the patient's compliance continues to be an issue. Failure of CPAP therapy may occur in up to 25% to 50% of patients, with patients typically discontinuing therapy within the first 2 to 4 weeks of treatment and 91% of patients discontinuing CPAP therapy within the first three years of therapy.^{6,7}

According to the clinical guidelines of the American Academy of Sleep Medicine, all potential PAP titration candidates should receive adequate PAP education, hands-on demonstration, careful mask fitting, and acclimatization prior to titration.⁸ Acclimatization is a technique used to familiarize patients with PAP therapy for compliance.

One of the main contributors to CPAP therapy failure is difficulty falling asleep. To aid in the machine's adaptation, hypnotic medicine was administered.⁹ Sedative medications now

came in a variety of categories. Non-benzodiazepines sometimes referred to as Z-drugs, are among those with the beneficial characteristics of not deteriorating OSA severity, not contributing to drug addiction, possessing a rapid onset, and exhibiting fewer adverse consequences. Zolpidem, eszopiclone and zaleplon are included in this drug class. According to a previous meta-analysis, eszopiclone greatly facilitated the use of CPAP.¹⁰ However, up until now limited research on zolpidem and zaleplon was conducted. This study aims to evaluate the effect of zolpidem on CPAP compliance in OSA patients as compared to a placebo.

Material and Methods

This a cross-over, randomized, double-blinded, placebo-controlled trial will be conducted in the otorhinolaryngology department, the faculty of medicine, Siriraj hospital, Thailand. The study was approved by the Siriraj Institutional Review Board (registration number 365/2566[IRB4]). This trial will be reported according to CONSORT 2010 statement extension for randomized crossover trial.

Participants

We included OSA patients whose sleep test demonstrated apnea-hypopnea index (AHI) \geq 15 /hour or AHI \geq 5 /hour with comorbid disease including hypertension, cardiovascular disease, and stroke. The enrolled individuals ranged in age from 18 to 75 years. All the patients were indicated for CPAP therapy but naïve for the device usage.

People having a history of zolpidem allergies, those who currently take hypnotic medications, and those who were denied permission to engage in the study and/or follow its protocol are all excluded from participation. According to the patients' statements and a review

of their medical records, individuals with liver diseases, including hepatitis from any cause, liver cirrhosis, and liver cancer, were also discarded.

Sample size

The nQuery Adviser Program was employed to calculate the sample size using the t-Test (ANOVA) for the difference of means in the 2*2 cross-over design formula. A power of 90% and 0.05 two-sided significant level were applied. The variable substitution of 1.8 standard deviation, 4.0 1st treatment mean, 2.92 2nd treatment mean, and 1.08 difference in means according to Quan et al¹¹ and Bradshaw et al¹² was applied. The estimated sample size for each group was 12. For the sole purpose of loss-to-follow up, we intended to recruit 15 participants per group.

Randomization & Allocation concealment

The enrolled participants will be allocated into 2 groups with different therapeutic sequence. The randomization was done using computer generated, permuted block randomization via central pharmacist allocation. The participants, physician, investigators, and outcomes assessors are all blinded to the randomization.

Interventions

The eligible participants will be informed and consented. After then, the participants in group 1 will receive 10 milligrams zolpidem contained in white-color opaque medicine capsule prepared by the pharmacist, meanwhile the participants in group 2 will receive placebo which is corn-starch contained in identical white-color opaque medicine capsule. The participants will be

advised to take the medication 30 minutes prior to the bedtime until the 1-week follow up visit. On the second week, the participants in group 1 will alternatively receive placebo, meanwhile the participants in group 2 will receive 10 milligrams zolpidem in identical capsules. The wash-out period is 24 hours as the fact that the half-life of zolpidem is 2 hours and total zolpidem elimination time is 10 to 12 hours.^{13,14}

During the study, all participants will be treated with auto-positive airway pressure device (AutoPAP) with a setting of 5 to 15 cmH₂O, ramp time 15 minutes, and start pressure 5 cmH₂O delivered via nasal mask.

Outcomes

The outcome assessment will be held on the end of the 1st as the 1st follow-up and the 2nd week as the 2nd follow-up. The primary outcome is average CPAP hour usage per night. The secondary outcomes including percent CPAP usage ≥ 4 hours, number of the participants with average CPAP usage ≥ 4 hours, and number of the participants with % CPAP usage ≥ 70 . The baseline demographic data (age; sex; bodymass index (BMI); OSA severity; comorbid diseases; drug allergy), polysomnographic data (AHI); oxygen desaturation index (ODI); time with oxygen below 90 (T90); aousal index; lowest oxygen saturation, mean oxygen saturation), drug compliance, and adverse events will also be recorded.

Statistical analysis

Test of normality of the continuous data will be done using Komogorov-Smirnov. Pair t-test and Wilcoxon Sign-Rank test will be applied for the analysis of parametric and non-parametric continuous data respectively. In the part of categorical data, Chi-square test will be

applied. Subgroup analysis for OSA severity and arousal index was planned with statistic one way ANOVA or Kruskal-Wallis H test. P-value less than 0.05 will be considered significant.

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