

Long-term Effect of Continuous Positive Air Pressure Therapy on Intraocular Pressure in Patients with Primary Open-angle Glaucoma with Obstructive Sleep Apnea

Pradtana Hirunpatravong¹, Tharnsook Kasemsup², Woravipa Na Ayudhya³, Polporn Apiwattanasawee⁴

ABSTRACT

Purpose: Prevalence of glaucoma is higher in obstructive sleep apnea (OSA) patients. The gold standard technique to treat OSA is continuous positive airway pressure (CPAP) therapy. The influence of long-term CPAP therapy on intraocular pressure (IOP), blood pressure, ocular perfusion pressure (OPP), and glaucoma progression in primary open-angle glaucoma (POAG) patients was evaluated.

Design: Prospective study.

Materials and methods: In this study, we enrolled 12 eyes from six POAG patients aged >35 years, with newly diagnosed OSA and with indication for CPAP therapy. The CPAP was performed for 12 months. We monitored the IOP every 3 months. Visual field was determined at baseline and 12 months.

Results: The mean IOP after CPAP therapy for 12 months was significantly higher than the mean baseline IOP (average IOP 3 months before CPAP therapy) (19.08 ± 3.47 vs 17.83 ± 2.88 mm Hg; $p = 0.006$). The IOP rising rate was 0.69 ± 0.47 /years ($p = 0.138$) before CPAP therapy and increased to 1.13 ± 0.47 /years ($p = 0.016$) after CPAP therapy. The OPP after 12 months of CPAP was significantly lower than the baseline (42.21 ± 5.29 vs 45.24 ± 7.09 mm Hg; $p = 0.06$). Results showed that the pattern standard deviation (PSD) value of 24-2 short wavelength automated perimetry (SWAP) visual field was reduced from 5.34 ± 3.92 to 4.77 ± 3.73 ($p = 0.025$). Antiglaucoma medication was administered to a patient due to increased IOP without glaucoma progression evidence.

Conclusion: The POAG and OSA patients demonstrated significant IOP rising after CPAP therapy but did not show progression of glaucomatous damage. Mean deviation (MD), PSD, and visual field index (VFI) were not significantly different after CPAP therapy.

Précis: Prospective study of POAG and OSA patients demonstrated significant IOP rising after CPAP therapy for a year. The study did not show progression of glaucomatous damage.

Keywords: Continuous positive air pressure, Glaucoma, Intraocular pressure, Obstructive sleep apnea, Primary open-angle glaucoma.

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder, which increases the risk of several life-threatening cardiovascular diseases in patients with an apnea-hypopnea index (AHI) score of ≥ 30 .¹⁻⁴ Obstructive sleep apnea is characterized by repeated partial or complete upper airway collapse (hypopnea and apnea), gasping episodes, and daytime sleepiness.⁵

Although many studies have demonstrated the potential connection between OSA and glaucoma, their results are considerably inconsistent.⁶⁻⁸ A large chart review of 156,336 patients diagnosed with sleep apnea initially showed an increased risk of primary open-angle glaucoma (POAG). However, this difference was not observed in the results of a multivariable analysis that accounted for confounding factors.⁶ However, many studies identified an association between POAG and OSA. Onen et al.⁷ investigated 212 patients with POAG and found that the prevalence of sleep-related breathing disorders (e.g., OSA) was 47.6%. In addition, other studies⁸⁻¹⁰ associated OSA with POAG and ocular hypertension. Patients with glaucoma and OSA exhibited higher intraocular pressure (IOP), worse visual field indices (VFIs), and a thinner retinal nerve fiber layer than the control group.⁸ Following the evaluation of 30 patients with POAG, Mojon et al.⁹ found that the prevalence of OSA was 20%. Moreover, a study involving 16 patients with normal-tension glaucoma (NTG) showed that the prevalence of OSA was 50%;¹⁰ they also found that the

^{1,2}Department of Ophthalmology, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

^{3,4}Department of Otolaryngology, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

Corresponding Author: Tharnsook Kasemsup, Department of Ophthalmology, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, Phone: +66 868100403, e-mail: tharnsookk@gmail.com

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prevalence of glaucoma among 69 patients with OSA was 7.2%. Notably, this prevalence is significantly higher than that expected in healthy individuals (2%).

Obstructive sleep apnea is diagnosed using polysomnography.¹¹ The severity of the disease is determined using the AHI score/hour, which is the sum of the number of apnea and hypopnea episodes. Apnea is defined as the cessation of the oronasal flow for a duration of ≥ 10 second. Hypopnea is defined as the reduction in the oronasal

flow by >50% with oxygen desaturation by 3–4%. Most studies have reported that an AHI score of ≥ 5 is indicative of OSA. Based on the AHI score, the severity of OSA is classified as follows: mild (AHI score, 5–15), moderate (AHI score, 15–30), and severe (AHI score, >30).

Sleep apnea can be treated using the standard therapy that comprises the application of continuous positive airway pressure (CPAP) at night to prevent upper airway collapse.¹² However, many studies have reported that variations in diurnal IOP are high in patients with OSA and that these variations increase after CPAP therapy. Kiekens et al.¹³ measured the 24-hour IOP (every 2 hours) in 21 patients who were newly diagnosed with OSA and after 1 month of CPAP therapy. They found that CPAP therapy caused an additional increase in IOP, particularly at night. At the baseline, a day before the start of CPAP therapy, fluctuations in the 24-hour IOP (i.e., the difference between the lowest and the highest IOPs) of ≥ 8 mm Hg were noted in seven patients. Following 1 month of CPAP therapy, this number increased to 12 patients. The mean difference \pm standard deviation (SD) between the lowest and the highest IOPs at the baseline and those after CPAP therapy was 6.7 ± 1.5 and 9.0 ± 2.0 mm Hg, respectively. Another study conducted by Cohen et al.¹⁴ showed an increase in mean IOP in both the patients who underwent and did not undergo CPAP therapy. Moreover, the mean IOP measured in the sitting position prior to sleeping was 13.33 ± 2.04 and 14.02 ± 2.44 mm Hg, respectively ($p = 0.9$). After 7 hours of sleep in the supine position, the IOP significantly increased and the mean IOP in patients who underwent and did not undergo CPAP therapy was 19.2 ± 5.68 and 19.69 ± 5.61 mm Hg, respectively. Notably, after 7 hours of sleep, three patients with OSA and glaucoma treated with CPAP exhibited a mean IOP of 23.75 mm Hg.

Since the IOP is influenced by OSA and CPAP therapy, previous studies about the effect of treating OSA using CPAP are varied, with most done in a short-term. In the present study, we analyzed IOP and the progression of glaucoma for 1 year after the initiation of CPAP therapy in patients with POAG who were newly diagnosed with OSA to determine the long-term effect of CPAP therapy. Notably, vascular perfusion plays an important role in glaucomatous neuropathy and is frequently reported in OSA.¹⁵ Therefore, blood pressure and pulse rates were also assessed.

MATERIALS AND METHODS

Patients

This prospective study included 16 eyes from eight patients aged ≥ 35 years, who were newly diagnosed with OSA based on full-night diagnostic polysomnography. All patients with an AHI score of ≥ 15 were referred for CPAP therapy.

All enrolled patients had POAG with a controlled IOP for ≥ 3 months and a normal anterior chamber with an open angle. Patients with any neurological abnormalities, any abnormalities that prevented reliable assessment using applanation tonometry, and previous intraocular surgery, except simple uncomplicated phacoemulsification with an intraocular lens for >3 months, were excluded.

All patients provided informed consent prior to their participation in the study. This study was approved by the institutional ethics committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, and was performed according to the tenets of the declaration of Helsinki.

Study Design

Ophthalmic evaluation was performed for all patients at the baseline. This examination comprised the assessment of medical history, best-corrected visual acuity, and central corneal thickness and slit-lamp biomicroscopy, funduscopy, gonioscopy, and visual field analysis (Humphrey Field Analyzer; Sita Standard 24-2; Carl Zeiss Meditec, Inc., Dublin, CA). The IOP was measured using a Goldmann applanation tonometer after instilling an anesthetic eye drop (0.5% tetracaine hydrochloride, Alcon). The baseline IOP was defined as the average IOP of 3 months prior to the initiation of CPAP therapy. Moreover, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate were measured.

The CPAP titration was performed during full-night polysomnography to determine the optimal CPAP pressure, and the CPAP treatment was continued for 1 year.

The ocular perfusion pressure (OPP) is defined as the pressure that forces blood through the ocular vascular bed. The OPP is the difference between the mean arterial and venous pressure. The venous pressure in the eye is almost equivalent to IOP. The OPP was calculated based on IOP, SBP, and DBP, according to the results of ophthalmodynamometric studies as follows:¹⁶

$$\text{OPP} = 2 / 3[\text{DBP} + 1 / 3(\text{SBP} - \text{DBP})] - \text{IOP}$$

The IOP, SBP, DBP, and pulse rate were recorded every 3 months. Visual field analysis was performed at 12 months after initiating the CPAP therapy.

The primary outcome was a change in IOP 12 months after initiating the CPAP therapy. The secondary outcome was OPP and the progression of glaucoma (worsened visual field and prescription of antiglaucoma drugs).

Statistical Methods

Data were analyzed using the STATA software (ver. 14.1; StataCorp, College Station, TX, USA). The rates of change in IOP prior to and after CPAP therapy were calculated using multilevel linear regression. Paired *t* test was performed to compare the differences in IOP, OPP, SBP, DBP, pulse rate, VFI, MD, and pattern standard deviation (PSD) prior to and after CPAP therapy. Mean values were compared using 95% confidence intervals. A *p* value of <0.05 was considered to indicate statistical significance.

RESULTS

Sixteen eyes of eight patients with POAG who were newly diagnosed with OSA, in whom CPAP therapy was indicated and continued for 12 months, were included in our study. Of these, four eyes (25%) were excluded because of intolerance to CPAP therapy (two eyes) and loss to follow-up (two eyes). Finally, 12 eyes from six patients who continued CPAP therapy for 12 months with a compliance of 5.7 hour/night (range: 5–7.3 hour/night) were included in the study.

Characteristics

The characteristics of patients are shown in Table 1. The mean age \pm SD was 60.6 ± 4.53 (range: 52–72) years. Four patients were male (75%), and the remaining two patients were female (25%). Two eyes had undergone phacoemulsification with an intraocular lens implantation (16.7%). Four patients (66.7%) had hypertension, two patients (33.3%) had dyslipidemia, two patients (33.3%) had atrial fibrillation, and one patient (16.7%) had diabetes without diabetic

retinopathy. The average AHI score was 37.42 ± 15.62 per hour prior to CPAP treatment. This value reduced to 2.53 ± 1.55 /hour after CPAP treatment.

Intraocular Pressure

Twelve months after the initiation of CPAP therapy, the mean IOP significantly increased compared with that at the baseline (19.08 ± 3.47 vs 17.83 ± 2.89 mm Hg, respectively; $p = 0.006$). In addition, the increase in mean IOP at 3, 6, and 9 months was 17.17 ± 2.63 ($p = 0.05$), 18.58 ± 3.68 ($p = 0.27$), and 17.50 ± 3.40 ($p = 0.56$), respectively (Table 2).

Baseline IOP rising rate was 0.69 ± 0.47 mm Hg/year [95% confidence interval (CI): -0.18 to 0.13 ; $p = 0.138$], whereas it was 1.13 ± 0.47 mm Hg/year after CPAP therapy (95% CI: 0.21 – 2.05 ; $p = 0.016$). The difference in IOP after CPAP therapy (1.13 ± 0.47 mm Hg/year) was more than the baseline (0.69 ± 0.47 mm Hg/year) but was not statistically significant ($p = 0.059$) (Fig. 1).

Table 1: Patient characteristics

	Mean \pm SD	Range
Age	60.6 ± 4.53	52–72
BMI (kg/m ²)	26.6 ± 1.84	24.4–31.5
AHI (per hour)	37.42 ± 15.62	17.2–67.3
VA (LogMAR)	0.11 ± 0.22	0–0.6
CCT (microns)	582.31 ± 33.94	546–651

BMI, basal metabolic index; AHI, apnea–hypopnea index; n/h, number per hour; CCT, central corneal thickness

Table 2: Mean IOP at 3, 6, 9, and 12 months after the initiation of CPAP therapy compared with baseline IOP

	IOP (mm Hg)	95% CI	p value
3 months	17.17 ± 2.63	-0.02 to 1.33	0.05*
6 months	18.58 ± 3.68	-2.16 to 0.66	0.27
9 months	17.50 ± 3.40	-0.88 to 1.55	0.56
12 months	19.08 ± 3.48	-2.06 to (-0.43)	0.006*

IOP, intraocular pressure; CPAP, continuous positive airway pressure
*p value ≤ 0.05 which suggest statistically significant

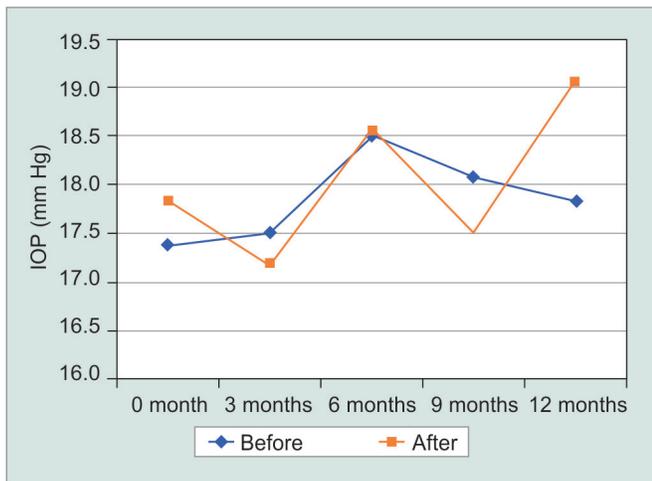


Fig. 1: Comparison of intraocular pressure curves prior to the initiation of continuous positive airway pressure therapy and throughout the 12 months after initiating CPAP therapy (multilevel linear regression)

Progression of Glaucoma

The results showed that the PSD value of the 24-2 SWAP visual field significantly reduced from 5.33 ± 3.92 to 4.77 ± 3.73 ($p = 0.03$). The MD was reduced from -5.29 ± 5.09 to -5.43 ± 4.97 ($p = 0.81$). The VFI increased from 86.75 ± 13.9 to 87.67 ± 14.62 ($p = 0.54$).

Hemodynamics

The paired *t* test showed that the difference between mean OPP \pm SD at the baseline and that at 12 months after initiating CPAP therapy was not statistically significant (45.24 ± 7.09 vs 42.21 ± 5.29 , respectively; $p = 0.06$). Compared with those at the baseline, SBP and DBP decreased at 12 months after initiating CPAP therapy (for SBP; from 123.17 ± 8.56 mm Hg to 122.50 ± 10.70 mm Hg; $p = 0.81$ and for DBP; from 80.33 ± 8.69 mm Hg to 76.67 ± 6.02 mm Hg; $p = 0.18$) (Table 3). Moreover, there was a statistically significant decrease in mean pulse rate \pm SD from 83.00 ± 13.28 beats per minute (bpm) to 72.33 ± 4.42 bpm ($p = 0.01$).

DISCUSSION

In the present study, we evaluated the long-term effect of the first use of CPAP therapy on IOP in patients with POAG who were newly diagnosed with OSA. Studies investigating the relationship between sleep apnea, glaucoma, and CPAP therapy were mostly conducted during the night and over a short period of time. Very few studies have evaluated the effect of CPAP on the risk of glaucoma in patients with OSA. To the best of our knowledge, this is the first study to investigate changes in IOP, hemodynamic parameters, and the progression of glaucoma following long-term CPAP therapy (1 year). The strengths of the present study include its prospective design, the 12-month follow-up period, and the low rate of discontinuation (25%).

Numerous studies have reported that variations in diurnal IOP are higher in patients with OSA and increase further after CPAP therapy. Cohen et al.¹⁴ also reported an increase in mean IOP to 23.75 mm Hg after 7 hours of sleep in three patients with obstructive sleep apnea syndrome (OSAS) with glaucoma treated with CPAP therapy. Moreover, Kiekens et al.¹³ observed a significant increase in overnight IOP after 1 month of CPAP therapy from that at the baseline. Regarding fluctuations in 24-hour IOP, the mean difference between the lowest and highest IOP was 6.7 ± 1.5 mm Hg at the baseline that increased to 9.0 ± 2.0 mm Hg after CPAP therapy. The results showed that CPAP therapy did not influence IOP while patients were awake. In our study, the difference between mean IOP at the baseline and that at 12 months after initiating CPAP therapy was statistically significant. The IOP was measured

Table 3: Mean systolic and diastolic blood pressure, pulse rate, and ocular perfusion pressure at baseline and 12 months after the initiation of CPAP therapy

	Baseline	12 months after CPAP	p value
Systolic blood pressure (mm Hg)	123.17 ± 8.56	122.50 ± 10.70	0.81
Diastolic blood pressure (mm Hg)	80.33 ± 8.69	76.67 ± 6.02	0.18
Pulse rate (beats per minute)	83.00 ± 13.28	72.33 ± 4.42	0.01*
Ocular perfusion pressure	45.24 ± 7.09	42.21 ± 5.29	0.06*

CPAP, continuous positive airway pressure
*p value ≤ 0.05 suggests statistical significant



using applanation tonometry during office hours. The results of the present study are consistent with those of previous studies even though diurnal variation or supine position was not used or frequent awakening of the patient to perform IOP measurements was not performed in our study.

The reason for the observed increase in IOP after CPAP therapy is still unclear. It is suggested that CPAP therapy leads to an increase in the intrathoracic pressure, which results in the elevation of pressure in the venous circulation. This effect may reduce the aqueous humor outflow through the episcleral veins, thus explaining the observed increase in IOP.

Contradictory to the results of the present study, Pépin et al.¹⁷ observed an improvement in 24-hour IOP following the initiation of CPAP therapy. They found that CPAP therapy decreases nighttime and daytime IOP. Both the IOP and blood pressure were measured every hour for 24 hours in 18 patients at the time of OSAS diagnosis and after 1 month of CPAP therapy. The authors concluded that CPAP therapy may exert a beneficial effect on glaucoma in patients with OSAS.

Obstructive sleep apnea causes insufficient blood supply and nourishment to the retinal nerve fiber layer (RNFL) and optic nerve.¹⁸ The CPAP therapy is known to ameliorate hemodynamic parameters in patients with OSA by decreasing hypoxia and the risk of damage due to vascular perfusion. However, our study revealed a decrease in OPP from 45.24 ± 7.09 at the baseline to 42.21 ± 5.29 at 12 months after initiating CPAP therapy, with *p* value of 0.06. Decreases in OPP may be a potential risk factor for a higher prevalence of glaucoma. In the present study, the patients examined were in a seated position. Liu et al.¹⁹ found that nocturnal OPP in the supine position was significantly higher than diurnal OPP in the seated position. These results are inconsistent with the OPP findings reported in healthy individuals.

Kiekens et al.¹³ also reported that the increase in nocturnal IOP is enhanced and paralleled by a decrease in OPP during CPAP therapy at night. In contrast to the OPP findings observed in healthy individuals, Liu et al.¹⁹ showed that nocturnal OPP in the supine position was significantly higher than diurnal OPP in the seated position.

In a retrospective cohort study conducted in Taiwan using data from the Longitudinal Health Insurance Database 2000, Chen et al. stated the treatment options for OSA and identified the risk factors associated with the development of glaucoma. The study included a large sample of patients with OSA (*n* = 2,528) and randomly selected age-matched controls (*n* = 10,112). The results showed that CPAP therapy did not reduce the risk of glaucoma in patients with OSA compared with that in healthy controls (hazard ratio = 1.65, 95% CI: 1.09–2.49).²⁰

The current results show that CPAP therapy does not accelerate the progression of glaucoma. Kadyan et al.²¹ found that the prevalence of glaucoma in their study was similar to that observed in healthy individuals (2%, *p* = 0.429). They speculated that this observation may be related to the use of CPAP in the majority of patients with OSA.

In a case study involving patients with NTG and OSAS, the progression of glaucoma ceased after 3.5 years of CPAP therapy. This effect was directly attributed to the therapy.²²

The present results showed that CPAP therapy did not reduce the risk of glaucoma, which was correlated with IOP or OPP, in patients with OSA. However, these data cannot determine whether the use of CPAP therapy exerts a deleterious effect on the development or progression of glaucoma.

The limitations of the present study include the small sample size and absence of a matched control group. Furthermore, visual field damage may be detected 12 months after optic nerve damage from CPAP therapy. Because of the small sample size, it was not possible to evaluate the association between glaucoma and the severity of OSA as a potential risk factor. However, the number of patients included in most of the previous studies was limited.

In conclusion, the results of this study showed that CPAP therapy did not reduce the risk of glaucoma. Patients with OSA demonstrated significant increases in IOPs and decreases in OPPs after CPAP therapy. In this study, MD, PSD, and VFI did not demonstrate significant differences after CPAP therapy. Hence, the current results support the notion that CPAP therapy does not accelerate the progression of glaucoma. However, the present findings cannot determine whether the use of CPAP therapy exerts a deleterious or beneficial effect on the progression of glaucoma. Therefore, patients with OSA receiving CPAP therapy should undergo regular screening for glaucoma and the IOP monitoring.

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