

High Intraocular Pressure: A Comparative Study between Obstructive Sleep Apnea (OSA) and Non-OSA Subjects

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ABSTRAK

Obstructive Sleep Apnea (OSA) memberi kesan kepada 2-5% daripada populasi pertengahan umur dan merupakan keadaan yang mengancam nyawa. Kajian terdahulu mengenai OSA dan glaukoma telah melaporkan penemuan tidak konklusif. Ini adalah kajian perbandingan keratan rentas dengan tempoh kajian satu tahun untuk membandingkan kejadian tekanan intraokular yang tinggi di kalangan subjek OSA dan subjek bukan OSA. Kajian ini berlaku di sebuah hospital tertiar di mana sejumlah 50 subjek dengan OSA dan 50 subjek bukan OSA direkrut. Umur purata ialah 37.0 tahun (19,65) dalam populasi kajian multietnik (76% (Melayu), 18% (Cina) dan 6% (India)). Semua pesakit menjalani polisomnogram yang dibantu dengan komputer sepenuh masa (SOMNOCheck Effort Weinmann, Hamburg, Jerman), Epworth Sleepiness Scale (ESS), Mullers manouvre (MM) untuk menilai tahap halangan dan tonometri. Kejadian tekanan Intra Okular (IOP) yang tinggi di kalangan subjek OSA adalah 52% dengan perbezaan yang signifikan antara subjek bukan OSA dan OSA. Korelasi antara ESS dan IOP adalah signifikan ($p < 0.05$) bagi kedua-dua mata. Terdapat perbezaan yang signifikan dalam IOP min antara subjek bukan OSA dan OSA untuk kedua-dua mata ($p < 0.05$). Hubungan yang signifikan didapati antara kehadiran keruntuhan di rantau retropalatal dan retrolingual dengan tinggi IOP ($p < 0.05$). Kejadian IOP yang tinggi di kalangan pesakit OSA (52%) memberi gambaran baru dalam pengurusan pesakit dengan OSA. Hubungan penting wujud antara parameter OSA (ESS dan kehadiran keruntuhan pada Mullers manouvre) dan IOP yang tinggi. Kami mengesyorkan penilaian oftalmik secara berkala pada pesakit dengan OSA.

Kata kunci: indeks apnea-hypopnea, obstructive sleep apnea, tekanan intraokular

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ABSTRACT

Obstructive Sleep Apnoea (OSA) affects 2-5% of the middle-aged population and is a potentially life-threatening condition. Previous studies on OSA and glaucoma have reported mixed findings. This was a cross-sectional comparative study with a study duration of one year to compare the incidence of high intraocular pressure among OSA subjects and non-OSA subjects. This study took place in a tertiary hospital where a total of 50 subjects with OSA and 50 non-OSA subjects were recruited. The average age was 37 years (19,65) in a multiethnic study population (76% (Malay), 18% (Chinese) and 6% (Indian)). All patients underwent a full night computer-assisted polysomnogram (SOMNOCheck Effort Weinmann, Hamburg, Germany), Epworth Sleepiness Scale (ESS), Mullers manouevre (MM) to assess the level of obstruction and tonometry. The incidence of high Intra Ocular Pressure (IOP) among OSA subject was 52% with a significant difference between non-OSA and OSA subjects. Correlation between ESS and IOP were significant ($p < 0.05$) for both eyes. There was a significant difference in mean IOP between non-OSA and OSA subjects for both eyes ($p < 0.05$). A significant association was found between the presence of collapse at retropalatal and retrolingual region with high IOP ($p < 0.05$). The incidence of high IOP among OSA patient (52%) provides a new insight in the management of patients with OSA. Significant associations exist between OSA parameters (ESS and presence of collapse on Mullers manouevre) and high IOP. We strongly recommend periodic ophthalmic assessment of intraocular pressure in patients with OSA.

Keywords: apnea-hypopnea index, intraocular pressure , obstructive sleep apnea

INTRODUCTION

Sleep apnea was first described in 1965 and is a serious and potentially life threatening condition. Obstructive sleep apnea (OSA) is a condition characterized by recurrent complete or partial upper airway obstructions during sleep with each episode generally being terminated by awakening when upper airway muscle tone increases (Deegan and McNicholas 1995). These obstructive respiratory disturbances presents with snoring and excessive daytime somnolence. The diagnosis of

OSA is centred on polysomnographic (PSG) apnea-hypopnea index (AHI) findings (Marcus et al. 2001). This index is frequently used in diagnosing and defining the severity of OSA. A normal AHI is 5 and less. AHI 6-20 is categorized as mild OSA, 21-40 as moderate and greater than 41 as severe (Gross et al. 2006). Among the three types of sleep apnea: central, obstructive and mixed, the obstructive apnea is a more common morbid health problem. This problem is more common in the middle-aged population where its prevalence

is estimated at 2-5% (Deegan and McNicholas 1995). It has a male gender predominance with about 2% of women and 4% of men between 30 and 60 years who are likely to be affected (Ohayon et al. 1997; Young et al. 1993).

Glaucoma is one of the many comorbidities associated with OSA (Deegan and McNicholas 1995). Its clinical symptoms include blurred or loss of peripheral vision, eye pain, headaches and is the second leading cause of blindness worldwide (Quigley and Broman 2006). Previous studies on OSA and glaucoma have reported mixed findings. Most of the studies emphasized the relationship between OSA and normal tension glaucoma (NTG) (Faridi et al. 2012; Kiuchi et al. 2006; Sergi et al. 2007). Sergi et al. reported that severity of OSA correlated with relatively high intraocular pressure (Sergi et al. 2007). The potential association between OSA and glaucoma was explained by two theories, a vascular theory and a mechanical theory (Faridi et al. 2012). The vascular theory postulates that repeated or prolonged episodes of hypoxia secondary to upper airway collapse during sleep in OSA patients may reduce the oxygen supply to the optic nerve, leading to optic neuropathy (Faridi et al. 2012). While, the mechanical theory postulates raise in the intraocular due to disrupted sleep architecture and an increase in sympathetic tone, a key element in pathophysiology of OSA (Faridi et al. 2012). In the present study, the incidence of high IOP was compared between OSA and non-OSA subjects.

The relationship between OSA parameters (AHI, ESS and severity of obstruction on Muller's manoeuvre) and IOP was also examined.

MATERIALS & METHODS

A cross-sectional study was conducted in Universiti Kebangsaan Malaysia Medical Centre (UKMMC), a tertiary hospital between January 2008 and February 2009.

SUBJECTS

Patients who underwent polysomnography (PSG) test in the sleep laboratory of Universiti Kebangsaan Malaysia Medical Centre (UKMMC) were recruited based on the inclusion and exclusion criteria. The inclusion criteria were adult patients aged between 18-65 years, normal healthy volunteers and patients who were clinically suspected of having OSA and were subjected to overnight polysomnography for investigation. The exclusion criteria were patients less than 18 years and more than 65 years, patients with matured cataract, patients with family history of glaucoma, patients with ocular inflammation or surgery to the eyes 3 months before recruitment, patients with corneal abnormality and patients wearing glasses (myopia > -6D). All subjects gave informed consent.

Sample size was calculated using formula for two sample comparison of percentages where p_1 was taken as prevalence of high IOP among normal subjects and p_2 was taken as prevalence of high IOP among OSA

subjects. From the study by Giuffrè et al., the prevalence of high intraocular pressure (IOP) more than 21 mmHg in Mediterranean population is 4.3% (Giuffrè et al. 1995). If p_2 was taken as 52%, this study required 14 non-OA subjects and 14 OA subjects to obtain a good study power of 90%. In the present study we increased the sample number to 50 in each group.

INSTRUMENTS

The study objectives were to measure and compare the prevalence of high IOP among non-OA and OA subjects and to determine relationship between OA parameters (AHI, ESS and severity of obstruction on Muller's manoeuvre) and IOP. The ESS is a self-administered eight-item validated questionnaire that is a reliable method in measuring hypersomnolence (Johns 1992). A written permission from the copyright holder and license provider was obtained for usage of this questionnaire. The Muller's manoeuvre (MM) is a clinic based subjective endoscopic assessment of presence and degree of collapse at different levels of the upper airway to mimic the obstructive episodes occurring during sleep (Terris et al. 2000).

All PSG was done in a hospital based sleep laboratory using a computer-assisted device Somno Check Effort Weimann (Hamburg, Germany 2005) partial sleep study and the results were analyzed. The PSG parameters documented include AHI, apnea, hypopneas, arousal index, respiratory disturbance index and minimum oxygen saturation. OA subjects were

defined as patients who satisfied the polysomnographic criteria of OA. In this study, obstructive apneas were defined as complete cessation of airflow lasting at least 10 seconds followed by respiratory arousals (Friedman et al. 2004). Obstructive hypopneas are characterized by either a 50% reduction in airflow from baseline lasting at least 10 seconds or a 4% oxygen desaturation followed by respiratory arousals (Friedman et al. 2004). An AHI value of more than 5 satisfied definition of a subject with OA (Gross et al. 2006).

The measurement of the IOP was performed on the next morning subsequently after the PSG test completed. The reading was taken using Tonopen (Reichert, NY, USA), a hand held tonometer which provides IOP readings that agrees with Goldmann Applanation tonometer (GAT) (Cook et al. 2012). Tonopen was selected because it is easy to handle, can be done at the bedside, portable and need not to be mounted on the slit lamp. The measurement was taken by a single ophthalmologist who was blinded from the PSG results. Participants' eyes were anesthetised with gutt Alcaïne® (Proparacaine hydrochloride ophthalmic solution, USP) 0.5%. Three IOP measurements were taken while the subjects were lying supine and averaged for the analysis. IOP ≥ 21 mmHg was considered as high IOP. Both eyes were included in the analysis. Subsequently, the subjects underwent MM test to assess the level and grading of obstruction and other relevant examinations to evaluate the body mass index, tonsils and adenoid

size. The MM was performed with the subject in sitting position (45°) after topical nasal anaesthesia applied. A flexible nasopharyngolaryngoscope (FNPLS) (Olympus ENF P4 size 3.6 mm) was inserted through the anaesthetized nasal cavity to the lower oropharynx. Collapse of the retropalatal and the retrolingual region was assessed during maximal inspiratory effort against a closed mouth and sealed nose. The severity of airway collapse was classified as collapse <50%, collapse ≥50% and total collapse.

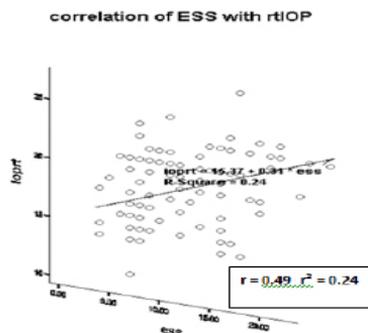
A thorough physical examination was done to the subjects and several parameters such as body mass index (BMI) and neck circumference were taken. The subjects were interviewed to elicit history of OSA and Epworth Sleepiness Scale (ESS).

STATISTICAL ANALYSIS

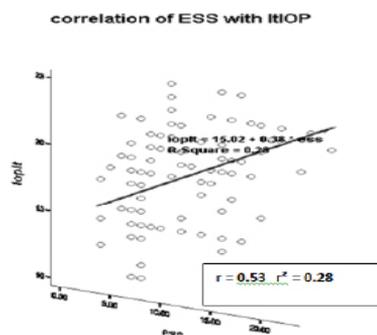
Demographic data was presented descriptively in mean and standard deviation. When data had a normal distribution, the variables were analyzed using unpaired t-test. A non parametric analysis was performed when data was not normally distributed. A probability value of less than 0.05 was deemed significant.

RESULTS

A total of 100 subjects who fulfilled the eligibility criteria were enrolled for this study. Based on the PSG results, 50 subjects with OSA and 50 non-OSA subjects were enrolled. The age of subjects ranged between 19 to 65 years with a mean of 37.0±13.40



(a)



(b)

Figure 1a and 1b: Relationship between ESS and right (1a) and left (1b) eye IOP

years. The mean age among the OSA subjects was higher (41.34±11.34 years) compared to non-OSA subjects (32.64±3.40 years). There was a total of 57 males and 43 females. The study population consisted of multiple ethnicity including 76 Malays (76%), 18 Chinese (18%) and 6 Indians (6%).

EPWORTH SLEEPINESS SCALE (ESS)

In this study, mean ESS score was 8.0±5.3. The mean value among non-OSA subjects was 4.9±3.2 whereas, for OSA subjects was 11.1±5.1. Majority of the non-OSA subjects had normal ESS score (86%) and only 14% had

Table 1: Distribution of BMI among study subjects

BMI (kg/m ²)	Non-OSA subjects (n)	OSA subjects (n)
Underweight (<18.5)	3	0
Normal (18.5-<22.9)	21	0
Pre obese (22.9-<27.5)	18	12
Obese class 1 (27.5-<35)	6	19
Obese class 2 (35-<40)	1	8
Obese class 3 (>40)	1	11
Total	50	50

mild and moderate ESS score (12% and 2%, respectively). None of the non-OSA subjects had severe ESS score. Correlation between ESS and intraocular pressure was assessed using 2-tailed Pearson Correlation. The assessment for the right and left eye were performed separately. Correlation between ESS and IOP were significant ($p < 0.05$) for both eyes with fair relation (right eye $r^2 = 0.24$, left eye $r^2 = 0.28$) as shown in Figure 1a and 1b.

BODY MASS INDEX

The mean BMI was 29.11 ± 9.06 (15.60, 66.00) kg/m² (Table 1). The mean value among non-OSA subjects was 23.72 ± 4.95 kg/m², meanwhile the mean value among OSA subjects was 34.50 ± 9.06 kg/m². Non OSA subjects had normal BMI or underweight.

Majority of OSA subjects were pre obese or obese class 1 (62%). Twenty-two percent was obese class 3 (morbid obesity). For the non-OSA subjects, most of them had normal BMI (42%) or underweight (6%). A small percentage of the normal subjects (4%) were obese class 2 and 3.

INTRA OCULAR PRESSURE (IOP)

IOP was measured for both eyes in each subject. The IOP of both eyes were analysed separately. Among the non-OSA subjects, 90% had normal IOP. Only 10% (5/50) had high IOP with wide age variability between 22 to 63 years. Most of them had at least one systemic co-morbidity. Meanwhile, 52% (26/50) of the OSA subjects had high IOP. Most of these patients had other systemic co-morbidities. The

Table 2: Comparison of IOP between Non-OSA and OSA subjects

IOP	Study Group (n)	Mean (mmHg)	P value
Right eye	Non-OSA subjects (50)	15.98 ± 2.81	<0.05
	OSA subjects (50)	19.80 ± 2.85	
Left eye	Non-OSA subjects (50)	15.84 ± 3.14	<0.05
	OSA subjects (50)	20.22 ± 2.96	

Table 3: Comparison of mean IOP between subjects with and without retropalatal collapse

IOP	Presence of retropalatal collapse (n)	Mean (mmHg)	P value
Right eye	No collapse (39)	15.77±2.80	<0.05
	Presence of collapse (61)	19.25±3.07	
Left eye	No collapse (39)	15.59±3.07	<0.05
	Presence of collapse (61)	19.59±3.30	

Table 4: Comparison of mean IOP between subjects with and without retrolingual collapse

IOP	Presence of retrolingual collapse (n)	Mean (mmHg)	P value
Right eye	No collapse (84)	17.40±3.29	0.05
	Presence of collapse (16)	20.44±2.92	
Left eye	No collapse (84)	17.50±3.68	<0.05
	Presence of collapse (16)	20.81±2.83	

commonest medical illness in the OSA subjects was hypertension (56%) followed by diabetes mellitus (18%). The other medical illnesses were Ischemic Heart Disease, hypercholesterolemia, asthma, hyperthyroidism and Chronic Obstructive Airway Disease.

APNEA-HYPOPNEA INDEX (AHI)

AHI assessment was based on the PSG report. Highest AHI documented in this study population was 100 and the lowest 0, with a mean of 17.2±23.5. AHI was further categorized based on the severity into mild (AHI=6-20 events/Hr), moderate (AHI=21-40 events/Hr) and severe (AHI=>40 events/Hr). There were 50 subjects with normal AHI and 50 subjects with varying degrees of OSA. There were 20 subjects (40%) in the mild category, 14 subjects (28%) in the moderate category and lastly 16

subjects (32%) in the severe category.

COMPARISON OF IOP BETWEEN NORMAL AND OSA SUBJECTS

Comparison of high IOP between non-OSA and OSA subjects was assessed separately between the right and left eye. Statistical analysis using unpaired t-test revealed significant difference of mean IOP of the right and left eye between non-OSA and OSA subjects (p<0.05) (Table 2).

COMPARISON OF IOP BETWEEN SUBJECTS WITH PRESENCE OF COLLAPSE ON MM

Relationship of retropalatal collapse with IOP was assessed using unpaired t-test. There was significant difference in mean IOP readings in subjects with and without retropalatal collapse for

both right eye ($p < 0.001$) and the left eye ($p < 0.001$) (Table 3).

Relationship of retrolingual obstruction with IOP was assessed using unpaired t-test. There was significant difference in mean IOP readings in subjects with and without retrolingual collapse for both right eye ($p < 0.05$) and the left eye ($p < 0.05$) (Table 4). However, there was no significant relationship between severity of collapse either the retropalatal or retrolingual and intraocular pressure ($P > 0.05$)

DISCUSSION

Obstructive sleep apnea (OSA) is a disease characterized by cyclical and periodic complete or partial upper airway obstruction during sleep. These events causes intermittent cessation of breathing (apneas) or a decrease in airflow (hypopneas) despite ongoing stimulation by the respiratory centre. The upper airway is the main anatomical site responsible for OSA. Diagnosis of the disease is based on clinical symptoms and physical findings and is corroborated by laboratory examinations (Deegan and McNicholas 1995).

The complications of OSA involves multiple end organs and they include cognitive impairment leading to increased risk of motor vehicle accident,, systemic hypertension, pulmonary hypertension, myocardial infarction, cardiac arrhythmia and stroke (Onen et al. 2000). Several studies have indicated that OSAS may have neuro-ophthalmological consequences (Marcus et al. 2001;

Sergi et al. 2007). The relation between OSA and high IOP was thought to be due to interruption of the circulating nitric oxide level in the hemodynamic circulation. Ip et al. conducted a comparative study of serum nitrites and nitrates in the early morning of OSAS subjects and normal subjects. Serum nitrite and nitrate levels were found to be significantly lower in OSAS subjects (Ip et al. 2000). Nitric Oxide (NO) is important in blood pressure regulation. The cyclical periodic apnoea that happens in OSA causes a decrease in vasodilator function of the endothelium. This in turn increases peripheral vascular resistance (Ip et al. 2000). Theoretically, the reduction of NO level in patient with OSAS causes rise in IOP as the episcleral venous pressure increases.

Gold standard measurement of IOP is done by using Goldmann Applanation Tonometer. Previous studies have indicated that mean IOP measured using this technique is 16 mmHg, with a standard deviation of 3 mmHg. Many past studies used the value of 21 mmHg as a cut-off point to differentiate normal and abnormal pressures (Quigley and Broman 2006). In this study, the Tonopen (hand-held instrument) was used since its reading agrees with Goldmann Applanation tonometer (Cook et al. 2012). Measurement of IOP was done after the sleep study in sitting position. This is because the position during sleep which is mostly supine, gives rise to postural related increase in IOP (Kiuchi et al. 2006). It is important to standardize measurement in which a subject changes his or her position

from supine to erect, then walks to the examination room before finally sitting during the examination (Kiuchi et al. 2006).

In this study, OSA was diagnosed via polysomnogram (Somno Check Effort Weimann partial sleep study 2005). Fifty subjects were diagnosed to have OSA with varying degrees, while another 50 subjects who had AHI of 5 and less were considered as non-OSA subjects for comparison. The incidence of high IOP in OSA subjects was 52%, compared to non-OSA subjects, 10% ($p < 0.05$). There was significant difference in mean IOP between non-OSA and OSA subjects for both eyes ($p < 0.05$). Previous non-comparative studies documented normal IOP among subjects with OSA (Kiuchi et al. 2006; Sergi et al. 2007). To the best of our knowledge, this was the first cross-sectional study to demonstrate significant difference in mean IOP and incidence of high IOP in OSA subjects comparing to non-OSA subjects (Chaitanya et al. 2016). A large sample retrospective cohort study comparing 1012 patients in disease cohort and 6072 randomly selected controls by Lin et al. concluded that OSA patients were associated with 1.67 times more risk of developing open angle glaucoma within the first 5 years of initial diagnosis (Lin et al. 2013).

In 1993, Young et al. studied the prevalence of sleep disordered breathing in the general population of 602 state employees aged between 30-60 years (Young et al. 1993). They found that men are 2 to 3.7 times as likely as women to have sleep-

disordered breathing (Young et al. 1993). Similarly in our study population, there were more men in the OSA group. Mean age among OSA patient was 41.34 ± 11.34 years and this was comparable with study by Friedman et al. in 2004 (Friedman et al. 2004). As Malaysia is a multi racial country, the racial distribution was majority Malay followed by the Chinese and Indian. This racial distribution was seen similarly in our study population where majority of the patients were Malay (76%) followed by Chinese and Indian.

Epworth Sleepiness Scale (ESS) is a validated self-administered questionnaire used internationally to quantify the severity of daytime somnolence. The higher the cumulative value of the subjects' score, the more severe the daytime somnolence is - (Johns 1992). In this study the mean of ESS score was 8.0 ± 5.3 . The mean value among non-OSA subjects was 4.9 ± 3.2 whereas, for OSA subjects, it was 11.1 ± 5.1 . Correlation between ESS and IOP was significant with p value < 0.05 . However, the correlation coefficient was only fair in both eyes. This may be due to the subjectivity of the ESS questionnaire, not capturing the true levels of sleepiness in our subjects. To the best of our knowledge, no other study assessed the correlation of ESS with IOP especially in OSA subjects.

Relationship between IOP and OSA were mentioned in several studies. Sergi et al. 2006, in their study of 51 patients diagnosed of having obstructive sleep apnea, found significant association between OSA and prevalence of Normal Tension Glaucoma (NTG)

(Sergi et al. 2007). It was highlighted that the relative risk of OSA patients to develop NTG was 3.34 compared to normal subjects (Sergi et al. 2007). Factors that may be involved in the etiology of high IOP include abnormal blood flow, autonomic dysfunction, oxidative stress and others (Faridi et al. 2012).

In this study, significant association was found between presence of collapse at retropalatal and retrolingual region with high IOP ($p < 0.05$). However, no relationship existed between IOP and severity of obstruction on MM. These findings contradict Lundmark, who reported forced inspiratory efforts generated by MM to be associated with a reduction in IOP and an increase in ocular blood flow (Lundmark et al. 2003). The study involved seven healthy young adult volunteers, a small number to start with. We think the significance of the study findings are limited as MM cannot be assumed as simulated obstructive apnoea. This manoeuvre was performed for a few seconds in a conscious patient. It does not represent the actual periodic apnea which occurs in OSA patient during sleep. We postulate that presence of collapse during MM, either retrolingual or retropalatal signifies the critical point of obstruction in patients with OSA, explaining why significant association was found between presence of collapse and high IOP in this study. No study was found to assess the relation between MM findings with IOP in OSA subjects.

The nerve fiber thicknesses of the macula, choroid and retina in relation

to AHI was evaluated in a recent study by Yuvaci et al. This prospective controlled study observed a statistically significant thinning of the posterior ocular tissues which was detected using optical coherence tomography in patients with severe OSA (Yuvaci et al. 2016). This recent study provides additional literature to the various ocular complications of OSA.

This study utilises full night, computer assisted overnight polysomnography as a research tool. This ambulatory polysomnography is unattended, posing potential inaccuracies in AHI readings. However, we believe this limitation is less likely to cause significant derangements in study results as all the subjects underwent the same polysomnography throughout the study duration. As highlighted before, MM cannot be assumed as simulated obstructive apnoea as this manoeuvre is performed in a conscious patient. Its clinical value is limited to demonstrating presence of obstruction at retropalatal and retrolingual levels. Severity of obstruction at these levels may not hold clinical significance. We suggest future studies to utilise a better tool like Drug Induced Sleep Endoscopy to assess presence of collapse and ascertain the severity of collapse in OSA patients.

CONCLUSION

Incidence of high IOP among OSA patient (52%) provides a new insight in management of patients with OSA. Significant association exists between OSA parameters (AHI, ESS and presence of collapse on Mullers

maneuvre) and high IOP. We strongly recommend periodic ophthalmic assessment of intraocular pressure in patients with OSA. Future studies could look into whether sustained, effective treatment in OSA subjects could reduce the incidence of high IOP.

ACKNOWLEDGEMENT

The authors would like to acknowledge the contribution of clinical and supporting staff of the sleep laboratory and Otorhinolaryngology Outpatient Clinic, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The staff provided technical help in performing polysomnography and preparation of patients as well as instruments for clinic endoscopy used in this study. The authors also acknowledge the kind contribution by Dr. Murray W Johns from Melbourne Australia who allowed them to use the Epworth Sleepiness Scale as one of their research tools. The contribution by Mapi™ Research Trust in Lyon, France was instrumental in providing the authors with the English and Malay versions of the Epworth Sleepiness Scale.

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Received: 16 Aug 2016

Accepted: 16 Jul 2018