Efficacy of Donepezil in the Treatment of Obstructive Sleep Apnea: A Placebo-Controlled Trial

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Background: *The treatments of obstructive sleep apnea (OSA) consist of surgical such as uvulopalatopharyngoplasty and non-surgical approaches such as continuous positive airway pressure (CPAP), weight reduction, dental appliance, and some medications. Cholinergic nerve system has been shown an important role in respiratory regulation and in sleep apnea. Donepezil, a reversible acetylcholine esterase inhibitor, can increase cholinergic nerve activity especially during sleep. There were some studies on the efficacy of donepezil in treatment of OSA patients and found significant improvement in the apnea-hypopnea index (AHI) and oxygen saturation compared to pretreatment and placebo.*

Objective: *To evaluate the efficacy of donepezil in the treatment of obstructive sleep apnea (OSA).*

Material and Method: *A prospective, randomized study was conducted at HRH Princess Maha Chakri Sirindhorn Medical Center. OSA patients diagnosed by polysomnography and Epworth Sleepiness Scale scores were randomly allocated into study group and control group. The study group received donepezil (5 mg), 1 tablet a day for 4 weeks then increased to 2 tablets a day for the next 4 weeks. The control group received placebo drug in the same doses. The value of apnea-hypopnea index (AHI), minimum oxygen saturation (minimum SpO_2) and Epworth Sleepiness Scale scores were used in comparison both before and after the end of the study.*

Results: *At the end of the study, 41 patients were collected of which 21 patients were in study group and 20 patients were in control group. Before treatment, there were no significant difference in age ($p = 0.53$), body mass index ($p = 0.80$), sex ($p = 0.44$), minimum SpO_2 ($p = 0.36$), Epworth sleepiness Scale scores ($p = 0.86$), and AHI ($p = 0.06$) between two groups. After treatment, no statistically significant difference in the value of AHI, minimum SpO_2 and Epworth Sleepiness Scale scores were identified both in the same group and between two groups ($p>0.05$).*

Conclusion: *Treatment OSA patients with donepezil did not show better results than placebo.*

Keywords: *Obstructive Sleep Apnea, Donepezil*

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Obstructive sleep apnea (OSA) is a sleep disorder that characterized by repetitive cessation (apnea) or significant decrease (hypopnea) in airflow in the presence of breathing effort during sleep. This may lead to arterial oxygen desaturation and arousals from sleep with sleep disruption[1]. The prevalence of OSA has been reported about 2% in women and 4% in men[2]. OSA may be associated with many diseases or disorders such as hypertension, congestive heart failure, sexual dysfunction, depression, gastro-esophageal reflux, and arrhythmia[1]. The common symptoms of OSA include snoring, nocturia, insomnia, gasping or choking sensations, morning headache, dry or sore throat, excessive daytime sleepiness, and fatigue or tiredness. Poor development, decreased learning ability, and restless sleep may be seen in children with OSA[3]. Common findings in patients with OSA are widening of neck circumference, obesity (body mass index: >30 kg/m^2), and hypertension in adults. Enlarged tonsils and adenoid are usually found in children[3]. The pathophysiology of OSA is the collapse of the upper airway during sleep[3]. Most patients with OSA demonstrate upper airway obstruction at either the level of the soft palate (nasopharynx) or the level of the tongue (oropharynx). Both anatomic factors (i.e. enlarged tonsils, volume of the tongue, pharyngeal soft tissue, length of the soft palate, abnormal position of the maxilla and mandible) and neuromuscular factors (decreased reflex activity) have important role in

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OSA[4-8]. Some publications have shown the importance of the cholinergic system for respiratory regulation[9,10] and acetylcholine in the carotid bodies may have a major role in sleep apnea[11,12].

The treatments of OSA consist of surgical and non-surgical approaches such as weight reduction, dental appliance, continuous positive airway pressure (CPAP), and various medications. Smith et al[13] had conducted a systematic review in drug therapy for OSA in adults and found that some medications such as fluticasone, mirtazipine, physostigmine and nasal lubricant were effective in short-term outcome but lacked of long-term studies. The role of acetylcholine in respiratory regulation had led to some trials of acetylcholine esterase inhibitors (physostigmine and donepezil) in OSA treatment. Donepezil is a reversible acetylcholine esterase inhibitor that has been widely used in the treatment of Alzheimer's disease (AD). The doses of donepezil varied from 5 to 20 mg/day and showed safe and well tolerated[14]. Donepezil had been evaluated in treatment of OSA in Alzheimer's patients by Moraes et al[15] and found significant improvement in the apnea/hypopnea index (AHI) and oxygen saturation compared to pretreatment and placebo. Recently, a study from Sukys-Claudino et al[16] also revealed significant improvement of OSA parameters in non-Alzheimer's patients treated with donepezil. They supported the concept that donepezil improved the coordination between diaphragm and upper airway muscles especially genioglossus activity[17]. Furthermore, increased saliva secretion by cholinergic stimulation may decrease collapsibility of the upper airway[18-20].

The objective of this study is to evaluate the effect of donepezil in the treatment of OSA.

Material and Method

From July 2014 to September 2015, a randomized, prospective, placebo-controlled trial was performed in the patients who met the diagnostic criteria for OSA according to International Classification of Sleep Disorders Version 3[21] and signed the written informed consent. Inclusion criteria were OSA patients age between 20 to 80 years, no smoking or alcohol drinking, no major cardiac or respiratory diseases, not on psychoactive drugs or other anticholinesterase inhibitor, and no previous surgery for OSA. Exclusion criteria were pregnancy or on breast feeding, unaccepted drug adverse effects, and unwilling to continue in the study. The present study was approved by the Ethic Review Boards of the Faculty of Medicine, Srinakharinwirot University.

Data collected

The baseline data including age, sex, and body mass index (BMI) were recorded. The Epworth sleepiness scale (ESS) scores and polysomnographic parameters, i.e. apnea-hypopnea index (AHI) and minimum oxygen saturation (minimum SpO_2), were recorded before and after treatment.

Study protocol

All patients were asked to answer to ESS questionnaire. Sleep studies were performed by Stardust®, Philips. OSA patients diagnosed by polysomnography and Epworth Sleepiness Scale scores were randomly allocated into study group and control group. The study group received donepezil (5 mg), 1 tablet a day at bedtime for 4 weeks then increased to 2 tablets a day for the next 4 weeks. The control group received placebo drug in the same doses. Any adverse effects occurred during the therapy were recorded. The patients not tolerated to the adverse effects were excluded from the study.

Statistical analysis

Qualitative variables were compared with Chi-square or Fisher's exact test, whereas quantitative variables were done with Student's t or Wilcoxon nonparametric test. The criterion for statistical significance was $p<0.05$.

Results

At the end of the study, a total of 41 patients were collected. There were 21 patients in donepezil/study group and 20 patients in placebo/control group. The basic characteristics of the patients in both groups were no statistically difference (Table 1).

Baseline polysomnographic value and ESS scores of the patients in both groups were not statistically different (Table 2).

Table 1. Basic characteristics of the patients

	Placebo group	Donepezil group	*p*-value
Age in years	55.05±13.87	57.62±11.78	0.53
BMI	29.45±8.62	28.91±4.52	0.80
Male/female	12/8	15/6	0.44

Age and BMI shown in mean ± SD

After complete the studying period, post-treatment OSA characteristics in placebo group were found no significant difference compared to baseline (Table 3). In the study group, the differences between pre- and post-treatment OSA characteristics were also no statistical significance (Table 4).

When comparing the results of the therapy in both groups, the change in OSA characteristics in donepezil group was more favorable than in placebo group but no statistical significant difference (Table 5).

Discussion

After therapy, there was no significant improvement in OSA characteristics (ESS scores, AHI, and SpO_2) in both groups. When comparing the results of the therapy in both groups, the study group has tendency to improve in ESS scores and AHI but no significant difference. The results of the present study were contrast with the previous studies by Moraes et al[15] and Sukys-Claudino et al[16]. The study by Sukys-Claudino et al has revealed a significant improvement in AHI, oxygen saturation, and the ESS scores with donepezil treatment ($p<0.05$). They support the concept of deficient cholinergic transmission may have a role in the pathogenesis of OSA. Because of the effect of donepezil on respiratory parameters was mild in most patients, they suggested that donepezil should be used as adjuvant treatment in specific cases rather than main treatment.

The contrast results of the present study compared to the previous studies[15,16] may occur from some factors. First, Sukys-Claudino et al study[16] revealed significant improvement in AHI especially REM-AHI rather than non-REM AHI but the present study used total AHI instead of REM-AHI. Second, the patients in the present study has lower AHI scores (23.83±9.34) than in the previous study (42.2±19.4)[16]. This may reflex that donepezil has more efficacy in severe OSA than in moderate OSA. Third, the difference in craniofacial anatomy between Mongolian and Caucasian may have some effects on OSA treatment. Lastly, the etiologies of OSA are multifactor. Improvement of cholinergic function on respiratory regulation by donepezil alone had limited effect in this study.

The limitations of the present study are the clinical experience from a single institution and the small number of subjects.

Conclusion

The present study demonstrated that treatment with donepezil in OSA did not show better results than placebo. Nevertheless, more sample sizes and well-designed studies are needed to verify the beneficial effects of donepezil in OSA.

What is already known on this topic?

The main treatment of OSA, i.e. moderate to severe OSA is CPAP via a mask during sleep. However this is not tolerated by all patients. Many drugs have been tested as an alternative to CPAP in some patients with varying success. Cholinergic nerve activity was proposed to have a role in upper airway muscle tone during sleep to prevent OSA. Donepezil is a cholinesterase inhibitor that has been used in the treatment of OSA in AD and non-AD patients. The previous studies have revealed significant improvement

Table 2. Patient's baseline polysomnographic data and ESS scores

	Placebo group	Donepezil group	*p*-value
AHI	31.62±15.23	23.83±9.34	0.06
Minimum SpO_2 (%)	76.75±8.34	82.19±7.15	0.36
ESS scores	9.45±5.22	11.00±5.31	0.86

Data shown in mean ± SD

Table 3. Comparison of OSA characteristics in placebo group

	Baseline	Post-treatment	Difference (Δ)	*p*-value
AHI	31.62±15.23	34.01±18.02	5.75 (-3.7, 14.5)	0.59
Minimum SpO_2 (%)	76.75±8.34	80.40±9.27	3.00 (1, 8)	0.09
ESS scores	9.45±5.22	7.75±5.35	0.00 (-3, 2)	0.18

Data shown in mean ± SD, difference (Δ) shown in median (range)

Table 4. Difference (Δ) of patient's OSA characteristics in Donepezil group after treatment

OSA characteristics	Difference (Δ)	*p*-value
ΔAHI	-4.30 (-7.2, 23.6)	0.56
ΔMinimum SpO_2 (%)	3.00 (-2, 9)	0.37
ΔESS scores	-1.00 (-3, 0)	0.10

Difference (Δ) shown in median (range)

Table 5. Comparison of OSA characteristics differences (Δ) between Donepezil group and placebo group after treatment

OSA characteristics	Placebo group	Donepezil group	*p*-value
ΔAHI	5.75 (-3.7, 14.5)	-4.30 (-7.2, 23.6)	0.44
ΔMinimum SpO_2 (%)	3.00 (1, 8)	3.00 (-2, 9)	0.65
ΔESS scores	0.00 (-3, 2)	-1.00 (-3, 0)	0.27

OSA characteristics differences (Δ) reported in median (range)

in OSA parameters.

What this study adds?

The present study revealed that treatment with donepezil in OSA patients did not have better results than placebo. The contrast outcomes compared to the previous studies may need more sample sizes and well-designed studies to verify the beneficial effects of donepezil in OSA.

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Potential conflicts of interest

None.

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ประสิทธิภาพของยา Donepezil ในการรักษาโรคหยุดหายใจขณะหลับจากการอุดกั้น: การศึกษาเปรียบเทียบกับยาหลอก

นิรันดร์ หุ่นฉายศรี, วรปภัส เฉลิมสุวิวัฒนาการ

ภูมิหลัง: *การรักษาผู้ป่วยโรคหยุดหายใจขณะหลับจากการอุดกั้น ประกอบด้วยการผ่าตัดเช่นการผ่าตัดลิ้นไก่และเพดานอ่อน และการรักษาแบบไม่ผ่าตัด เช่น การใช้เครื่องอัดอากาศ การลดน้ำหนัก การใส่อุปกรณ์ทางทันตกรรมและการใช้ยาบางตัว ตามที่ได้มีการแสดงว่าระบบประสาท cholinergic มีความสำคัญต่อการควบคุมการหายใจและการหยุดหายใจขณะหลับ จึงมีการศึกษาการใช้ยา donepezil เป็นยาที่ออกฤทธิ์ต้านเอนไซม์ acetylcholine esterase ทำให้ระบบ cholinergic ทำงานดีขึ้นโดยเฉพาะอย่างยิ่งขณะหลับ มีการศึกษาประสิทธิภาพของยา donepezil ในผู้ป่วยโรคหยุดหายใจขณะหลับจากการอุดกั้นพบว่าทำให้ค่า apnea-hypopnea index (AHI) และค่า oxygen saturation ดีขึ้นอย่างมีนัยสำคัญทางสถิติ เมื่อเปรียบเทียบกับก่อนการรักษาและยาหลอก*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยา Donepezil ในการรักษาโรคหยุดหายใจขณะหลับจากการอุดกั้น*

วัสดุและวิธีการ: *เป็นการศึกษาไปข้างหน้าแบบสุ่มในโรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี โดยผู้ป่วยที่ได้รับการวินิจฉัยโรคหยุดหายใจขณะหลับจากการอุดกั้นจากการตรวจ polysomnography และทำแบบสอบถาม Epworth Sleepiness Scale จะถูกแบ่งเป็นสองกลุ่มโดยการสุ่ม กลุ่มทดลองจะให้รับประทานยา donepezil วันละ 1 เม็ด (5 มก.) ใน 4 สัปดาห์แรกและเพิ่มเป็น 2 เม็ดใน 4 สัปดาห์ถัดมา ส่วนกลุ่มควบคุมจะให้รับประทานยาหลอกในขนาดเดียวกัน การประเมินผลใช้ค่า AHI, minimum oxygen saturation (minimum SpO_2) และคะแนน Epworth Sleepiness Scale เปรียบเทียบก่อนและหลังการศึกษา*

ผลการศึกษา: *มีผู้ป่วยโรคหยุดหายใจขณะหลับจากการอุดกั้นจำนวนทั้งสิ้น 41 ราย เป็นผู้ป่วยในกลุ่มทดลอง 21 ราย กลุ่มควบคุม 20 ราย ก่อนการทดลองไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในเรื่อง อายุเฉลี่ย ($p = 0.53$) ค่าดัชนีมวลกาย ($p = 0.80$) เพศชาย/เพศหญิง ($p = 0.44$) Minimum SpO_2 ($p = 0.36$) คะแนน Epworth Sleepiness Scale ($p = 0.86$) และค่า AHI ($p = 0.06$) ในผู้ป่วยทั้ง 2 กลุ่ม เมื่อสิ้นสุดการศึกษาพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p>0.05$) ของค่า AHI, minimum SpO_2 และคะแนน Epworth Sleepiness Scale ภายในกลุ่มเดียวกันและระหว่างกลุ่ม*

สรุป: *การรักษาโรคหยุดหายใจขณะหลับจากการอุดกั้นด้วยยา donepezil ได้ผลลัพธ์ไม่ดีกว่ายาหลอก*