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ORIGINAL ARTICLE

A randomized, double-blind, placebo-controlled trial on the effect of intranasal corticosteroid as a treatment for moderate to severe obstructive sleep apnea with coexisting chronic rhinitis

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Abstract

Background: Chronic rhinitis is a common co-existing disease with obstructive sleep apnea (OSA). Current evidence on intranasal steroid efficacy as a treatment modality is scarce.

Objective: This study assessed the efficacy of intranasal steroid in moderate to severe OSA with coexisting chronic rhinitis.

Methods: A prospective randomized, double-blind, placebo-controlled trial was conducted in non-2nd to 3rd degree obese, non-severe oropharyngeal obstruction, moderate to severe OSA with coexisting chronic rhinitis (total nasal symptom score (TNSS) ≥ 6, BMI < 30 kg/m^2, modified Mallampati < 3). We randomized the patients to receive intranasal steroid (fluticasone furoate, 110 mcg/day) or placebo for one-month duration. The primary end point was the change in apnea hypopnea index (AHI).

Results: A total of 34 patients were randomly assigned to receive intranasal steroid (N = 18) or placebo (N = 16). The adjusted absolute difference mean change of AHI did not show significant difference (11.5 ± 7.9 events/hour [95% CI; -4.9 to 27.8; p = 0.16]). Interestingly, significant reduction in non-supine respiratory disturbance index (RDI) (56.1 ± 21.9 events/hour [95% CI; 18.9 to 93.2; p = 0.01]) was observed in intranasal steroid group. When comparison was made within group, only intranasal steroid group demonstrated significant reduction in AHI, RDI, NREM RDI, TNSS, and Thai Pittsburgh sleep quality index (p = 0.02, 0.02, 0.01, 0.003, and < 0.001; respectively) after receiving the drug.

Conclusion: In moderate to severe OSA patients with coexisting chronic rhinitis, intranasal steroid demonstrated significant reduction in obstructive respiratory events during non-supine sleep. Intranasal steroid may be considered as adjunctive or alternative to OSA treatment.

Key words: obstructive sleep apnea, chronic rhinitis, intranasal corticosteroid, positional therapy, oral appliance

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Abbreviations:

OSA	Obstructive sleep apnea
TNSS	Total nasal symptom score
BMI	Body mass index
AHI	Apnea hypopnea index
RDI	Respiratory disturbance index
CPAP	Continuous positive airway pressure
PSQI	Pittsburgh sleep quality index
ESS	Epworth sleepiness scale

Introduction

Chronic rhinitis (allergic and non-allergic rhinitis) and obstructive sleep apnea (OSA) are commonly observed diseases with rising prevalence.[1-4] Previous studies have demonstrated that nasal congestion was associated with 1.8 fold increase in the risk of developing moderate to severe OSA.[1] Vice versa, Houser SM et al.[5] have demonstrated that OSA patients had significantly higher nasal congestion than non-OSA patients documented by acoustic rhinometry measurement.[2] Prolonged mouth breathing associated with nasal congestion is mechanically associated with an increase in air-flow resistance due to reduction in pharyngeal diameter from mandible displacement which increase the risk for OSA.[6]

An American Academy of Sleep Medicine Clinical Practice Guideline published in 2019 recommended the use of continuous positive airway pressure (CPAP) as the main treatment modality for OSA particularly with coexisting excessive daytime sleepiness or impaired sleep-related quality of life.[7] However, CPAP compliance was unpredictable especially in long term aspect.[8-10] Several studies have reported positive effect of intranasal steroid in reducing both allergic and non-allergic rhinitis symptoms as well as attenuating immune response in the upper airway.[11-14] Assanasen P, et al.[15] reported 84.3% prevalence of chronic allergic rhinitis coexisting in OSA raising the importance of addressing allergic rhinitis among OSA patients.

According to review article by Chirakalwasan N, et al.,[16] out of five studies on the effect of intranasal steroid on OSA outcome, only two adult studies demonstrated significant reduction in AHI.[13,14] However, those two studies were performed in obese[13] and mixed primary snoring and OSA population.[14]

Our study aimed to evaluate the efficacy of 1 month-duration of intranasal steroid in non-2nd to 3rd degree obese as classification of Asian population, non-severe oropharyngeal obstruction population of moderate to severe OSA. The prevalence of non-obese OSA is high among Asians[17] and moderate to severe OSA is currently the vulnerable group that treatment is generally recommended.[18] Therefore, we aimed to study the efficacy of intranasal steroid in this specific phenotypic Asian OSA patients with coexisting chronic rhinitis.

Methods

Participants

A prospective randomized (permuted block of size 4), double-blind, placebo-controlled trial was conducted in patients with moderate to severe OSA with coexisting chronic rhinitis indicated by total nasal symptom score (TNSS) ≥ 6, non-2nd to 3rd degree obese (body mass index (BMI) < 30 kg/m^2), and non-severe oropharyngeal obstruction (modified Mallampati < 3). The generation of allocation sequences was conducted by computer-generated program and contained in a set of sealed envelopes by non-trial investigators who also prepared the concealed nasal sprays. The study was conducted between June 2018 and February 2019 with approval from institutional review board, faculty of medicine, Chulalongkorn university, Bangkok, Thailand (IRB#248/61). The study was also registered in www.clinicaltrials.in.th (TCTR20190614004). Split-night polysomnography was utilized to diagnose OSA. The patients were enrolled if OSA severity was at least moderate degree indicated by apnea hypopnea index (AHI) of at least 15 events per hour during the diagnostic portion of the split-night study. Furthermore, CPAP titration portion of the study was required to achieve optimal titration quality with recommended pressure associated with respiratory disturbance index (RDI) of less than 5 events per hour and tested for at least 15 minutes including supine-REM sleep. Exclusion criteria were poor controlled or resistant hypertension, uncontrolled cardiovascular or cerebrovascular disease, ongoing usage of CPAP or oral appliance, previous upper airway or nasal surgery, intranasal steroid usage within the previous 3 months, poor technique of intranasal steroid drug use, inability to discontinue antihistamine or leukotriene inhibitor drug 7 days before enrolment, or active sickness which may alter polysomnography result. Written informed consent was obtained from all participants.

Study protocol

The split-night polysomnography[19] included electroencephalography (EEG), electrocardiogram (EKG), electrooculography (EOG), electromyography (EMG), oxygen saturation monitoring, airflow measurement, and respiratory effort measurement. The first half of the study was performed as a diagnostic study and the second half was conducted as CPAP titration study. The American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events 2016 was utilized for sleep stage and respiratory events scoring.[19] During split-night polysomnography, sleep parameters were analysed including respiratory disturbance index (RDI), supine RDI, non-supine RDI, rapid eye movement RDI (REM RDI), non-REM RDI (NREM RDI), oxygen indices, total sleep time, sleep efficiency, wake after sleep onset (WASO), sleep latency, REM latency, the percentage of time spent in NREM stage 1-3 and REM stage, arousal index, and CPAP optimal and recommended pressures. The questionnaires including TNSS, Thai version of Epworth sleepiness scale (ESS) for daytime sleepiness assessment, and Thai version of Pittsburgh sleep quality index (PSQI) for sleep quality assessment were also completed. The TNSS were the summed individual nasal symptom scores based on the degree of quality of life interference which rated subjectively on a 4-point Likert scale (0 = no interference, 1 = mild interference, 2 = moderate interference, 3 = severe interference). All enrolled patients underwent skin prick test and acoustic rhinomanometry for nasal volume evaluation (mean of left and right nasal cavity) as baseline information. The patients were subsequently randomized using block of 4 to receive intranasal steroid (fluticasone furoate, 110 mcg/day and excipients: glucose anhydrous, dispersible cellulose, polysorbate 80, benzalkonium chloride, disodium edetate and purified water) or placebo (same excipients without fluticasone furoate) once daily in the morning for one-month duration. Weekly phone call from the investigator was conducted in order to ensure drug compliance and evaluate drug adverse effect. After one month, split-night polysomnography along with TNSS, ESS, PSQI questionnaires, and acoustic rhinomanometry were repeated.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range) and frequency (%) to describe baseline characteristics. The continuous variables were evaluated by t test or Mann-Whitney U test. The categorical variables were compared using chi-square test or Fisher's exact test. The linear regression analysis was used for relationship calculation. We applied repeated ANOVA for the statistical comparison within group. Fifteen events per hour difference in AHI was calculated for sample size estimation with 80% power. Significance tests were two-sided, with an alpha value of 0.05. All analyses were performed using STATA version 12(Stata-Corp LLC, College station, Texas, United states).

Sample size

The sample size was estimated based on the latest study by Acar M, et al.[13] A total of 34 patients were required based on type one error, power of test, intervention per control ratio, and estimated drop-out rate of 5%, 80%, 1:1, 20%; respectively.

Results

From June 2018 to January 2019, we screened 819 patients diagnosed with moderated to severe OSA for eligibility. Seven hundreds and eighty-five patients were excluded for the following reasons (**figure 1**). Thirty-four patients were enrolled and underwent randomization, 18 patients were assigned to receive intranasal steroid and 16 patients were assigned to receive placebo. One of 18 patients (5.6%) in intranasal steroid group was excluded due to active infection during the time of repeated polysomnography. One of 16 patients (6.3%) in control group was excluded from undergoing nasal surgery during the study period. The compliance of both intranasal steroid and placebo was 100% according to weekly phone check and self-recording during the study.

The baseline clinical characteristics of the patients in intranasal steroid and placebo groups were similar (**table 1**).

Table 1. Baseline clinical characteristics, sleep architecture, and questionnaire of intranasal steroid and placebo groups

Baseline Characteristic	Intranasal steroid group (n = 17)	Placebo group (n = 15)
Clinical characteristics		
Male sex - no. (%)	10 (58.8%)	8 (53.3%)
Age – year*	42.9 ± 11.9	47.5 ± 12.8
Weight – kg*	69.8 ± 10.1	69.4 ± 10.6
Body mass index – kg/m²*	25.4 ± 2.7	25.9 ± 3
Neck circumference – inches*	14 ± 1.4	14.2 ± 1.4
Skin prick test positive - no. (%)	11 (64.7%)	6 (40%)
Sleep architectures		
Total AHI (events/hour)	44.9	38.4
Total RDI (events/hour)	45.2	39.2
Total sleep time (mins)	191.3	195.7
Sleep efficiency (%)	84.6	85.3
WASO (mins)	29.9	25.1
Mean O_2 saturation (%)	94.8	95.2
Nadir O_2 saturation (%)	83	83.9
Questionnaires		
TNSS	10.6	10.3
ESS	10.1	10.9
PSQI	8.4	8.1

*mean ± SD

Abbreviations: AHI-apnea hypopnea index, RDI-respiratory disturbance index, WASO-wake after sleep onset, TNSS-total nasal symptom score, ESS-Epworth sleepiness scale, PSQI-Pittsburgh sleep quality index

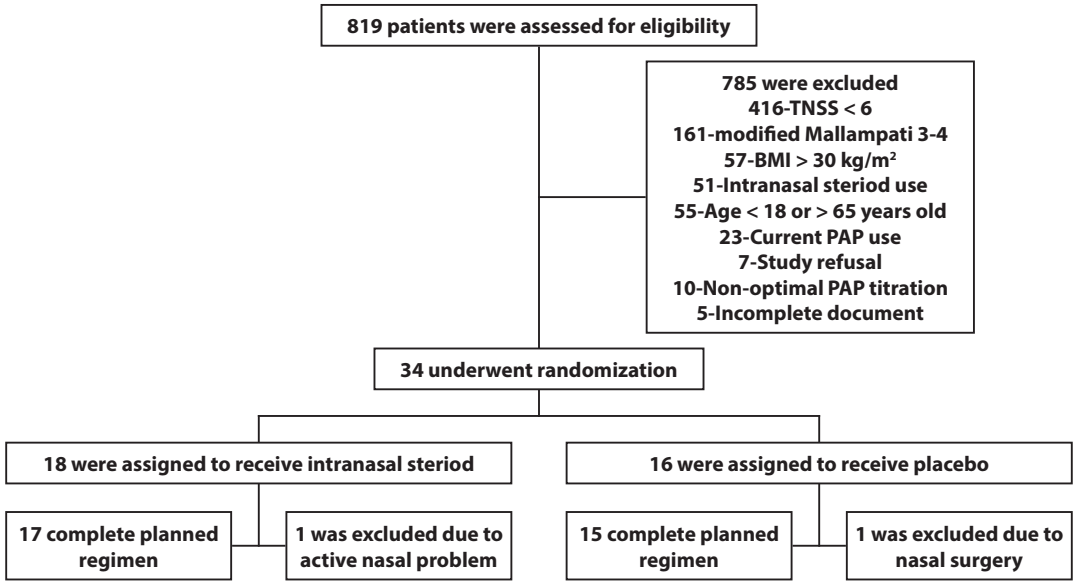

Figure 1. Allocation and randomization

Abbreviations: TNSS-total nasal symptom score, BMI-body mass index, PAP-positive airway pressure

The overall mean age of the patients was 45.2 years, 50% were male, and mean BMI level was 25.6 kg/m^2. The skin prick test was positive in 53% of the patients (11 of 17 (64.7%) in intranasal steroid group and 6 of 15 (40%) in placebo group).

The baseline polysomnographic chracteristics showed insignificant difference between intranasal steroid and placebo group (**table 1**). The overall mean total AHI was 41.9 events/hour, mean oxgen saturation was 95%, and nadir oxygen saturation was 83.4%. Baseline of TNSS, Thai version of ESS, Thai version of PSQI were 10.5, 10.5, 8.3; respectively.

The outcome was adjusted for variables in the linear regression models including age, sex, BMI, TNSS, and left and right nasal volume. For the primary outcome, the adjusted absolute difference change of AHI did not show significant difference between two groups despite more reduction observed in intranasal steroid group compared to the placebo group (11.5 ± 7.9 events/hour [95% CI; -4.9 to 27.8; p = 0.16]) (**figure 2**). Interestingly, significant reduction in non-supine RDI was observed (56.1 ± 21.9 events/hour [95% CI; 18.9 to 93.2; p = 0.01]). There was also a trend towards significant reduction in WASO (15.3 ± 8.2 minutes [95% CI; -1.7 to 32.2; p = 0.08]) in intranasal steroid group compared to placebo group. Pittsburgh sleep quality index (PSQI) score was not significantly reduced in intranasal steroid group compared to placebo group (1.3 [95% CI; -0.2 to 2.8; p = 0.09]). The results of other secondary outcomes were shown in **table 2**.

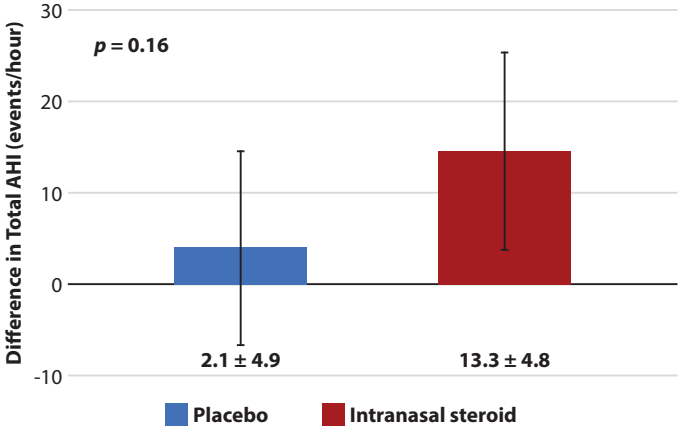

Figure 2. Comparison of mean difference in total apnea hypopnea index (AHI) between placebo group and intranasal steroid group

Table 2. Mean change in secondary outcomes (before-after) of intranasal steroid and placebo group

Characterisitc	Intranasal steroid Mean change (95% CI)	Placebo Mean change (95% CI)	Absolute difference Mean change (95% CI)	p value
Sleep architecture				
Total AHI (events/hour)	13.3 (2.9 to 23.7)	2.1 (-8.5 to 12.7)	11.5 (-4.9 to 27.8)	0.16
Total RDI (events/hour)	13.5 (3.1 to 23.9)	2.7 (-7.9 to 13.3)	11 (-5.3 to 27.4)	0.18
Supine RDI (events/hour)	10.2 (-0.7 to 21.1)	2.5 (-9.2 to 14.2)	5 (-12.3 to 22.4)	0.55
Non supine RDI (events/hour)	14.8 (-17.4 to 47)	4.8 (-10.2 to 19.8)	56.1 (18.9 to 93.2)	0.01
REM RDI (events/hour)	11.5 (-5.7 to 28.7)	12.7 (-3.6 to 29)	3.2 (-21.6 to 28)	0.79
NREM RDI (events/hour)	14.5 (4.5 to 24.4)	1.2 (-9.8 to 12.3)	12.7 (-4 to 29.3)	0.13
Total sleep time (mins)	-2.9 (-18.2 to 12.3)	6.4 (-10.5 to 23.3)	-11 (-34.1 to 12.1)	0.34
Sleep efficiency (%)	-1.7 (-7.5 to 4.1)	1.9 (-4.8 to 8.7)	-4.2 (-12.6 to 4.1)	0.31
WASO (mins)	7.8 (-2.5 to 18.1)	-6.8 (-22.5 to 8.7)	15.3 (-1.7 to 32.2)	0.07
Sleep latency (mins)	-5.1 (-12.4 to 2.3)	2.3 (-3.9 to 8.4)	-6.9 (-17.4 to 3.7)	0.19
REM latency (mins)	32.3 (3.9 to 60.6)	-1.2 (-25.1 to 22.6)	33.6 (-9.2 to 76.4)	0.12
% supine time	-7.7 (-26 to 10.6)	-2.2 (-20.4 to 16)	-5.2 (-34.7 to 24.3)	0.72
% NREM1/TST	7.2 (0.8 to 13.6)	-1.9 (-8.8 to 5.1)	7.5 (-1.9 to 17)	0.12
% NREM2.TST	-3.1 (-10.3 to 4.1)	-0.3 (-7.8 to 7.3)	1.9 (-7.5 to 11.2)	0.69
% NREM3/TST	2.7 (-4.3 to 9.8)	4.1 (-3.1 to 11.3)	-4.1 (-14.7 to 6.5)	0.43
% REM/TST	-3.7 (-8.7 to 1.3)	-1.9 (-7.8 to 3.9)	-3.3 (-10.7 to 4.1)	0.36
Arousal index	4.8 (-1.2 to 10.8)	3.9 (-5.6 to 13.4)	0.2 (-11.6 to 11.9)	0.98
Mean O_2 saturation (%)	-0.5 (-1.6 to 0.7)	-0.2 (-1.6 to 1.2)	-0.4 (-2.3 to 1.4)	0.63
Nadir O_2 saturation (%)	0.6 (-3.4 to 4.7)	1.4 (-2.2 to 5.0)	-1.4 (-7.1 to 4.4)	0.62
% O_2 saturation < 90% (%)	-0.2 (-1.7 to 1.4)	-1.1 (-3 to 0.7)	1.0 (-1.5 to 3.6)	0.42
% O_2 saturation < 88% (%)	-0.4 (-1.7 to 0.8)	-0.7 (-1.7 to 0.3)	0.6 (-1.2 to 2.4)	0.51

Table 2. (Continued)

Characterisitc	Intranasal steroid Mean change (95% CI)	Placebo Mean change (95% CI)	Absolute difference Mean change (95% CI)	p value
Sleep architecture (Continued)				
Optimal pressure (cmH_2O)	0.1 (-0.9 to 1)	-0.4 (-1.4 to 0.5)	0.3 (-1.3 to 1.8)	0.73
Recommended pressure (cmH_2O)	0.1 (-0.5 to 0.6)	1.1 (-0.2 to 2.4)	-1.4 (-2.9 to 0.4)	0.06
Questionnaire				
TNSS	3.6 (1.5 to 5.7)	2.5 (-0.1 to 5.1)	1 (-2.4 to 4.5)	0.54
ESS	0.8 (-0.9 to 2.4)	1.5 (-0.7 to 3.8)	-0.5 (-3.4 to 2.5)	0.75
PSQI	1.8 (1 to 2.6)	0.7 (-0.5 to 1.9)	1.3 (-0.2 to 2.8)	0.09
Acoustic rhinomanometry				
Nasal volume (cm^3)	-0.3 (-0.8 to -0.1)	0.1 (-0.2 to 0.4)	-0.4 (-1.0 to 0.1)	0.10

Abbreviations: AHI-apnea hypopnea index, RDI-respiratory disturbance index, REM-rapid eye movement, NREM-non-rapid eye movement, WASO-wake after sleep onset, TNSS-total nasal symptom score, ESS-Epworth sleepiness scale, PSQI-Pittsburgh sleep quality index

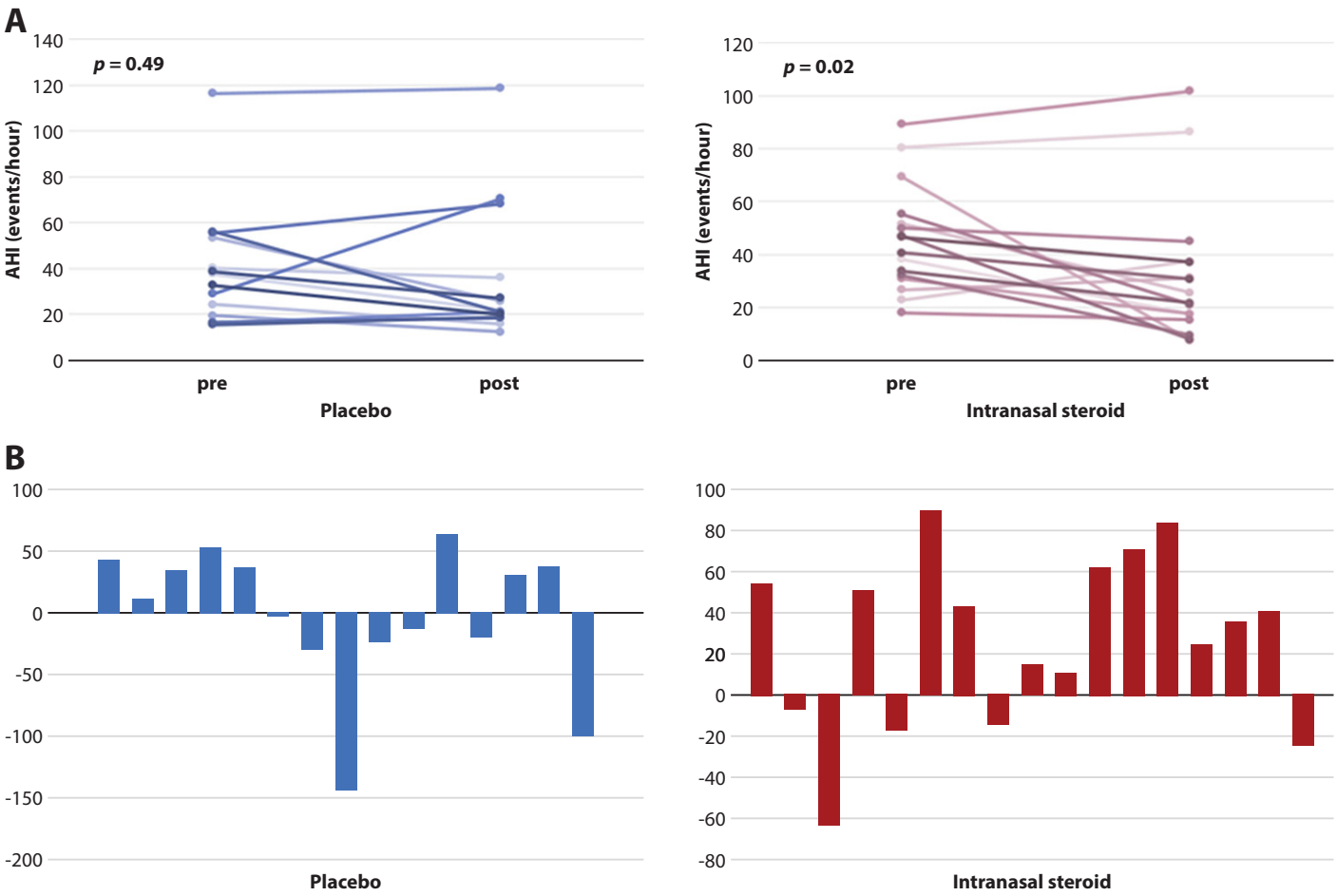

Figure 3.
A) Pre and post treatment change in apnea hypopnea index (AHI) in placebo group and intranasal steroid group
B) Pre and post treatment percent change in apnea hypopnea index (AHI) ([pre treatment – post treatment]/pre treatment)*100) in placebo group and intranasal steroid group

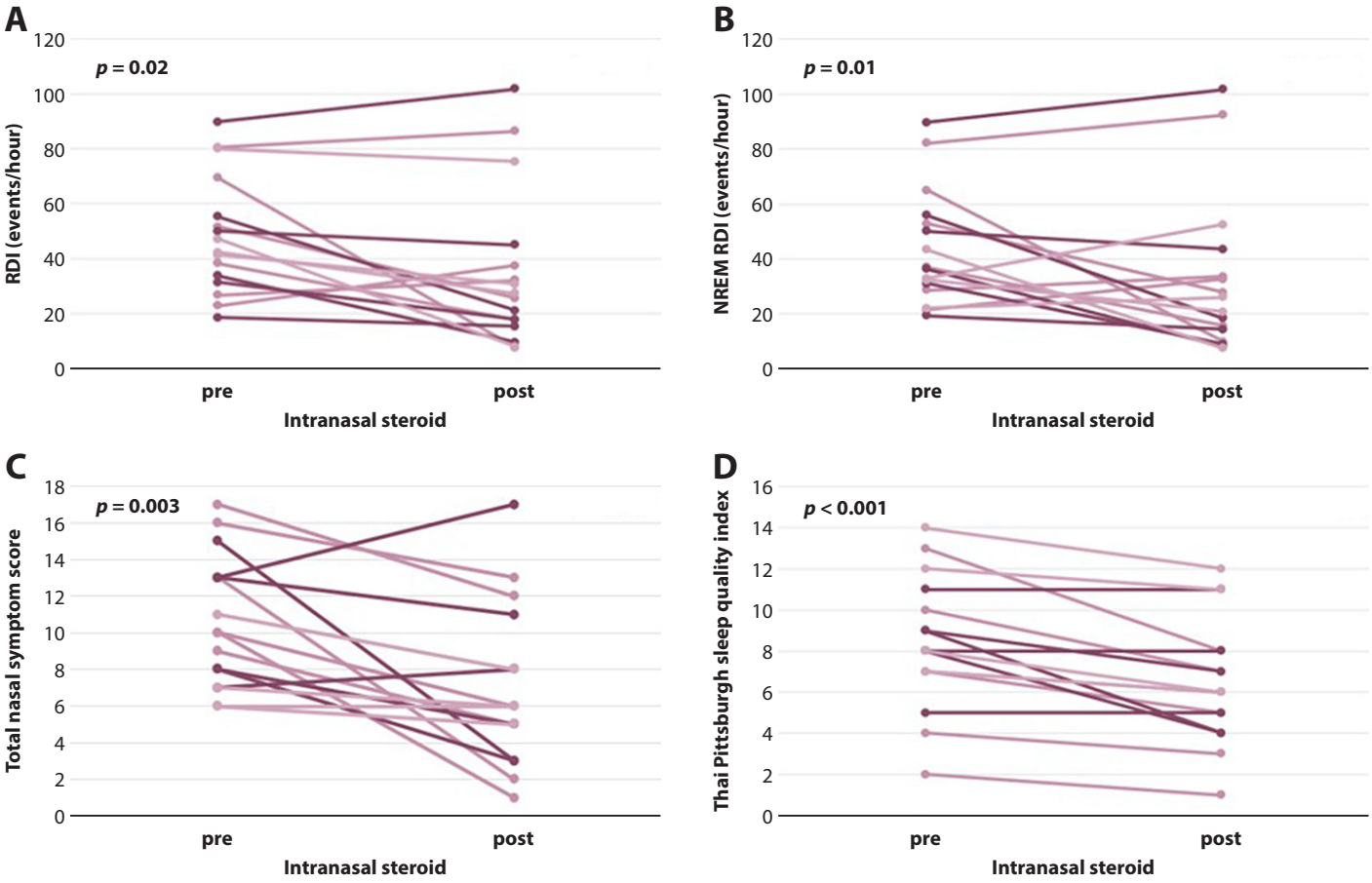

Figure 4. A change in pre and post treatment with intranasal steroid for 4 weeks. A - Respiratory disturbance index (RDI) (p = 0.02), B – NREM RDI (p = 0.01), C – Total nasal symptom score (TNSS) (p = 0.003), D– Thai Pittsburgh sleep quality index (Thai PSQI) (p < 0.001)

When comparison was made within the group, the intranasal steroid group demonstrated significant reduction in AHI (**figure 3**). Furthermore, RDI, NREM RDI, TNSS, and Thai PSQI were significantly improved after 4 weeks of intranasal steroid use (p = 0.02, 0.02, 0.01, 0.003, and < 0.001; respectively) (**figure 4**). None of the aforementioned parameters were improved in the placebo group.

Moreover, twenty percent of the patients in intranasal steroid group were observed to have post treatment AHI less than 15 events per hour. None of these parameters in placebo group achieved this reduction.

Discussion

Obstructive sleep apnea (OSA) is a disorder characterized by recurring episodes of upper airway obstruction during sleep.[20] Primary pathophysiology of OSA in Asian population is compromised craniofacial and upper airway structures, even more so than body mass index (BMI).[21-23] Even though, previous studies demonstrated that intranasal steroid improved OSA indicating by significant reduction in AHI, none were conducted in specific disease severity or OSA characteristics.[13,14]

Our study is the first study to evaluate the effect of intranasal steroid in non-2nd to 3rd degree obese, moderate to severe OSA, the OSA phenotype commonly observed among Asians.[17] Interestingly, we observed that intranasal steroid significantly reduced RDI during non-supine position compared to placebo.

Positional OSA was described as the unique form of OSA in which the respiratory events predominate during supine sleep. General criteria used to diagnose positional OSA was supine RDI of at least two times higher than non-supine RDI. Cevizci R, et al.[12] reported the relationship between nasal obstruction and positional OSA vs non-positional OSA. Their study demonstrated that nasal obstruction predisposes OSA to be non-positional. The assumption was made that serious nasal obstruction could have caused increase in nasal resistance or pharyngeal collapsibility to the point that positional changes did not have any effect. Based on this notion, intranasal steroid which reduces nasal obstruction would theoretically improve nasal obstruction, in turn, promotes positional dependency of OSA.

According to American Academy of Sleep Medicine (AASM) practice parameter,[24] positional therapy, a method that keeps the patient in a non-supine position, is an effective secondary therapy or supplemental therapy for OSA in patients who have a low AHI in the non-supine compared to supine position. Recent Cochrane review demonstrated that even though, positional therapy was less effective compared to CPAP in reducing the overall RDI, positional therapy was more effective than inactive control.[25] Furthermore, positional therapy demonstrated better compliance compared to CPAP with comparable effectiveness in quality of life and cognitive function improvement.

Oral appliance in the form of mandibular advancement device (MAD), another treatment option of OSA, is recommended in patients with OSA who are intolerant of CPAP therapy or prefer alternate therapy.[26] In fact, oral appliance has been shown to be as effective as CPAP in positional OSA.[27] Therefore, intranasal steroid which reduced respiratory events during non-supine sleep as we demonstrated in this current study, can theoretically converted the patients from non-positional OSA to positional OSA and promote the success of alternative treatment to CPAP. Furthermore, Teerapraipruk B, et al.[28] demonstrated prevalence of positional OSA in Thai population to be as high as 70%, compared to the prevalence of 55% in the Caucasian population. The use of intranasal steroid in this group of positional OSA can further reduce respiratory events during non-supine position and be adjunctive treatment to positional therapy or oral appliance. Moreover, we also demonstrated that intranasal steroid significantly improved continuity of sleep compared to placebo. Improvement in sleep quality can be explained by reduction in nocturnal rhinorrhea and congestion and reduction in inflammatory mediators known to cause sleep disturbance such as histamine and CysLTs.[16] In our study, 20% of the patients in intranasal steroid group (1 in allergic rhinitis group and 2 in non-allergic rhinitis group) had their OSA severity reduced from severe to mild. Therefore, further treatment may not be needed. Likely due to limited sample size, no parameters were identified to predict the success of intranasal steroid in improvement of AHI or OSA severity.

Our study has the strength of randomized, double-blind, placebo-controlled trial with objective sleep parameter measurement by attended-in laboratory polysomnography. However, our study was most likely underpowered to detect the differences in secondary outcomes or to identify predictors of intranasal steroid success since large different margin of AHI -15 events per hour was utilized for sample size calculation. The duration of one-month for intranasal steroid use was based on the minimal recommended treatment duration for allergic rhinitis treatment.[29] However, the maximal effect may require longer duration.[30] We used weekly telephone call for intranasal steroid compliance monitoring which may not be totally accurate. Future study incorporating longer duration of intranasal steroid with objective compliance monitoring and larger sample size will help elucidate our findings.

Conclusion

In non-2nd to 3rd degree obese, non-severe oropharyngeal obstruction, moderate to severe OSA patients with coexisting chronic rhinitis, intranasal steroid demonstrated significant reduction in obstructive respiratory events during non-supine sleep. The potential role of intranasal steroid may be considered as adjunctive to OSA treatment with positional therapy or oral appliance or alternative treatment to CPAP.

Conflicts of interest

All authors have no conflict of interest.

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Author contribution

VP, KR, DM, and NC conceived and designed the study. All authors analysed the data and drafted the manuscript. All authors interpreted the data, critically revised the draft for important intellectual content, and gave final approval of the manuscript to be published. All authors contributed equally in the preparation of this manuscript.

Consent form

Obtained from all of the patients

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