

The use of topical nasal steroids to improve continuous positive airway pressure compliance in patients with obstructive sleep apnea: An updated systematic review and meta-analysis of randomized control trials

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Abstract

Background: Nasal steroids are commonly prescribed to reduce nasal side effects, which are the primary cause of continuous positive airway pressure (CPAP) intolerance in obstructive sleep apnea (OSA) patients.

Objectives: We conducted a systematic review and meta-analysis of OSA patients to assess the effect of nasal steroids on CPAP compliance and nasal symptoms.

Methods: PubMed, Scopus, Ovid, and Cochrane Library were searched through March 2022. Randomized controlled trials (RCTs) evaluating the effects of nasal steroids on CPAP compliance in adult patients, which reported quantitative data on CPAP use and nasal symptoms, were included.

Results: Three RCTs (224 patients) were eligible for the meta-analysis. At the 4-week follow-up, the study did not demonstrate a statistically significant difference in CPAP compliance (average hours of CPAP use per night: mean difference 0.45; 95% confidence interval (CI) (-0.01, 0.90); $P = 0.06$, percentage of nights device used: mean difference 1.79; 95%CI (-2.59, 6.17); $P = 0.42$). There was also no difference in overall nasal symptoms (mean difference 0.47, 95%CI (-0.00, 0.94); $P = 0.05$), with significantly more sneezing and rhinorrhea among patients with nasal steroids (sneezing: mean difference 0.64, 95%CI (0.23, 1.05); $P = 0.002$, rhinorrhea: mean difference 0.78, 95%CI (0.24, 1.31); $P = 0.005$).

Conclusion: At the 4-week follow-up, the pooled results did not demonstrate significant benefits of nasal steroids on CPAP compliance. There was also no significant benefit for relieving nasal symptoms. To further explore the benefit of nasal steroids on CPAP use, additional, longer-term studies are required.

Key words: Continuous positive airway pressure, Nasal steroid, Steroid, Obstructive sleep apnea, Obstructive sleep apnea syndrome

Citation:

Segsarnviriyaya, C., Prakassajjatham, M., Chirakalwasan, N., Hirunwiwatkul, P., Chaitusaney, B., Charakorn, N. The use of topical nasal steroids to improve continuous positive airway pressure compliance in patients with obstructive sleep apnea: an updated systematic review and meta-analysis of randomized control trials. *Asian Pac J Allergy Immunol.* <https://doi.org/10.12932/ap-081122-1498>

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Introduction

Obstructive sleep apnea (OSA), defined by recurrent episodes of upper airway blockage with associated arousal or oxygen desaturation during sleep,¹ is a common sleep disorder with a high prevalence of up to 38%.² It is related to various long-term morbidities and mortality by causing an increased risk of various medical and psychological issues, including cardiovascular problems. The recurrent arousals that followed the upper airway obstruction may also lead to decreased daytime alertness, which is a substantial risk for a motor vehicle or other accidents resulting in serious injuries and death.³

The current gold standard treatment for OSA is continuous positive airway pressure (CPAP),⁴ a device that passes the positive air pressure to stabilize the upper airway via a CPAP mask, which is available in different types.⁵ Good adherence with CPAP therapy is often defined as using the device for at least 4 hours a night and at least 70% of cumulative nights.⁶ Nevertheless, studies showed that almost half of all patients fail to comply after a year of treatment.⁷ A large proportion of CPAP users reported nasal side effects such as runny nose and mucosal dryness.⁷ As a result, these patients may be less likely to adhere to the treatment or become intolerant. Mouth breathing from nasal congestion is another possible reason that can lead to difficulty wearing a CPAP mask.⁸ To increase CPAP compliance, heated humidifiers, nasal decongestants, topical steroids, and nasal surgery are some of the common methods to alleviate nasal side effects.⁹

Topical nasal steroids are frequently prescribed to patients who suffered from nasal adverse effects from CPAP usage. Though several studies, including a recent meta-analysis, did not demonstrate a clear benefit of its use.¹⁰⁻¹² As there is additional data, we performed an update on systematic review and meta-analysis to assess the effects of nasal steroids on CPAP usage, based on the machine's quantitative data. The effects of the drug regarding changes in nasal symptoms, both overall and for each symptom, were the secondary outcomes.

Methods

We applied PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conducting a comprehensive literature search.¹³ Two reviewers (CS and NC) searched PubMed, Scopus, Ovid, and the Cochrane Library for studies published before March 11, 2022. The search algorithm was based on the terms of the following: "continuous positive airway pressure," "obstructive sleep apnea," and "steroids". An example of a search terms on PubMed is ("continuous positive airway pressure" [MeSH Terms] OR "sleep apnea, obstructive" [MeSH Terms]) AND "steroids" [MeSH Terms]).

The relevance paper was determined by reviewing the abstracts of all studies. Eligibility was assessed using the full-text versions of selected articles. Additionally, we looked for other qualifying studies in the reference lists of relevant published data. Furthermore, when a potentially relevant article was identified during the title and abstract review, the "related citations/articles" and "cited by" functions of the four databases and Google Scholar were explored to identify any other relevant literature. The review protocol was registered in the PROSPERO (PROSPERO registration number: CRD42022321733).

Study selection

The following were the criteria for inclusion: (1) type of design: randomized, controlled trials (RCT) (2) population: adult OSA patients who were prescribed CPAP (3) interventions: topical nasal steroids (4) comparison: control or placebo (5) primary outcomes: quantitative data of CPAP compliance including the average hours per night and the percentage of nights device used (6) secondary outcome: nasal symptoms assessment. The exclusion criteria included (1) studies in the pediatric population, and (2) non-English language studies.

Data extraction and study quality assessment

Two independent reviewers (CS and NC) conducted literature searches and evaluated the titles and abstracts. For additional assessment, the full-text versions of eligible articles were retrieved. The patient's age, body mass index (BMI), Epworth sleepiness scale (ESS), quantitative CPAP compliance data, and nasal symptom score were all collected. The corresponding authors of studies whose data were insufficient for the meta-analysis were contacted via email to obtain missing or supplemental data (e.g., study means, standard deviations (SD), etc.).

The Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 recommended by the Cochrane Collaboration was used by two authors (CS and NC) to independently assess the methodological quality of included studies.¹⁴ Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases were all considered in the assessment process. All items were rated as "low risk," "unclear risk," or "high risk."

Statistical analysis

The Cochrane Collaboration's Review Manager (REVMAN) Software Version 5.4.1 was used to conduct a meta-analysis of selected studies using a continuous measure that compared mean and standard deviation. We measured treatment effects using the mean difference for the average hour of CPAP use per night, percentage of nights device used, and nasal symptoms of nasal steroids and control. We also conducted a subgroup analysis for each nasal symptom score, including sneezing, rhinorrhea, and nasal obstruction.

The null hypothesis was no difference in quantitative data of CPAP compliance and nasal symptoms between nasal steroids and placebo. If there was heterogeneity in the treatment effects, we utilized the REVMAN random-effects model for pooling effects; otherwise, we used a fixed-effects model. The I^2 statistic (low: 25%; moderate: 50%; and high: 75 percent) was used to quantify forest plot heterogeneity after visual inspection.¹⁵ Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement were adhered to as much as possible.¹⁶

Results

A PRISMA flow diagram was used to document the selection process (Figure 1). After excluding duplicates, the web-based search revealed a total of 1723 studies and abstracts. Following a preliminary assessment of titles and abstracts, 829 studies were identified as potentially relevant, and full texts were obtained for further review. In summary, three studies with 224 patients met the criteria and were included in this study.^{11-12,17} The mean patient age was 50.4 ± 11.1 years; the mean BMI was 32 ± 11.5 kg/m², the mean apnea-hypopnea index (AHI) was 36.9 ± 23.1 , and the mean ESS was 11.8 ± 5.3 (Table 1).

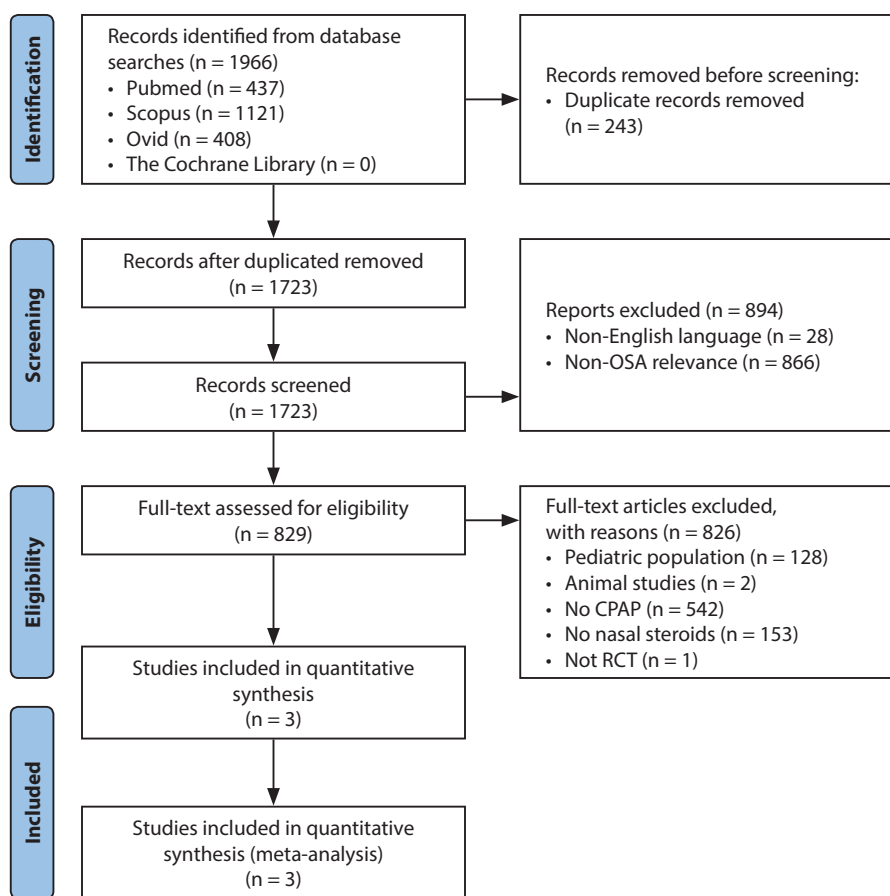


Figure 1. PRISMA flow diagram of literature search and study selection.

Abbreviations: N, number of articles

Table 1. Patients' characteristics of the trials included in the meta-analysis.

References	Design	n	Intervention (n)	Control (n)	Study duration	Mean age (years)	BMI (kg/m ²)	AHI (events/hour)	ESS
Ryan (2009)	RCT	81	Fluticasone propionate 50 µg twice daily (42)	None (39)	4 weeks	48 ± 10.2	33.5 ± 6	35 ± 21	13 ± 6
Strobel (2011)	RCT, double blind	63	Fluticasone propionate 50 µg twice daily (32)	Placebo (31)	4 weeks	52 ± 11.5	31.5 ± 6.6	34 ± 19	10.6 ± 4.2
Segsarnviriyaya (2020)	RCT	80	Fluticasone furoate 55 µg once daily (40)	None (40)	4 weeks and 90 days	51.7 ± 11.4	31 ± 17.3	41 ± 27.4	11.4 ± 5.2

Abbreviations: RCT, randomized controlled trial; N, number of participants; BMI, body mass index; AHI, apnea hypopnea index; ESS, Epworth sleepiness scale

Quantitative data on CPAP compliance, including the average hour of CPAP use per night, the percentage of nights device used, and overall nasal symptoms score at 4-week follow-up, were reported in all studies. The studies of Ryan et al. and Segsarnviririya et al. demonstrated each nasal symptom in detail.

Methodology quality of included studies

A summary of the quality assessment results for the included studies is shown in Figure 2 and Figure 3. Strobel's and Segsarnviririya's studies conducted adequately concealed allocations, while Ryan's studies did not mention the randomization method. The lack of blinding participants and outcome assessors in Ryan and Segsarnviririya's studies may have influenced CPAP use and nasal symptoms, giving those studies a significant risk of performance bias. None of the studies demonstrated any sort of detection bias because outcome measurement was not affected by the lack of the outcome assessors blinding. All studies mentioned that drop-out participants were missing data and had a low risk of attrition bias and reporting bias.

CPAP compliance at 4-week follow-up

At the end of four weeks of treatment, three studies (224 patients) gave quantitative data outcomes of CPAP machines. They all identified the average hours of CPAP use per night and the average percentage of nights device used and SD. Thus, the analysis was performed for both parameters (Figure 4). The difference in the average hours of CPAP use per night between nasal steroids and control was not statistically significant (mean difference 0.45, 95%CI (-0.01, 0.90); P = 0.06). The test for heterogeneity was not significant (P = 0.95), and inconsistency was low heterogeneity (I² = 0%). This indicates that pooling the data was valid; thus, the fixed effect model was applied.

In terms of the percentage of nights device used, the study did not demonstrate a statistically significant difference between nasal steroids and control after four weeks of treatment as well (mean difference, 1.79, 95%CI (-2.59, 6.17); P = 0.42). The test for heterogeneity was not significant (P = 0.60). Furthermore, low heterogeneity was demonstrated (I² = 0%). Thus, the fixed effects model was utilized for heterogeneity among these studies.

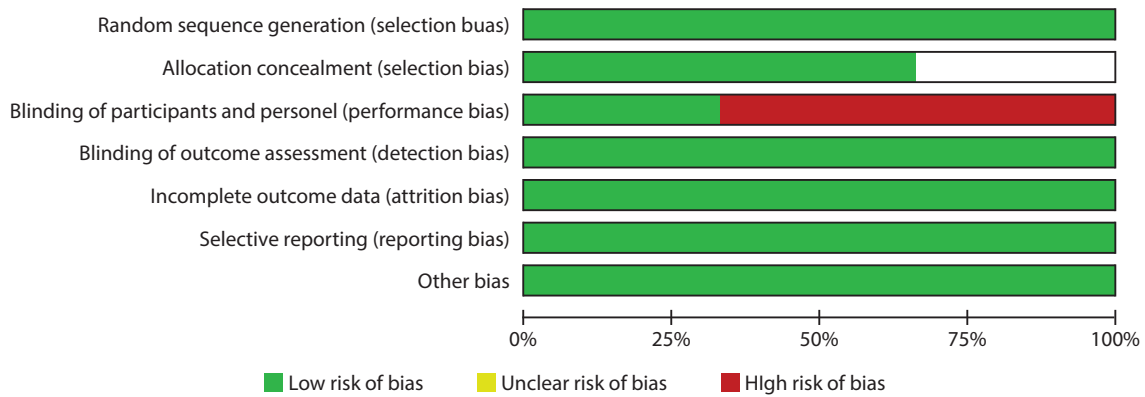


Figure 2. Quality assessment summary for included studies: risk of bias graph

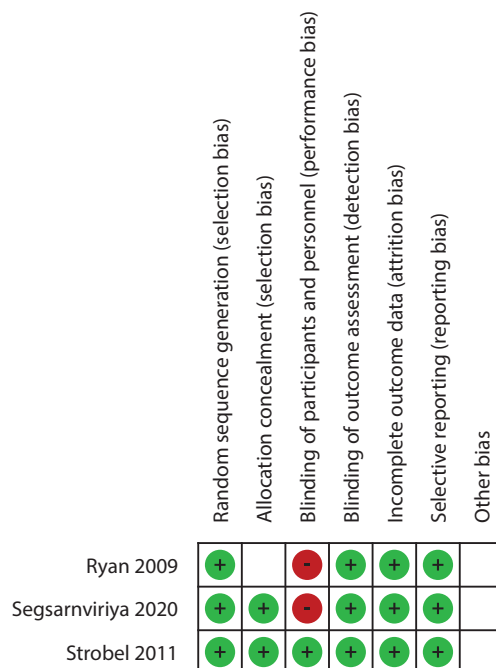


Figure 3. Methodology quality assessment for each included study.

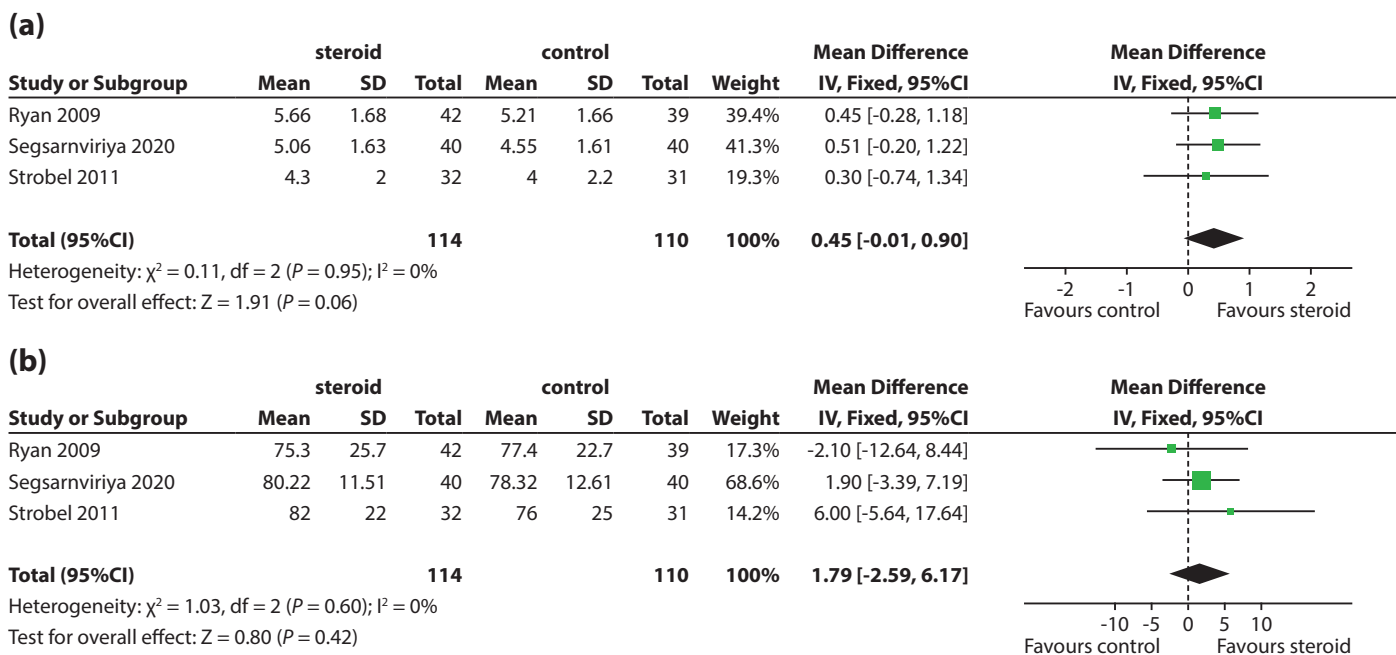


Figure 4. Forest plot: (a) meta-analysis of mean difference of average hours of CPAP use per night (hour) between nasal steroids and control at 4-week follow-up. (b) meta-analysis of mean difference of percentage of nights device used between nasal steroids and control at 4-week follow-up.

Abbreviations: IV, independent variable; SD, standard deviation

Overall nasal symptoms at 4-week follow-up

Three studies evaluated nasal symptom scores between the groups of nasal steroids and the control. Two of them (Ryan et al. and Segsarnviriyaya et al.) also detailed the score for each symptom. Ryan et al. classified nasal symptoms by using the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ), a questionnaire that defines nasal symptoms including sneezing, nasal blockage, and rhinorrhea as the score that ranges from 0 to 6 (0 indicating no trouble and 6 indicating extreme trouble). Strobel et al. described nasal symptoms including sneezing, blocked nose, and runny nose (each symptom is scored on a scale of 0 to 3, with 0 indicating no symptoms and 3 indicating severe symptoms). All scores were summed for a total score of 0 to 9. Segsarnviriyaya et al. classified nasal symptoms based on the Total Nasal Symptom Score (TNSS),¹⁸ assessing four nasal symptoms, including rhinorrhea, itching, congestion, and sneezing (the score of each symptom ranges from 0 to 3, and the total score ranges from 0 to 12). According to different assessments, we excluded itching symptoms from Segsarnviriyaya's study before calculating overall nasal symptoms and later converted all values in these studies to a comparable scale of 9.

There was no statistically significant difference in overall nasal symptoms between nasal steroids and control after four weeks of treatment (mean difference, 0.47, 95%CI (-0.00, 0.94); $P = 0.05$). The test for heterogeneity was not significant ($P = 0.47$). In addition, low heterogeneity was demonstrated ($I^2 = 0\%$). Hence, the fixed-effects model was used for analyzing these studies (Figure 5a).

Subgroup analysis of nasal symptoms

At a 4-week follow-up, the symptom score of sneezing, nasal obstruction, and rhinorrhea was described in two studies (Ryan et al. and Segsarnviriyaya et al.). The subgroup analysis of these studies (161 patients) was performed to determine the effect of nasal steroids on each nasal symptom. Ryan et al. described the score of each nasal symptom ranging from 0 to 6 while Segsarnviriyaya et al. reported the score range from 0 to 3; Therefore, we converted the score in Segsarnviriyaya's study to a comparable scale of 6.

Sneezing was more prominent among patients with nasal steroids. The analysis of sneezing symptom scores revealed a statistically significant difference between nasal steroids and control (mean difference, 0.64, 95%CI (0.23, 1.05); $P = 0.002$). The test for heterogeneity was not significant ($P = 0.23$), and low heterogeneity was presented ($I^2 = 32\%$). The fixed-effect model was applied (Figure 5b). Rhinorrhea was also significantly prominent among patients with nasal steroids (mean difference, 0.78, 95%CI (0.24, 1.31); $P = 0.005$). The test for heterogeneity was not significant ($P = 0.48$), and inconsistency was low heterogeneity ($I^2 = 0\%$). Thereby, the fixed effect model was applied (Figure 5c).

In terms of nasal obstruction, there was no discernible significance between nasal steroids and control (mean difference, -0.14, 95%CI (-0.69, 0.40); $P = 0.60$). The test for heterogeneity was not significant ($P = 0.99$), and inconsistency was low in heterogeneity ($I^2 = 0\%$). Thus, the fixed effect model was applied (Figure 5d).

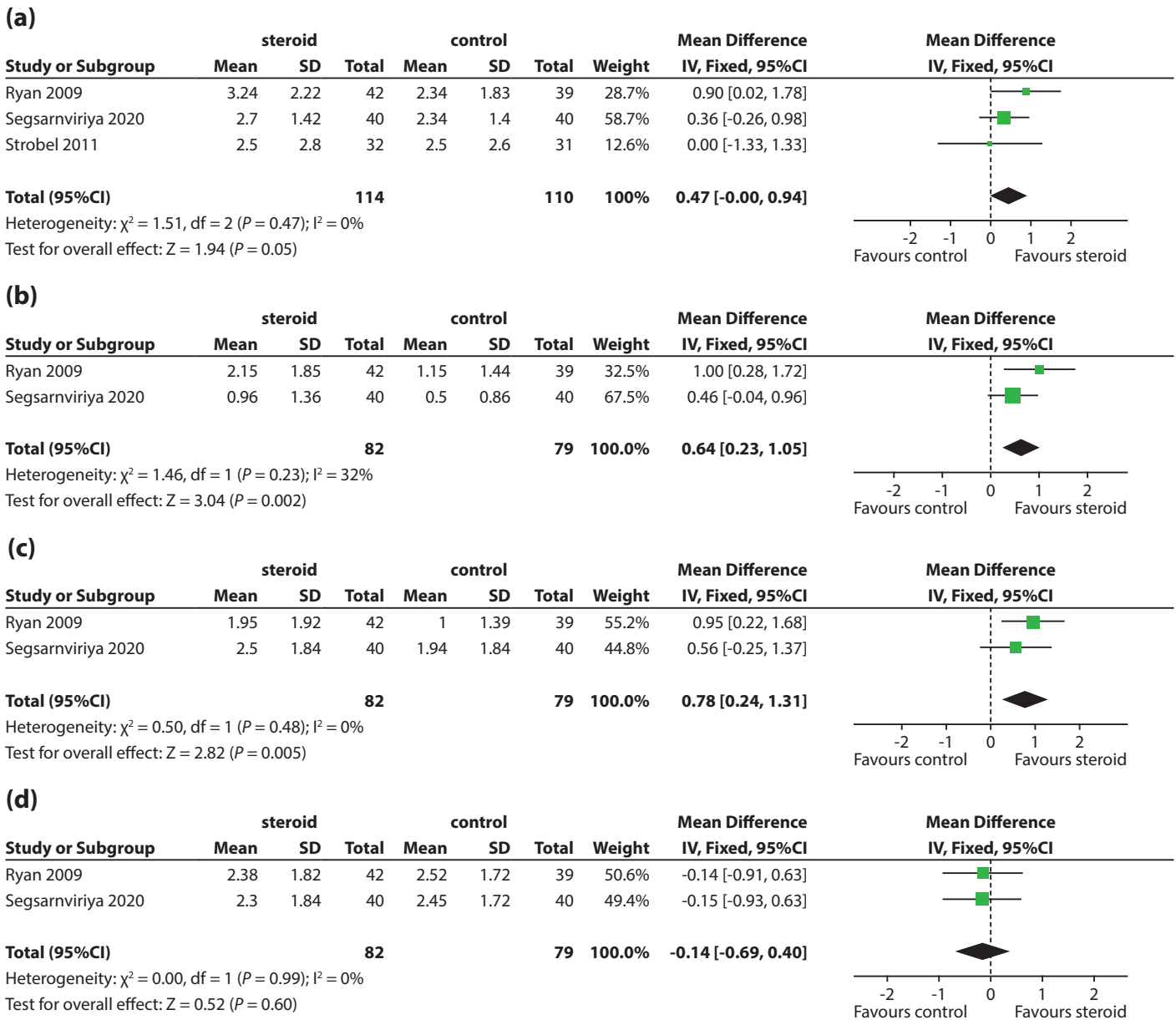


Figure 5. Forest plot: meta-analysis of mean difference of (a) overall nasal symptoms score, (b) sneezing score, (c) rhinorrhea score and (d) nasal obstruction score between nasal steroids and control at 4-week follow up.

Abbreviations: IV, independent variable; SD, standard deviation

Discussion

To treat OSA with CPAP effectively, maintaining good compliance is necessary. Various issues can lead to poor CPAP compliance, including nasal side effects. Nasal symptoms such as congestion, rhinorrhea, and sneezing are common among CPAP users.⁷ Exposure of the positive air pressure to the nasal mucosa, especially in individuals with previous rhinitis symptoms, can cause vasodilation and mucus generation, leading to mucosal edema and nasal discharge that may impair the nasal airway patency.¹⁹ In comparison with the compliant user, nasal resistance was higher in the non-compliant one.²⁰ Unrecognized high nasal resistance may lead to nasal symptoms while the CPAP is on, causing mask-off during sleep.⁸

Topical corticosteroids are the mainstay modality for allergic rhinitis. The drug acts directly on the nasal mucosa, by controlling protein synthesis, suppressing various pro-inflammatory cytokine releases,²¹ thereby can relieve rhinitis symptoms in either allergic rhinitis or non-allergic rhinitis. The beneficial effects of the drug among OSA patients were proven. Kiely et al. reported that not only nasal congestion was improved, but one month period of intranasal fluticasone also significantly reduced an apnea-hypopnea index in OSA patients with co-existing rhinitis compared to placebo.²² Though the medication was commonly prescribed for CPAP users with nasal symptoms, the beneficial effect of intranasal steroids on CPAP compliance at a 4-week follow-up in our previous meta-analysis was inconclusive.¹⁰ However, the study was based on only two RCTs in unselected OSA patients.

We conducted a systematic review of three randomized controlled trials of topical nasal steroids to improve CPAP compliance and its effect on nasal symptoms. At the 4-week follow-up, although an average compliance of 27 minutes longer per night of CPAP use in the nasal steroids group in comparison with control was reported, a statistically significant difference was not demonstrated. A significant difference in the percentage of nights device used was also not observed.

The study of overall nasal symptoms score did not show a statistical difference between both groups at the 4-week follow-up. Surprisingly, subgroup analysis revealed statistically increasing symptoms of sneezing and rhinorrhea among patients with nasal steroids. More nasal symptoms during the initial usage of nasal steroids are likely caused by local irritation from the aqueous spray.¹¹ Regardless of the chemical or formulation utilized, at least 10 percent of intranasal steroids users frequently reported sneezing, a dry nose, and a burning sensation.²³ These symptoms might diminish after getting familiar with nasal steroids. In addition, cold or low-humidity air that was produced from CPAP may harm nasal mucosa,²⁴ causing some nasal symptoms in the new CPAP users.²⁵ The combination of annoying effects from the CPAP's air and local irritation from nasal steroids during the beginning of nasal steroids use may result in worse nasal symptoms in the nasal steroids group compared with the control in this study.

According to Balsalobre's study, nasal symptom reduction, increased intranasal volume, and enhanced peak nasal inspiratory flow on acute positive pressure exposure in allergic rhinitis patients can be detected after one month of nasal steroid treatment.²⁶ In this meta-analysis, all these included RCTs did not report the presence or absence of allergic rhinitis in their subjects. Though it is not a common practice to clarify the presence of allergic rhinitis in the clinic during CPAP clinic, nasal steroids might act unequally between allergic rhinitis and other types of rhinitis thus can possibly be a factor contributing to the inconclusive result of overall nasal symptoms during the first month in our study. Nevertheless, with the use of nasal steroids, the nasal symptoms may lessen over a longer period of follow-up, paralleling greater CPAP compliance, which can be explained by increased familiarity and effectiveness of both medication and device over time. Segsarnviriyas findings have supported this notion, in which higher CPAP compliance; including average hours of CPAP use per night and the percentage of nights device used; as well as improvement of overall nasal symptoms score; including symptoms of rhinorrhea and nasal obstruction, were statistically demonstrated at the 90 days of follow-up of OSA patients with nasal symptoms.¹⁷

Although this study included more RCTs in comparison with our previous study, only one study tracked patients for a longer period of 90 days, so there is insufficient evidence to conduct a meta-analysis of the 90-day follow-up. Future research is necessary and can be improved by recruiting more considerable and specific population, conducting longer follow-up trials, and controlling the potential confounding factors that can influence CPAP compliance.

Nasal symptoms may not be the single factor determining compliance with CPAP use. Other factors that can have an impact on CPAP compliance include lack of knowledge of CPAP benefits on OSA health consequences protection, bed partner's attitude, equipment issues, fear of enclosed spaces, psychological and social factors.²⁷ A multimodality approach should be applied to enhance CPAP compliance, including appropriate assessment of individual pressure required, education on mask and equipment use, mask fitting, heated humidification, ramp features, and pressure release modes.²⁸

Conclusion

Nasal steroids did not significantly improve CPAP compliance, including the average hours of CPAP use per night, the percentage of nights device used, and overall nasal symptoms when used continuously for 4 weeks. Additional longer follow-up RCTs with larger sample sizes and longer follow-ups are required to investigate the benefits of nasal steroids at a longer duration in enhancing CPAP compliance and alleviating nasal symptoms following CPAP use.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Funding

No funding was received for this research.

Ethical approval

No evaluation of an Ethical Committee was necessary because this study was designed as a meta-analysis.

Research involving human participant and/or animals

This study does not involve human participants or animals.

Informed consent

For this type of study, formal consent is not required.

Data availability statement

This study was a re-analysis of existing data, which is available at locations cited in the reference section.

Author contributions

- Charnsiri Segsarnviriyas and Natamon Charakorn contributed to the study conception and design and performed data extraction, study quality assessment, and statistical analysis.
- Review and editing were performed by all authors.
- The first draft of the manuscript was written by Charnsiri Segsarnviriyas, and all authors commented on previous versions of the manuscript.
- All authors read and approved the final manuscript.

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