Effects of oral and nasal steroids in nasal polyps: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Nattapong Tanghor, M.D.[1]; Nicharat Sawangroj, M.D.[2]; Chatnarin Phongnin, M.D.[3]; Thipphawan Chanasuek, M.D.[4]; Kiettisak Kondaung, B. Sc.[5]

[1]Na Yung Hospital, Thailand; [2]Khon Kaen Hospital, Thailand; [3]Song Dao Hospital, Thailand; [4]Waeng Noi Hospital, Thailand.

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Correspondence to: Nicharat Sawangroj; n.sawangroj@gmail.com

ABSTRACT

OBJECTIVE
To identify the effect of oral and nasal steroids in patients with nasal polyps.

METHODS
We systematically searched through electronic databases including Pubmed, The Cochrane Library, Scopus, Google scholar using keywords related to oral steroids or corticosteroids and nasal polyps. We included studies that used oral plus nasal steroids for treating patients with nasal polyps. The primary outcome was the decrease of nasal polyp size. Other outcomes included hyposmia, nasal obstruction, and nasal nitric oxide. The full texts of the included studies were appraised for risk of bias and their data were extracted for meta-analysis comparing between oral plus nasal steroids and nasal steroids alone or placebo.

RESULTS
Six randomized controlled trials were included in the present review with a total of 490 patients; 335 in oral steroids followed by nasal steroids group, 78 in nasal steroids alone group and 77 in the placebo group. The first comparison is using oral plus nasal steroids compared to nasal steroids alone which the result after 2 weeks of starting oral steroids treatment, oral steroids showed statistically significant decrease nasal polyp size, mean difference (MD) -1.66 (95% confidence interval (CI), -2.54 to -0.78). At the various ends of the studies, oral plus nasal steroids showed statistically significant decrease nasal polyp size, MD -0.43 (95% CI, -0.52 to -0.34). The second comparison is using oral plus nasal steroids compared to placebo which the result after 2 weeks of starting oral steroids treatment, oral steroids showed statistically significant decrease nasal polyp size, MD -0.64 (95% CI, -1.19 to -0.1). After 12 weeks of starting nasal steroids, the patients in treatment group showed the reduction of the nasal polyp size, MD -0.68 (95% CI -1.16 to -0.19).

CONCLUSION
We suggested the possible benefit of oral steroids followed by nasal steroids for decrease nasal polyp size. However, our conclusion was based on 490 patients, the randomized controlled trials with large of participants are suggested.

INTRODUCTION

Nasal polyps are noncancerous multiple masses that growth from paranasal sinus and extend to a nasal cavity. The polyps usually occur bilaterally and maybe the cause of nasal obstruction while the etiology is still unknown with the plausible link to chronic inflammation, allergies, and asthma.[1-6] The global incidence of nasal polyps is 1-4% among adults.[7-9] Nowadays the corticosteroids are the treatment of choice while topical nasal steroid is a preferred route of administration.[10,11] In addition, previous studies have suggested the benefits of oral steroids for nasal polyp treatment.[12,13] According to two previous systematic reviews in 2007 and 2011 comparing between oral steroids followed by nasal steroids and placebo stating that oral steroids had benefit for the relief of nasal symptoms and nasal polyp size reduction.[13,14]

Since those reviews five randomized controlled trials (RCT) further studies have been published Three of these studies suggested that oral steroids followed by nasal steroids had the better outcome for patients with nasal polyps comparing to placebo.[15-18] Another two studies compared oral steroids followed by nasal steroids to nasal steroids alone.[19,20] When using oral steroids followed by nasal steroids, both of them showed significant decrease of nasal polyp size but the improvement of hyposmia was still debatable; one study in 2012 with 67 patients showed significant improvement of hyposmia after the use of oral steroids followed by nasal steroids compared to nasal steroid alone while another one in 2011 with 30 patients did not.[19,20] Thus, we conducted a systematic review to evaluate whether oral steroids followed by nasal steroids had effects for decrease nasal polyp size, improvement of hyposmia, improvement of nasal obstruction and increase nasal nitric oxide compared to nasal steroids alone or placebo in patients with nasal polyps.

METHODS

SEARCH STRATEGIES

We searched for studies through the Cochrane Library, Pubmed, Scopus and Google Scholar. We used a combination of Medical Subject Headings (MeSH) for Pubmed and Cochrane Library searching; ("Nasal Polyps" [Mesh] OR "Rhinopolyps*" [Mesh] OR ("Polyps" [Mesh] OR "Polyp*" [Mesh] AND "NOSE" [Mesh] OR "Nasal" [Mesh] OR "Intranasal" [Mesh] OR "Sinonasal" [Mesh]) AND "Steroids" [Mesh] OR "Corticosteroid" [Mesh] OR "Adrenal cortex hormones" [Mesh] OR "Glucocorticoids"[Mesh] OR "Prednisolone" [Mesh] OR "Budesonide" [Mesh]) and used keywords ; "Polyp*" OR "Papillom*" OR "Rhinopolyp*" AND "Steroid*" OR "Glucocorticoid*" OR "Corticosteroid*" OR "Prednisolone*" in Scopus and Google scholar. We checked every reference of the included studies and manually searched for additional studies which were relevant.

Overall 3,587 titles and abstracts were reviewed. We conducted systematic searches for RCTs. There were no languages, publication years or publication status restrictions. The date of the last search was February 19, 2015.

INCLUSION CRITERIA

PARTICIPANTS

We selected only the studies which included patients with nasal polyps based on nasal endoscope.

INTERVENTIONS

Any dose of oral steroids followed by nasal steroids versus nasal steroids alone as well as any dose of oral steroids followed by nasal steroids versus placebo

OUTCOMES

Our primary outcome was nasal polyp size measured by Lildholdt 's scale for nasal polyp grading.[21] Secondary outcomes were hyposmia, nasal obstruction, and nasal nitric oxide.

EXCLUSION CRITERIA

We excluded studies that patients were given steroids after sinus surgery

DATA EXTRACTION

Five reviewers read full texts of the eligible articles and selected RCTs that involving oral steroids followed by nasal steroids compared with nasal steroids alone or placebo in patients with nasal polyps. All problems were solved by the discussion of five reviewers and data extracted from included studies and recorded by five reviewers. We used the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 to organize the standard forms to extract data.[22]

QUALITY OF REPORTING AND RISK AND BIAS

We used Jadad scale for assessed the risks in term of randomization, blinding and an account of all patients. Potential publication bias was assessed by using a funnel plot. Moreover, We used The Cochrane Handbook for Systematic Reviews of Interventions version 5.3.0 for assessed risk of bias of the included RCTs which risk of bias was weighed regarding random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Then the RCTs were classified into three groups; low risk, high risk and unclear risk by the risk of bias score.

DATA ANALYSES

To standardize the reporting of our results, we calculated mean difference (MD) for continuous data that outcomes were measured in the same manner; nasal polyp size, nasal obstruction, and nasal nitric oxide at week 2, week 12 compared to week 0. And we used standardized mean difference (SMD) for continuous data which outcomes were measured in various methods; hyposmia was the case in the present review. Both MD and SMD of the outcomes were presented together with their 95% confidence interval (CI). All analyses were performed with Revman 5.3.0 (RevMan, the programme provided by the Cochrane Collaboration) statistical software to assess the effectiveness of oral steroids followed by nasal steroids compared with either nasal steroids alone

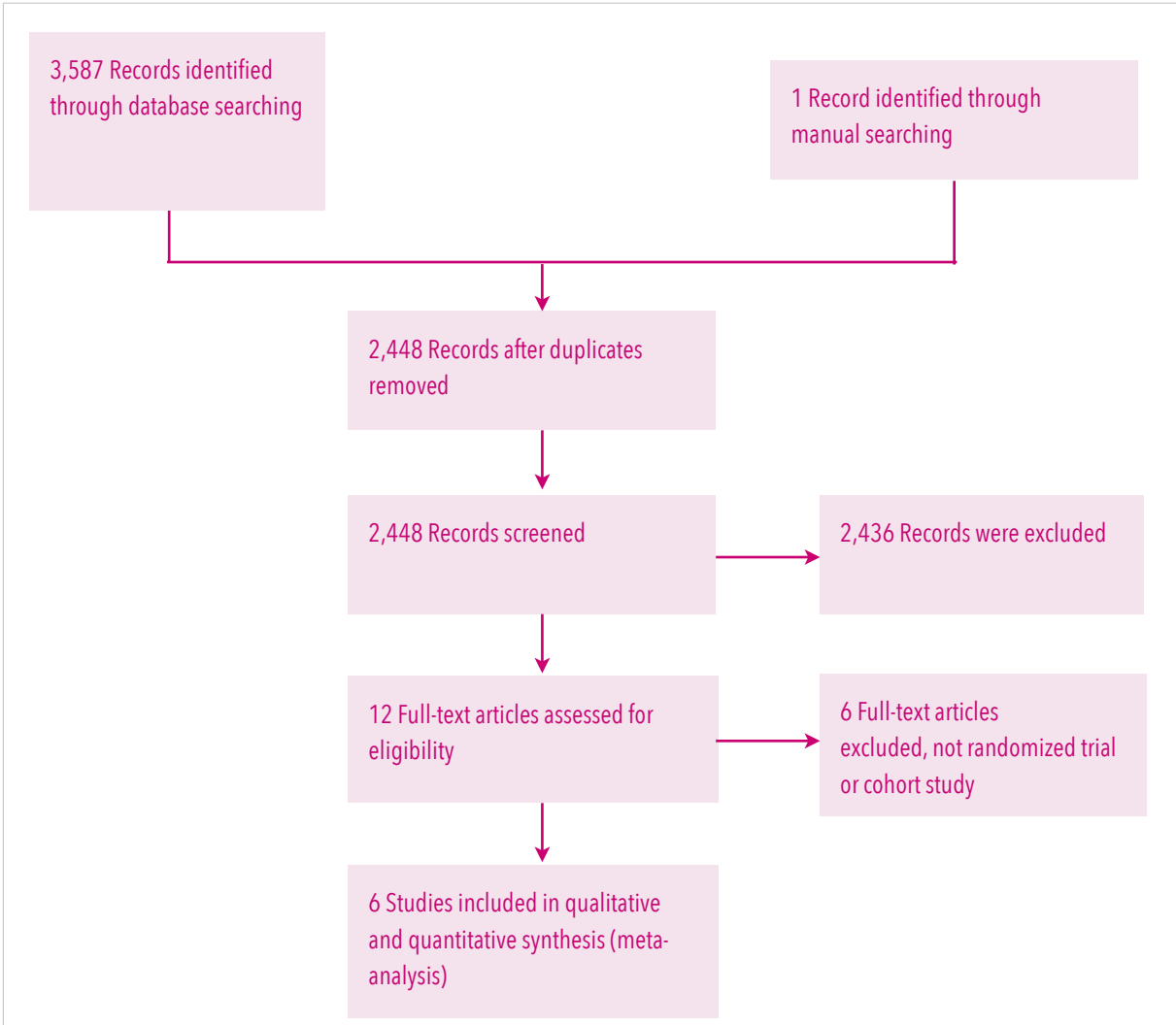


Figure 1. Flowchart presenting the number of articles retrieved, included and excluded in this systematic riew.

or placebo for nasal polyp treatment according to nasal polyp size, hyposmia, nasal obstruction and nasal nitric oxide.[23] The statistical test of heterogeneity was high if $P<0.10$ and I^2 statistic was more than 50%. We used a random effect model for the meta-analysis when heterogeneity was high and used a fixed effect model for the meta-analysis when heterogeneity was low. We did not perform sensitivity analysis due to the small number of trials that could be included in the analysis of the outcomes. This strategy was also applied elsewhere.[23]

Table.1 Characteristics of the included studies

Author	Location	Study design	Population	Duration of study	Sample size (I/C)	Mean age (year)	Duration of treatment (weeks)	Regimen of interventions	Jadad scale
Alobid 2006	Spain	RCTs	Patients with nasal polyps diagnosed endoscopically and radiologically, 22 to 84 yr	Feb 1999 to Jul 2003	78 (60/18)	50	48	Prednisone 30 mg daily for 4 days, followed by a two-days reduction of 5 mg for 2 weeks followed by intranasal budesonide (400 µg/twice a day)for 46 weeks	0
Benitez 2006	Spain	RCTs	Patients with severe NP diagnosis by nasal endoscopic,22 to 84 yr	Feb 1999 to Nov 2003	74 (63/21)	51.7	14	Oral prednisone for 2 weeks (30 mg daily for 4 days followed by a 2-day reduction of 5 mg) followed by 400 g intranasal budesonide twice a day for 12 weeks	2
Vaidyanathan 2011	United Kingdom	RCTs	Patients with moderate and large nasal polyps	-	58 (30/28)	-	28	Prednisolone 25 mg/day for 2 weeks, followed by fluticasone propionate nasal drops, 400 g twice daily, for 8 weeks and then fluticasone propionate nasal spray, 200 g twice daily, for 18 weeks.	4
Kirtsree sakul 2012	Thailand	RCTs	Patients with benign bilateral nasal polyps, 18-65 yr	May 2007 to Sep 2010	117 (69/48)	45.6	12	50 mg of prednisolone for 2 weeks then treated with mometasone furoate nasal spray (MFNS) at 200 microgram twice daily for 10 weeks	2
Alobid 2012	Spain	RCTs	Patients with moderate to severe nasal polyps	-	62 (46/16)	49	14	30 mg/day for 4 day followed by a 2 days Reducing 5 mg, 2 weeks and intranasal steroids 400 micrograms BID 12 weeks	2
Alobid 2014	Spain	RCTs	Patients with moderate to severe nasal polyps	-	89 (67/22)	42	14	30 mg/day for 4 day followed by a 2 days reducing 5 mg, 2 weeks and intranasal steroids 400 micrograms BID 12 week	3

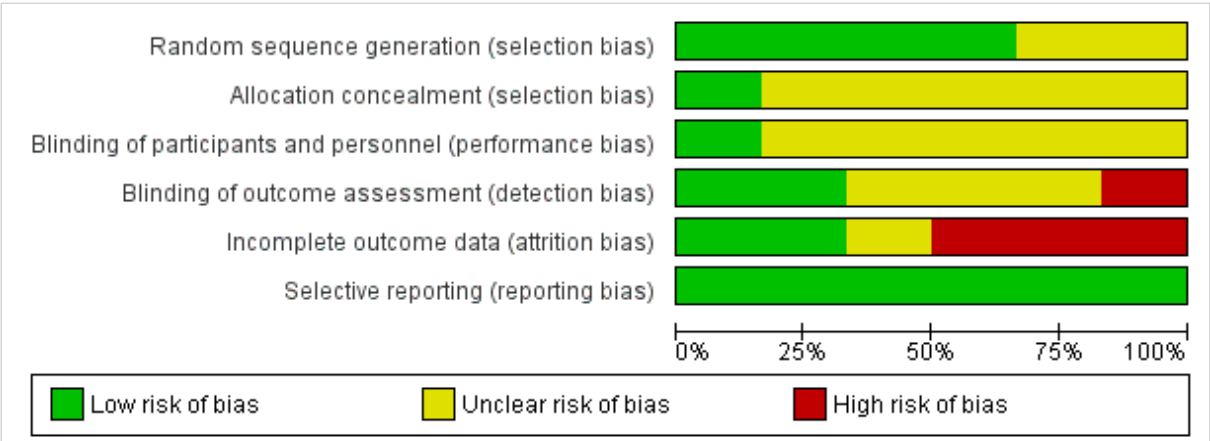


Figure 2. Risk of bias graph.

RESULTS

DESCRIPTION OF STUDIES

The literature search retrieved 3,587 citations and additional 1 citation was identified through manual searches reference lists of relevant articles (Figure 1). Of these, 2,548 citations after duplicates removed were identified. Later we screened for titles and abstracts, 2,536 citations were excluded. In the end, 12 full-text articles were assessed for eligibility according to inclusion and exclusion criteria. Ultimately, six articles were included in the present review.

INCLUDED STUDIES AND EXCLUDED STUDIES

The remaining six RCTs determined the effect of oral steroids to improve nasal symptoms and polyp grading in patients with nasal polyps were all designed and conducted between 2006 and 2014. They assigned 490 patients; 335 patients received oral plus nasal steroids, 78 patients received nasal steroids alone and 77 patients received placebo. 15-18 The characteristics of six included studies were summarized in Table 1.

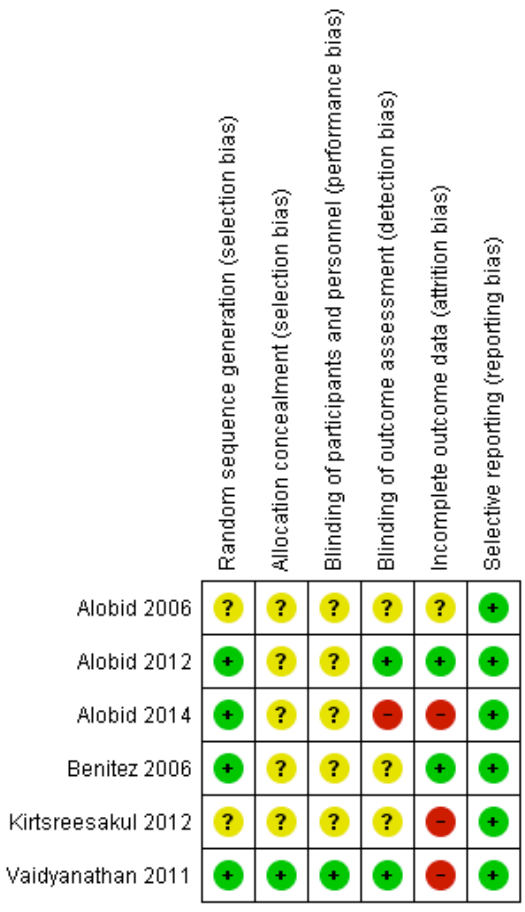


Figure 3. Risk of bias summary

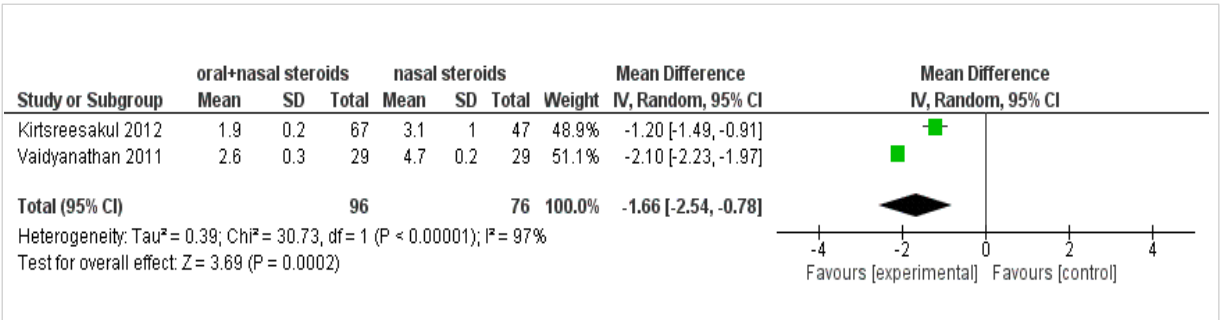


Figure 4. Forest plot of comparison of oral plus nasal steroids versus nasal steroids alone, outcome: polyp size at 2 weeks after oral steroids

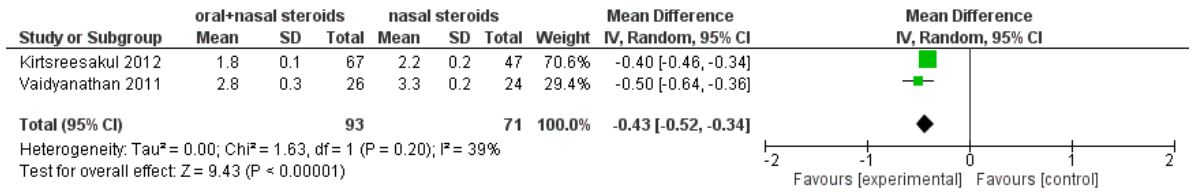


Figure 5. Forest plot of comparison of oral plus nasal steroids versus nasal steroids alone, outcome: polyp size at the end of study

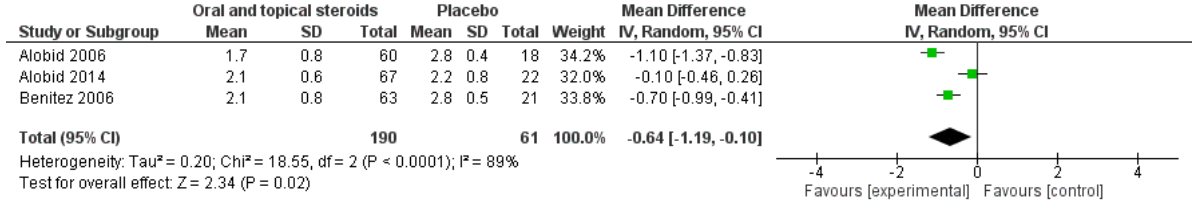


Figure 6. Forest plot of comparison of oral plus nasal steroids versus placebo, outcome: polyp size

RISK OF BIAS OF THE INCLUDED STUDIES

All RCTs were assessed quality using Jadad scale (Table1). The study by Vaidyanathan was scored 4 because of no detail of an account of all patients.[19] The study by Alobid in 2014 was scored 3 because of no detail of methods of blinding. Three studies by Alobid in 2011, Benitez and Kirtsreesakul were scored 2 because of no detail of methods of blinding and no detail of methods of an account of all patients.[16,17,20] The study by Alobid in 2006 was scored 0 because of no detail of methods of randomization, blinding, and account of all patients. Furthermore, the included six RCTs were assessed by The Cochrane Collaboration's tool for

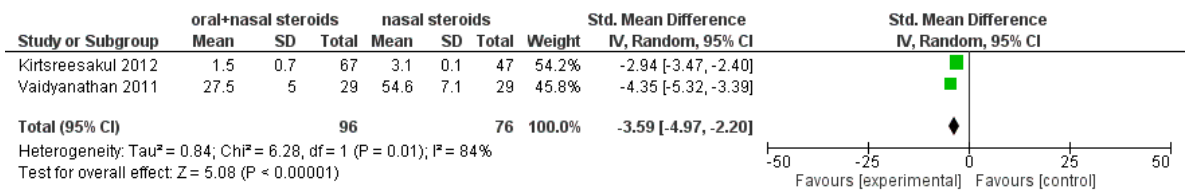


Figure 7. Forest plot of comparison of oral steroids followed by nasal steroids versus nasal steroids alone, outcome: Hyposmia at 2 weeks after oral steroids.

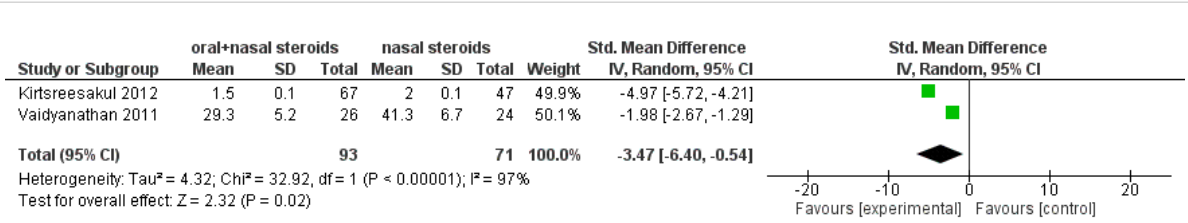


Figure 8. Forest plot of comparison: Oral steroids followed by nasal steroids versus nasal steroids alone , outcome: hyposmia at the end of study

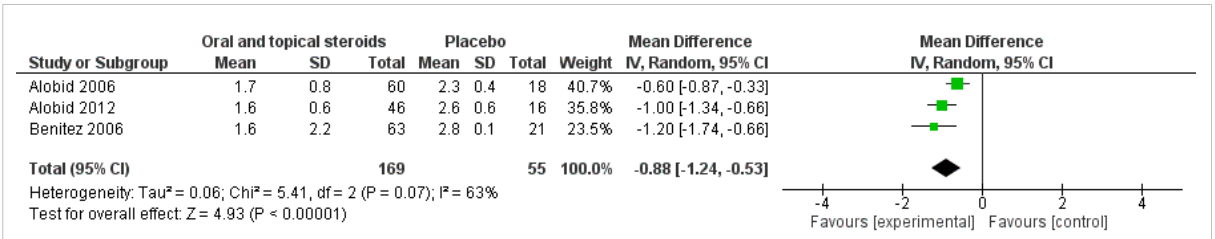


Figure 9. Forest plot of comparison: Oral steroids followed by nasal steroids versus placebo, outcome: hyposmia

assessing risk of bias which a risk of bias graph expressed methodological quality showed in Figure 2 and the risk of bias summary in each included study showed in Figure 3.

PRIMARY OUTCOME

We analyzed two trials which examined the effect of oral steroids followed by nasal steroids compared to nasal steroids alone.[19,20] At 2 weeks after starting oral steroids, the former group showed significant reduction of nasal polyp size, MD -1.66 (95% CI, -2.54 to -0.78, I^2=97%) (Figure 4). At the various ends of the studies, the former group again showed significant reduction of polyp size, MD -0.43 (95% CI, -0.52 to -0.34, I^2=39%). (Figure 5). Three RCTs studied the improvement of

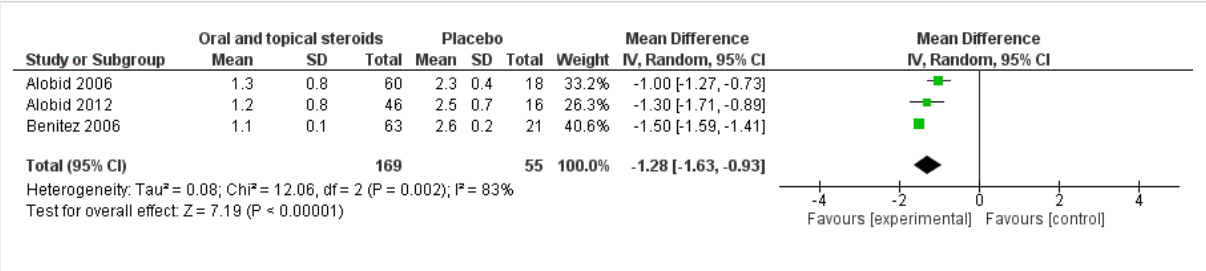


Figure 10. Forest plot of comparison: Oral steroids followed by topical steroids versus placebo, outcome: nasal obstruction

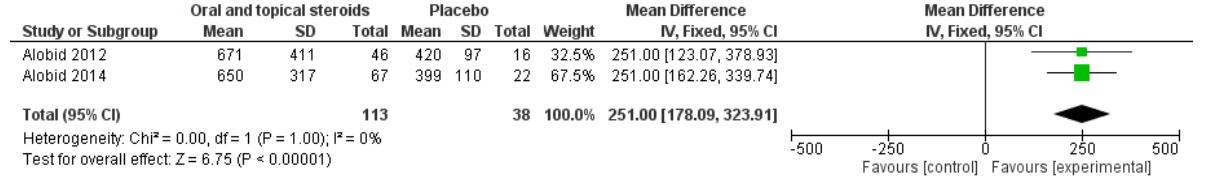


Figure 11. Forest plot of comparison: Oral steroids followed by topical steroids versus placebo, outcome: nasal nitric oxide

nasal polyp size that compared between oral plus nasal steroids and placebo.[15-17] At 2 weeks after starting oral steroids, the former group showed significant improvement of nasal polyp size, MD -0.64 (95% CI, -1.19 to -0.1, I^2=89%).(Figure 6). At 12 weeks after starting nasal steroids, the reduction of nasal polyp size comparing between week 12 and week 0 in treatment group was significant, MD -0.68 (95% CI -1.16 to -0.19) but in control group was not measured due to medical ethics of human researches as it cannot consider offering ineffective treatment to the control group for longer than 6 weeks

HYPOSMIA

Two RCTs studied the improvement of hyposmia that compared between oral plus nasal steroids and nasal steroid alone.[19,20] At 2 weeks after starting oral steroids, the former group showed significant improvement of hyposmia, SMD -3.59 (95% CI -4.97 to -2.20, I^2=84%) (Figure 7). At the various ends of the studies, oral plus nasal steroids showed significant improvement of hyposmia, SMD -3.47 (95% CI -6.40 to -0.54, I^2=97%) (Figure 8).

Three RCTs studied the improvement of hyposmia that compared between oral plus nasal steroids and placebo.[15-17] At 2 weeks after starting oral steroids, the former group showed significant improvement of hyposmia, MD -0.88 (95% CI -1.24 to -0.53, I^2=97%) (Figure 9). At 12 weeks after starting nasal steroids, the improvement of hyposmia was not sustained, MD -0.35 (95% CI -0.10 to 0.29) (Figure 9).

NASAL OBSTRUCTION

Three RCTs studied the improvement of nasal obstruction that compared between oral plus nasal steroids and placebo.[15-17] At 2 weeks after starting oral steroids, the former group showed significant improvement of nasal obstruction, MD -1.28 (95% CI -1.63 to -0.93, I^2=83%)(Figure 10) and after 12 weeks of starting nasal steroids, nasal steroids can maintain the improvement of nasal obstruction, MD -1.06 (95% CI -1.45 to -0.69).

NASAL NITRIC OXIDE

Two RCTs studied the improvement of nasal obstruction that compared between oral plus nasal steroids and placebo.[17-18] At 2 weeks after starting oral steroids, the former group showed a significant increase nasal nitric oxide, MD 251.00 (95% CI 178.09 to 323.91, I^2=0%) (Figure 11) and after 12 weeks of starting nasal steroids, nasal steroids can also maintain the level of nasal nitric oxide, MD 198.50 (95% CI 166.73 to 230.27)

We did not create the funnel plot as our outcomes were derived from the combined findings of only two and three RCTs. The number of the included studies were too few to assess the publication bias.

DISCUSSION

SUMMARY OF MAIN RESULTS

In the present systematic review and meta-analysis, we found that using oral steroids for 2 weeks was effective to decrease polyp size, improve hyposmia, relief nasal obstruction and increase nasal nitric oxide in patients with nasal polyps. When using oral steroids followed by nasal steroids, polyp size and hyposmia were more improved than using nasal steroids alone. Moreover, oral steroids followed by nasal steroids can also maintain improvement of polyp size, nasal obstruction, and nasal nitric oxide level.

OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

Both Vaidyanathan 2011 and Kirtsreesakul 2012 studied the effect of oral steroids followed by nasal steroids compared to nasal steroid only at different doses and forms.[19,20] At 2 weeks, both of them showed the significant improvement of polyp size and hyposmia in the former group when compared with the latter group. After 2 weeks, nasal steroids was given to all of the patients and measured the outcomes at the variant times. At the end of both studies, they still showed significant improvement of polyp size after using oral followed by nasal steroids but hyposmia was different, Kirtsreesakul 2012 showed significant improvement of hyposmia at 12 weeks while Vaidyanathan 2011 did not at 28 weeks. In our meta-analysis of two studies suggested the significant improvement of hyposmia. However, the limitation of these analyses should be reminded that it was measured the final outcomes at the different times.[19,20]

Alobid 2006, Benitez 2006, Alobid 2012 and Alobid 2014 studied the effects of oral steroids followed by nasal steroids in treatment group compared with the patients in control group who received placebo by measuring various outcomes at 2 weeks after patients in treatment group receiving oral steroids and 12 weeks after the treatment group converting to use nasal instead oral steroids for 10 weeks.[15-18] After 2 weeks, the significant improvements of polyp size, hyposmia,

nasal obstruction and nasal nitric oxide were shown in patients with nasal polyps who received oral steroids.[15-18] The end of studies at 12 weeks, they still showed significant improvement of polyp size, nasal obstruction, and nasal nitric oxide but hyposmia was different. Alobid 2006 showed hyposmia can be maintained the improvement while Alobid 2012 and Benitez 2006 found that using oral followed by nasal steroids cannot maintain the improvement of hyposmia.[15-17]

QUALITY OF THE EVIDENCE

This systematic review has much strength. Five authors search RCTs by screening all titles and abstracts and read full-text articles to assess relevant studies. All of include studies were precisely assess quality and bias used the standard assessment such as the Cochrane Collaboration's tool for assessing risk of bias and Jadad scale. The limitation of this systematic review has high heterogeneity of included studies and possible publication bias. The RCTs with a large number of participants is suggested for stronger evidence to support the effect of oral steroids and nasal steroids in patients with nasal polyps.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEW

Our findings have benefit for receiving oral steroids followed by nasal steroids for nasal polyps treatment which decrease polyp size, improve hyposmia, relief nasal obstruction and increase nasal nitric oxide. A recent systematic review of oral steroids for nasal polyps by Martinez-Devesa P et al, 2011 found three RCTs which moderate to poor quality but they suggested a short-term benefit of oral steroids in those with multiple nasal polyps.[14] Our analysis differs Martinez-Devesa P et al. by being a meta-analysis and we included more studies, more diverse populations, and more comparison.[14] In six RCTs in our study, there are two RCTs: Vaidyanathan and Kirtsreesakul which used oral steroids followed by nasal steroids compared with nasal steroids alone while Martinez-Devesa P et al.'s used oral steroids followed by nasal steroids compared with placebo.[14,19-20]

About the hyposmia outcome, there were different outcomes of following for long-term usage in each RCTs, our results suggested the benefit of the short-term use but the long-term outcome was still unclear. There was a systematic review by Banglawala et al, 2014 reviewed the olfactory outcome in chronic rhinosinusitis with nasal polyposis.[25] The results of their meta-analysis demonstrated that oral and nasal steroids significantly improve olfaction in patients suffering from chronic rhinosinusitis with nasal polyposis.[25]

CONCLUSION AND IMPLICATION

We suggest the possible benefit of oral steroids followed by nasal steroids for decrease nasal polyp size. However, our suggestion was based on 490 patients with relatively high heterogeneity, the further RCT with larger of participants are needed.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing on interest.
FUNDING: None

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