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# Meta Analysis Study and Systemic Review of the Efficacy of Combination of H1 Antihistamine with Intranasal Corticosteroid in Management of Allergic Rhinitis

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**Abstract**

A combination of Intranasal H1 antihistamine (AH) with intranasal corticosteroid (INCS) is commonly prescribed to patients with allergic rhinitis (AR) who have an inadequate response to monotherapy. In this systematic review we aimed to determine the effects of AH combined with INCS (INAH-INCS) for treating AR using meta analysis and up to date with different upcoming new modalities. Literature searches were performed using Medline and Embase. Randomized, controlled trials that studied the effects of INAH-INCS vs INCS monotherapy for treating patients with AR were included. The primary (main) outcome was reflective total nasal symptom scores (rTNSS). The secondary outcomes were disease-specific Rhinoconjunctivitis quality of life Questionnaire (RQLQ) and adverse events. Seven studies (1616 patients) met the inclusion criteria. Six of them used in study difference of rTNSS , Three of them in study difference of RQLQ and Two of them in study of adverse events (headache,epistaxis,URTI and nausea) . Compared with INCS, INAH-INCS decreased reflective total nasal symptom scores (standardized mean difference [SMD], – 0.178; 95% confidence interval [CI], -0.295 to-0.060; *p =0.003*) favoring INCs / INAH over INCs alone or OAH alone. Subgroup analysis indicated no benefit with the INAH-INCS combination in RQLQ or Adverse events . This systematic review favors the combination of Intranasal AH plus INCS over INCS alone. There were no differences between use of the oral AH plus INCS combination and INCS alone. Also, we found no differences between the 2 groups with regard to adverse events.

**Keywords:** Antihistamines, Histamine antagonist, Steroids, Corticos- teroids, Allergic rhinitis.

## 1. Introduction

Rhinitis is heterogeneous disorder characterized by one or more of the following nasal symptoms sneezing ,itching ,rhinorrhea and /or nasal congestion . Rhinitis frequently is accompanied by symptoms involving the eyes , ears , and throat , including post nasal drainage [1].

Treatment of allergic rhinitis includes avoiding allergens (when possible), intranasal corticosteroids, short term decongestants, oral or topical H1 receptor antagonists (antihistamines), intranasal cromoglycate, anticholinergic agents, and allergen immunotherapy [2].

Topical intranasal corticosteroids are said to be more effective than oral antihistamines in controlling nasal blockage and discharge. Furthermore, oral antihistamines are said to be better at treating nasal itch, sneezing, and eye symptoms [3].

There is also a perception, especially in popular reviews on allergic rhinitis, that intranasal corticosteroids do not improve eye symptoms.To address these issues we reviewed published randomized controlled trials comparing intranasal corticosteroids with oral antihistamines, and performed a meta-analysis on the efficacy of these interventions on relevant clinical outcomes [4].

## 2. Materials and methods

### Identification and location of articles

The study included published medical articles concerning the effect of combination of H1 antihistamine and intranasal corticosteroid in management of allergic rhinitis through searching the Medline data base (www.pubmed.com) using a combination of the following key words: (treatment of allergic rhinitis with H1 antihistamine) (Treatment of allergic rhinitis with intranasal corticosteroids ) (Role of combination of H1 antihistamine and intranasal corticosteroid in treatment of allergic rhinitis )

Over 1500 articles were found, after removal of duplicates (550) they narrowed to about 950 articles, after exclusion of non relevant articles (924). There were 7 relevant articles, by application of inclusion criteria can undergo Meta-analysis.

### Screening and evaluation

The screening form of articles was used by the investigators to screen the articles, which were yielded by the Medline search after blinding the author name and journal name. Screen form of the articles:

1) Irrelevant articles: articles that may have one of the keywords but different purpose from our study (950).
2) Relevant articles: after exclusion of repeated and non relevant articles, relevant articles were (18).
3) Included articles: These are (7 articles) which fulfilled the following inclusion criteria and were suitable for further steps of data collection, analysis and reporting:

Concerned in evaluating the effect of combination of H1 antihistamine in addition to intranasal corticosteroid in management of allergic rhinitis .

Published in English language.

Conducted on human subjects.

4) Excluded articles: Articles which miss one or more of the above mentioned inclusion criteria and not suitable for meta-analysis (10)

### Data collection

Information was gathered for each individual study met the inclusion criteria about the effect of

combination of H1 antihistamine in addition to intranasal corticosteroid in management of allergic rhinitis .

**Data analysis and Statistical methods**

Statistical analysis was done using Comprehensive Meta Analysis version 2.2.046 (Biostat© Englewood, NJ) and MedCalc© version 18.2.1 (MedCalc© Software, Ostend, Belgium).

Binary outcomes were expressed as relative risk (RR) and 95% confidence limits (95% CI). Continuous outcomes were expressed as standardized mean difference (SMD) and 95% CI. Estimates from included studies were pooled using the fixed-effects (FEM) owing to absence of important heterogeneity across studies.

**3. Results**

The results of meta-analysis for difference of the reflective total nasal symptom score (rTNSS) before and after using INCs alone compared with combination of INAH-INCs Table (1).

There is unimportant heterogeneity Fig (1A) favoring INC/INAH over INCs

Examination of the funnel plot for change in rTNSS showed no evidence of publication bias. Using Trim and Fill these values are unchanged

The results of meta-analysis for difference between groups in improvement of disease –specific Rhinoconjunctivitis quality of life Questionnaire (RQLQ) Table (2) .

There is unimportant heterogeneity Fig (2A) favoring none of the interventions over the other.

Examination of the funnel plot for change in RQLQ showed no evidence of publication bias Using Trim and Fill these values are unchanged.

The results of meta-analysis for diffrence between groups with regard to adverse events

There is unimportant heterogeneity Fig (3A) favoring none of the interventions over the other.

Examination of the funnel plot for incidence of headache,epistaxis,URTI and nausea showed no evidence of publication bias Fig (3A) Fig (4A) Fig (5A) Fig (6A) favoring none of the interventions over the other.

**Table (1)** Change in rTNSS from baseline.

| | | | | 95% CI | | | |
|---|---|---|---|---|---|---|---|
| **Study name** | **SMD** | **SE** | **Variance** | **Lower limit** | **Upper limit** | **Z-value** | **P-value** |
| **Berger 2016** | -0.361 | 0.177 | 0.031 | -0.707 | -0.015 | -2.047 | 0.041 |
| **Julius 1998** | -0.009 | 0.115 | 0.013 | -0.235 | 0.217 | -0.079 | 0.937 |
| **Kim 2015** | 0.000 | 0.153 | 0.024 | -0.301 | 0.301 | 0.000 | 1.000 |
| **Lorenzo 2004** | -0.673 | 0.325 | 0.106 | -1.310 | -0.035 | -2.069 | 0.039 |
| **Meltzer 2012** | -0.213 | 0.103 | 0.011 | -0.414 | -0.012 | -2.076 | 0.038 |
| **Ratner 2013** | -0.428 | 0.200 | 0.040 | -0.821 | -0.036 | -2.139 | 0.032 |
| **Pooled (FEM)** | -0.178 | 0.060 | 0.004 | -0.295 | -0.060 | -2.967 | 0.003 |
| **Heterogeneity test** | | | | | | | |
| **Q-value** | 8.558 | | | | | | |
| **df (Q)** | 5 | | | | | | |
| **P-value** | 0.128 | | | | | | |
| **I-squared (%)** | 41.573 | | | | | | |

SMD = standardized mean difference, SE = standard error, 95% CI = 95% confidence interval, FEM = fixed effect model, Q-value = Cochran Q chi-squared statistic, df = degree of freedom.

**Table (2)** Change in RQLQ score from baseline.

| | | | | 95% CI | | | |
|---|---|---|---|---|---|---|---|
| **Study name** | **SMD** | **SE** | **Variance** | **Lower limit** | **Upper limit** | **Z-Value** | **p-Value** |
| **Julius 1998** | -0.082 | 0.116 | 0.013 | -0.308 | 0.145 | -0.707 | 0.480 |
| **Kim 2015** | -0.180 | 0.154 | 0.024 | -0.482 | 0.121 | -1.174 | 0.241 |
| **Ratner 2013** | -0.335 | 0.199 | 0.040 | -0.726 | 0.056 | -1.680 | 0.093 |
| **Pooled (FEM)** | -0.156 | 0.084 | 0.007 | -0.320 | 0.009 | -1.858 | 0.063 |
| **Heterogeneity test** | | | | | | | |
| **Q-value** | 1.245 | | | | | | |
| **df (Q)** | 2 | | | | | | |
| **P-value** | 0.537 | | | | | | |
| **I-squared (%)** | 0.000 | | | | | | |

SMD = standardized mean difference, SE = standard error, 95% CI = 95% confidence interval, FEM = fixed effect model, Q-value = Cochran Q chi-squared statistic, df = degree of freedom.

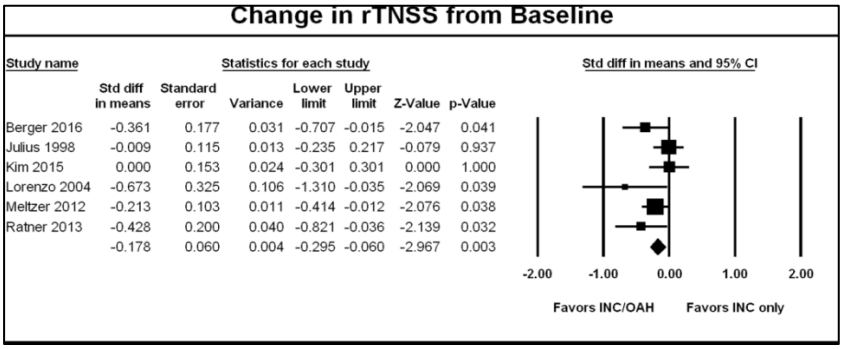


**Fig (1A )** Forest plot for change in rTNSS. There is unimportant heterogeneity (Cochran Q P-value = 0.128, I-squared = 41.517%). Pooling with fixed effect model (FEM) showed standardized mean difference (SMD) of -0.178 (95% CI = -0.295 to -0.060, P-value = 0.003) favoring INC/OAH over INC**.**

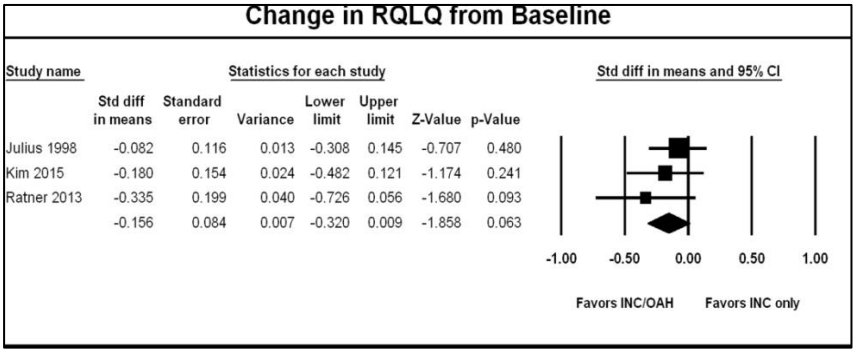


**Fig (2A)** Forest plot for change in RQLQ. There is unimportant heterogeneity (Cochran Q P-value = 0.537, I-squared = 0.000%). Pooling with fixed effect model (FEM) showed standardized mean difference (SMD) of -0.156 (95% CI = -0.320 to 0.009, P-value = 0.063) favoring none of the interventions over the other.

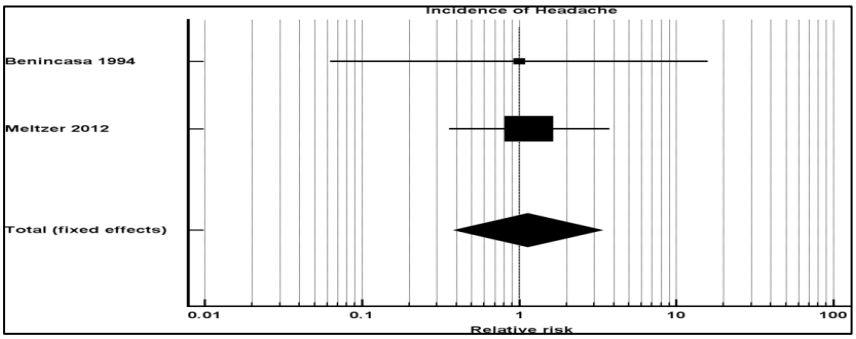


**Fig (3A**) Forest plot for incidence of headache. There is unimportant heterogeneity (Cochran Q P-value = 0.922, I-squared = 0.000%). Pooling with fixed effect model (FEM) showed relative risk (RR) of 1.136 (95% CI = 0.387 to 3.336, P-value = 0.816) favoring none of the interventions over the other.

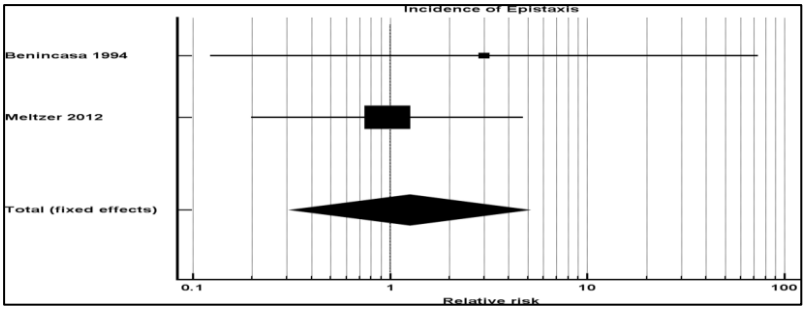


**Fig (4A)** Forest plot for incidence of epistaxis. There is unimportant heterogeneity (Cochran Q P-value = 0.534, I-squared = 0.000%). Pooling with fixed effect model (FEM) showed relative risk (RR) of 1.256 (95% CI = 0.314 to 5.021, P-value = 0.748) favoring none of the interventions over the other**.**

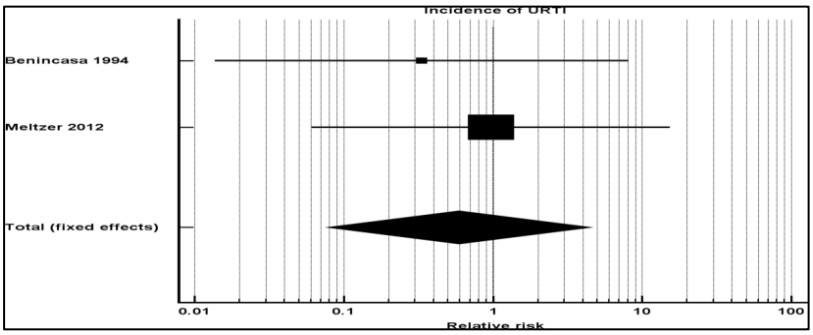


**Fig (5A)** Forest plot for incidence of URTI. There is unimportant heterogeneity (Cochran Q P-value = 0.620, I-squared = 0.000%). Pooling with fixed effect model (FEM) showed relative risk (RR) of 0.590 (95% CI = 0.078 to 4.467, P-value = 0.609) favoring none of the interventions over the other.

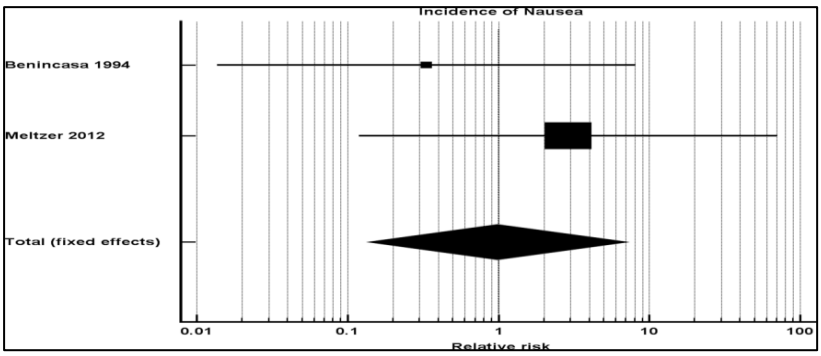


**Fig (6A**) Forest plot for incidence of nausea. There is unimportant heterogeneity (Cochran Q P-value = 0.347, I-squared = 0.000%). Pooling with fixed effect model (FEM) showed relative risk (RR) of 0.985 (95% CI = 0.138 to 7.018, P-value = 0.988) favoring none of the interventions over the other.

## 4. Discussion

The results of this study reveal the beneficial effects of AH-INCS for improving nasal and ocular symptoms in patients with AR. INCS bind to the glucocorticoid receptor. The receptor-glucocorticoid complex modifies the transcriptional activity, which increases the expression of anti-inflammatory molecules and $\beta$-adrenergic receptors and reduces the

expression of pro-inflammatory molecules and cells. These cells include Langerhans cells, lymphocytes, basophils, eosinophils, and mast cells [**5**].

For treatment of nasal allergic symptoms, intranasal AH have shown equality or superiority to oral AH in blinded RCTs [6].

Intranasal AH have a faster onset of action, in the range of 15–30 minutes, compared with 150 minutes via the oral route [7].

Intranasal AH show benefit even in patients who failed via oral AH treatment ,particularly in improvement of nasal congestion [8].

In this meta-analysis , six studies could be involved to assess the effect of combination INCs with OAH in treatment of AR using reflective total nasal symptom score ( rTNSS) .

Six studies (1162 patient ) met the inclusion criteria compared with INCs , AH-INCs decreased total nasal symptom score (rTNSS) (standardized mean difference [SMD ] – 0.178 ; 95% confidence interval [CI] -0.295 to-0.060 ; p=0.003) favoring INCs / OAH over INCs alone or OAH alone.

The results of this study show the benefit of intranasal AH-INCS over oral AH-INCS. The higher concentration of the intranasal AH at the site could provide more effective antihistaminic action. There may be other mechanisms other than antihistaminic activity from the intranasal AH, such as azelastine, as used in some of the studies. Azelastine desensitizes transient receptor potential vanilloid 1 (TRPV1) channels on sensory nerve endings in nasal mucosa. Thus, release of neuropeptides stimulated by the TRPV1 channel is inhibited, subsequently decreasing vasodilation and extravasation and resulting in the improvement of nasal congestion [9].

In this study have we aimed to determine whether the additional effects of AH to INCS may play a role in rapid improvement of allergic symptoms during the 2-week period needed for the INCS to achieve maximum effect. Our findings show greater benefits with use of AH-INCS over INCS alone. The effects were significant only for the INCS and intranasal AH combination. However, all 4 stud- ies assessing this combination only analyzed data at the sin- gle time-point of 2 weeks. It is not known whether these additional effects persist after a 2-week duration. Therefore, the optimal duration of the INCS and AH combination remains inconclusive due to lack of data.

A long-term study of 52 weeks by Price and colleagues compared the effects of intranasal azelastine plus fluticasone propionate vs intranasal fluticasone propionate alone, in 612 patients with chronic rhinitis [10].

They reported beneficial effects favoring AH-INCS. The significant differences on TNSS were found from day 1 and up to 28 weeks before they fluctuated. However, their trial enrolled a mixed population of perennial AR and nonallergic rhinitis patients and did not report separate outcomes of the AR subgroup. Therefore, the study was excluded from the present systematic review.

Our results are in alignment with existing international guidelines. The INCS and intranasal AH combination is recommended by the American Academy of Otolaryngology–Head and Neck Surgery,2 the International Consensus Statement on Allergy and Rhinology,42 the American College of Allergy Asthma and Immunology and ARIA [11].

The effects of intranasal AH- INCS are evident and this combination should play a role in clinical practice when INCS alone has a limitation on allergic symptom improvement. Other conditional recommendations, including immunotherapy, inferior turbinate reduction, or neurectomy, should be considered. This combination of INCS and intranasal AH may be used as a first line for patients with moderate-to-severe, persistent AR. Step-down and step-up approaches should be practical and given accordingly.

Based on our findings, the combination of INCS and oral AH is not recommended, which is consistent with the current international guidelines, including the American Academy of Otolaryngology-Head and Neck Surgery2 and the American College of Allergy Asthma and Immunology [11].

However, the INCS and oral AH combination is conditional for seasonal AR, according to ARIA, and optional for AR, according to the International Consensus Statement on Allergy and Rhinology [12].

This study has limitations, such as the quality of the included studies. About half of the included RCTs have risks of bias in random sequence generation, allocation concealment, and blinding of outcome assessment. Further studies are required. There were insufficient data on the duration of treatment, as the intranasal AH was only assessed over a 2-week duration.

## 5. Conclussions

This systematic review identified 7 studies assessing the effects of H1 antihistamine addition to intranasal corticosteroid for treating AR. Participants included both adults and children. AR was both seasonal and perennial and of differing severity.

The results favor the combination of intranasal AH plus INCS over INCS alone.

Both adult and pediatric patients demonstrated these additional beneficial responses.

There were no differences between use of the oral AH plus INCS combination and INCS alone. Also, we found no differences between the 2 groups with regard to adverse events.

Thus, AH-INCS is superior to INCS alone for treatment of AR.

## References

[1] M.S.Dykewicz, S.Fineman, D.P.Skoner, Diagnosis and management of rhinitis : complete guidelines of the Joint Task Force on Practice Parameter in

Allergy ,Asthma and Immunology , Vol.11, PP.18–97, 1998.

[2] International Rhinitis Management Working Group.International consensus report on the diagnosis and management of rhinitis. Allergy ; Vol.4, PP.1- 34. Pubmed 1994

[3] Kay ABCalderon,M.A.Zapata , R.J.Davies .Treatm ent and management of allergic rhinitis. In: Kay AB, ed. *Allergy and allergic diseases.* Oxford :Blackwell , Vol.88, PP.101-203 ,1997.

[4] B.M.Prenner, .Allergies for all seasons. Allergy Asthma, Vol.6, PP.8–9,1997

[5] N.Mygind, L.P.Nielsen, H.J.Hoffmann, Mode of action of intranasal corticosteroids. *J Allergy Clin Immunol*, Vol.7, PP.6-9, 2001

[6] C.F.LaForce, J.Corren, W.J.Wheeler, Rhini- tis Study Group. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symp- tomatic after treatment with fexofenadine. *Ann Al- lergy Asthma Immunol*. , Vol.11, PP.28–99,2004

[7] P.Patel, P.S.Roland, B.F.Marple, An assessment of the onset and duration of action of olopatadine nasal spray. *Otolaryngol Head Neck Surg*; Vol.3, PP.8-93,2007

[8] W.E.Berger, M.V.White, Rhinitis Study Group. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allergy Asthma Immunol* , Vol.46, PP.89–229, 2003

[9] U.Singh, J.A.Bernstein, L.Haar, Azelastine desensitization of transient receptor poten- tial vanilloid 1: a potential mechanism explaining its therapeutic effect in nonallergic rhinitis. *Am J Rhinol Allergy* , Vol.8, PP.88-109, 2014

[10] D.Price, S.Shah, S.Bhatia, A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. *J Investig Allergol Clin Immunol* , Vol.16, PP.8-9, 2013

[11] M.S.Dykewicz, D.V.Wallace, F.Baroody, Treatment of seasonal allergic rhinitis: an evidence-based focused guideline update. *Ann Allergy Asthma Immunol*, Vol.7, PP.12-66, 2017

[12] S.K.Wise, S.Y.Lin, E.Toskala, International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*, Vol.12, PP.66–99, 2018