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## Intranasal Corticosteroids for the Medical Management of Nasal Polyps in Adults: a Meta-Analysis

### ABSTRACT

**Background:** This systematic review aims to strengthen evidence of beneficial effects of intranasal corticosteroids on the medical treatment of adults diagnosed with nasal polyps.

**Objective:** (1) To determine efficacy of short-term (2-4 weeks) and long-term (4-12 weeks and > 12 weeks) use of intranasal corticosteroids for reduction of polyp size and rhinitis symptoms. (2) To determine difference in efficacy of a 400 and 800 µg dose. (3) To determine adverse effects of intranasal steroids.

**Study Design and Selection Criteria:** Meta-analysis of randomized controlled trials on intranasal steroids for nasal polyps. Patient-oriented outcomes were reduction of polyp size and overall reduction of rhinitis symptoms.

**Search strategy:** Comprehensive search of Cochrane's Controlled Trials Registry (CCTR) Issue 2, 2003, Medline 1966 - 2002, Embase 1974 - 2002, bibliographic review, requests for information from authors and pharmaceutical companies.

**Data collection and analysis:** Sixteen studies were evaluated for inclusion, and trial quality, validity assessment, and completion of data extraction were done. Ordinal data on rhinitis and polyp scores for each study were pooled to generate relative risks. Homogeneity was assessed using approximate chi-square tests. Preset *p* value of < 0.10 was deemed significant for heterogeneity. Data was analyzed using Revman 4.1 (Update Software, Oxford). Sensitivity analysis was done for outcomes with significant heterogeneity.

**Results and Conclusion:** Fourteen studies found significant benefit for the use of intranasal steroids in reduction of polyp size with 2 -4 weeks treatment (RR=3.00; 95% CI: 2.39, 3.77).

Overall rhinitis symptoms decreased significantly (RR=1.64; 95% CI: 1.25, 2.14) with 4-12 weeks treatment, with a tendency for reduction of rhinitis symptoms (RR=1.41; 95% CI: 1.05, 1.91) with more than 12 weeks treatment. Throat irritation was significantly increased (RR=2.06; 95% CI 1.31, 3.25). There was no difference in overall rhinitis symptoms (RR=0.91; 95% CI: 0.77, 1.07) with 400 µg and 800 µg doses.

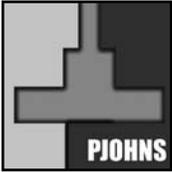
**Keywords:** *polyp, nose, steroids, intranasal steroids, glucocorticosteroid*

**The foremost objective** in the treatment of nasal polyps is their disappearance, if not reduction of polyp size<sup>1</sup>. Although surgical therapy continues to play an important role in the

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management of nasal polyps<sup>2</sup>, there is always the risk of complications and the recurrence rate is about 40 percent<sup>3</sup>.

In clinical practice, the main concern of patients with nasal polyps is reduction of overall rhinitis symptoms that include nasal obstruction, nasal discharge, sneezing, itchiness and anosmia. The goal of treatment of nasal polyps focuses on control of these symptoms and removal of the polyps without causing complications that will be detrimental to health.

Over the past decade, there have been improvements in the medical treatment of nasal polyps. A search made by the Cochrane ENT Registry Group revealed that 24 of the 45 Randomized Controlled Trials (RCTs) showed beneficial results in favor of intranasal corticosteroids.

Topical nasal steroids such as budesonide, betamethasone and fluticasone have been known since the 1960's to cause some polyp shrinkage<sup>4</sup>. Glucocorticoids display a favorable therapeutic profile directly preventing polyp formation and growth and reducing local pathology and inflammatory exudates together with bacterial colonization. Randomized Controlled Trials (RCTs) on intranasal steroids for nasal polyps looked at a variety of clinical outcomes. Studies looking at the same outcome often used different measurement scales. It would be helpful to the clinician if results could be compared across studies.

Because of the growing demand for medical treatment of nasal polyps, intranasal steroids will continue to be a cornerstone of polyp management. It is the aim of this review to quantify the effect of intranasal corticosteroids in terms of improvement of nasal symptoms and reduction in polyp size. A systematic review on RCTs was conducted to determine the favorable dose and duration as well as the occurrence of adverse effects.

**Objectives:** This study aimed to determine the efficacy and safety of intranasal corticosteroid therapy and sought to achieve the following specific objectives:

1. To compare short-term (2-4 weeks) intranasal corticosteroid therapy with placebo in the improvement of clinical outcomes, as measured by
  - a. reduction of polyp size;
  - b. reduction of overall rhinitis symptoms (a combination of nasal obstruction, nasal discharge, itchiness and sneezing); and
  - c. peak nasal inspiratory flow (PNIF)
2. To compare long-term (4-12 and >12 weeks) intranasal corticosteroid therapy with placebo in the improvement of the clinical outcomes stated above.
3. To compare the frequency of adverse effects between intranasal steroids and placebo.
4. To compare 400 µg versus 800 µg intranasal corticosteroids in the improvement of clinical outcomes stated above.

## METHODS

**Identification of Trials:** The electronic bibliographic database MEDLINE/Pubmed was searched for all articles in English using the standardized subject terms "nasal polyps," "intranasal steroids" or "steroids, fluorinated" and "randomized controlled trial" (Publication Type) from years 1970 to 2002.

Communication with the UK Cochrane Center ENT Research Group was done for further comprehensive search of articles especially for non-English titles. The ENT Specialist Registry Group searched the following: (1) Cochrane Central Register of Controlled Trials (CENTRAL), (2) Medline, (3) EMBASE (the Reed-Elsevier Excerpta Medica database) (4) Cumulative Index to Nursing and Allied Health Professionals (CINAHL), (5) Allied and Complementary Medicine (AMED), (6) Meta Register of Clinical Trials (mRCT), and (7) Latin American Caribbean Health Sciences Literature (LILACS). The abstracts retrieved by the Cochrane Group were not limited to RCTs. The bibliographies of candidate RCTs were further reviewed to identify more studies. Full text articles were requested from drug companies and friends from the United States.

**Study Selection:** Three reviewers independently read the methods section of the candidate articles for meta-analysis and applied the stated criteria for inclusion in this review. Disagreements were resolved by discussion until a consensus was reached. The following criteria were used to select the studies for meta-analysis:

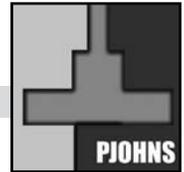
**Study design:** Restricted to randomized, parallel, double blind, placebo-controlled trials on intranasal glucocorticosteroids for nasal polyps.

**Study population:** RCTs on adults clinically diagnosed to have nasal polyps objectively on anterior rhinoscopy and nasal endoscopy in hospital outpatient clinics or specialty private clinics. Individual RCTs were excluded if any of the following patient characteristics were present: previous use of steroids, sinusitis, upper respiratory tract infection, presence of structural abnormality of the nose and significant co-morbidities.

**Types of intervention:** All types of intranasal corticosteroids (e.g. beclomethasone dipropionate, budesonide, and fluticasone propionate) compared to placebo were included. These variables were included; (1) solvent delivery (aqueous or powder); (2) manner of administration (spray, turbohaler); (3) duration of use -- short-term (2-4 weeks) and long-term (4-12 weeks and > 12 weeks); and (4) dosage (400 µg, and 800 µg). The placebo made use of the same method of delivery (isotonic aqueous solution or non-medicated powder), manner of administration, and kind of container.

**Outcome measures:** (1) reduction in size of polyp reported as polyp size score; (2) reduction in rhinitis symptoms; and (3) adverse effects such as epistaxis, nasal itchiness and throat irritation. The effects of duration (2 to 4 weeks, 4 to 12 weeks, and > 12 weeks) and dose (400 µg, 800 µg) of treatment on these outcomes were also studied. PNIF, an objective measure of nasal obstruction, was also included.

**Quality Assessment:** Three reviewers independently assessed the methodological quality of each candidate RCT using the quality assessment tool developed by the Philippine Cardiovascular Research Group (Appendix A).<sup>5</sup> This assessment instrument classified study quality according to selection, performance, detection, and exclusion biases, using A, B, or C ratings where A represents the highest score, B the middle score and C the poorest quality score. Factors checked to determine which bias was present included: allocation concealment for selection bias, blinding of patients for performance bias, dropouts for



Study	No. of patients	Age range (yrs)	Duration of treatment	Drug/ dose ( $\mu$ g)	Outcome			Quality Assessment Score
					Polyp size	Rhinitis symptoms	Adverse effects	
Holmberg, <sup>12</sup> 1997	55	21-71	2 to 4 weeks	fluticasone p aqueous 400 BDP aqueous 400	Y	Y	Y	B
Lund, <sup>13</sup> 1998	29	22-72	2 to 4 weeks 4 to 12 weeks	fluticasone d aqueous 400 BDP aqueous 400	Y	Y	Y	B
Tos, <sup>14</sup> 1998	138	20-82	2 to 4 weeks 4 to 12 weeks	budesonide aqueous 256 budesonide powder 240	Y	Y	Y	B
Lildholdt, <sup>15</sup> 1997	124	20-81	2 to 4 weeks	budesonide powder 400 budesonide powder 800	Y	Y	Y	B
Karlsson, <sup>16</sup> 1982	40	23-79	2 to 4 weeks	BDP aqueous 400	Y	N	N	B
Mygind, <sup>17</sup> 1975	35	19-78	2 to 4 weeks	BDP aqueous 400	Y	Y	N	B
Dingsor, <sup>11</sup> 1985	41	18-73	2 to 4 weeks 4 to 12 weeks	Flunisolide aqueous 200	Y	N	N	B
Virolainen, <sup>18</sup> 1980	40	28-72	2 to 4 weeks $\geq$ 12 weeks	BDP aqueous 400	Y	Y	Y	B
Chalton, <sup>19</sup> 1985	30	14-66	2 to 4 weeks	betamethasone aqueous 200	Y	N	N	B
Holopainen, <sup>20</sup> 1982	19	18-62	2 to 4 weeks	BDP aqueous 400	Y	Y	N	C
Toft, <sup>21</sup> 1982	42	23-78	2 to 4 weeks	BDP powder 400 BDP aqueous 400	N	N	Y	B
Lildholdt, <sup>1</sup> 1995	120		2 to 4 weeks	budesonide aqueous 400 budesonide aqueous 800	Y	Y	N	C
Ruhno, <sup>22</sup> 1990	36	20-68	2 to 4 weeks	budesonide aqueous 800	N	Y	Y	B
Jankowski, <sup>23</sup> 2001	161	18-76	2 to 4 weeks	budesonide 128 BID budesonide 256 OD budesonide 128 OD (all aqueous)	Y	Y	Y	B
Pentilla, <sup>10</sup> 2000	142	22-83	2 to 4 weeks 4 to 12 weeks $\geq$ 12 weeks	fluticasone p aqueous 400 fluticasone p aqueous 800	Y	Y	Y	C
Johansen, <sup>6</sup> 1993	91	18-78	2 to 4 weeks	budesonide aqueous 400	Y	Y	N	B

BDP – beclomethasone dipropionate

Y= Yes, N=no; A, B, C = classification of study quality

exclusion bias, and blinding of examiners for detection bias. The lowest score in any of the four bias groups corresponded to the total score of the assessment. Discrepancies in the ratings of the three reviewers were resolved by the rule of majority.

**Data Extraction:** Data for the specified outcomes were extracted independently by three reviewers based on reported summary statistics (means, SD, proportions). Data measured at several points were grouped into 2-4 weeks, 4-12 weeks and >12 weeks. All data were entered into Revman 4.1 (Update Software, Oxford).

All studies reported polyp size using Johansen's<sup>6</sup> 4-scale classification: 0, no polyps; 1, mild; 2, moderate; and 3, severe. For several rhinitis symptoms, the RCTs utilized 3 different classification schemes, as follows:

(1) Scale of 0 – 3: 0 – None; 1 – Mild; 2 – Moderate; 3 – Severe

(2) Scale of 0 – 5: 0 – Symptoms aggravated; 1–No control of symptoms; 2–Minor control of symptoms; 3 – Substantial control of symptoms; 4 – Total control of symptoms

(3) Johansen scale of 1-4: 1-absent; 2–a few episodes; 3–many

episodes; 4–continuous

These ordinal scores were dichotomized into positive or negative reduction. Positive reduction was defined as any one scale reduction towards benefit or difference before and after treatment. Negative reduction was defined as no reduction or any change in scale towards harm before and after treatment. Disagreements in data extraction were resolved by consensus.

#### Data Analysis

**Study Selection:** Kappa statistic<sup>7</sup> was used to assess the inter-observer agreement for study selection. A value of  $\kappa \leq 1.0$  was considered agreement beyond chance.

**Meta –analysis proper:** Where dichotomous outcome measures could be assessed, the treatment effect was calculated as the difference in relative risk before and after treatment. All analyses were performed according to the intention-to-treat method, i.e. including all randomized patients. Patients with results of no reduction in polyp size or overall rhinitis symptoms were considered as failures. The software package

(Revman 4.1) provided by the Cochrane Collaboration<sup>8</sup> was used. The pooled effect sizes and their corresponding 95% confidence intervals (CI) were reported for each outcome, using the fixed effects model.

The studies were grouped according to the size of the polyp using the classification of Mackay.<sup>9</sup> Small polyps were defined as those with a polyp scale score of one and big polyps as those with a polyp scale score of two and three. Duration and dose of intranasal steroid use were based on previous studies.<sup>10,5,11</sup> Differentiation between the usual dose of 400 µg and a high dose of 800 µg was done because one of the outcome measures was reduction in polyp size. Studies utilizing subjects with smaller polyps may show better results with intranasal steroids.

**Test of heterogeneity among studies:** Homogeneity among studies was tested by the chi-square test, where a  $p < 0.10$  was considered statistically significant. Statistical heterogeneity<sup>7</sup> (differences in the reported effects), methodological heterogeneity (differences in study design) and clinical heterogeneity (differences between studies in characteristics of the participants, interventions or outcome measures)<sup>8</sup> were also explored.

## RESULTS

**Description of the Studies:** The 27 studies were further reviewed by three otolaryngologists/clinical epidemiologists for inclusion or exclusion. Only 16 articles were finally included (Table 1). The kappa coefficient<sup>7</sup> between the two raters was 0.85 (standard error = 0.19), indicating substantial agreement.

The studies totalled 1,170 patients (mean age 49 years, range 14 to 83 years) with bilateral nasal polyps, who had one or more previous polypectomies that complied with the inclusion criteria, and from which we were able to obtain sufficient data either directly or after transforming continuous data to dichotomous data based on our preset definition of outcome measures or after corresponding with the first author or the sponsoring drug companies.

All 16 studies (Table 1) included were done in a multi-center outpatient clinic or specialty private practice (in Europe and Canada where all the studies occurred, these two settings are fairly equivalent and the seven countries included Denmark, Sweden, Canada, United Kingdom, Finland, Norway, France). The patients in the studies reported a history of nasal obstruction, sneezing, nasal discharge and occasionally anosmia. Diagnosis of nasal polyps was made by nasal examination with anterior rhinoscopy and nasal endoscopy, which showed polyps in the nasal cavity. The polyps were then measured using a defined scoring system.<sup>6</sup>

All 16 studies compared intranasal steroids with placebo. Two studies<sup>14,21</sup> showed the effect of different formulations (aqueous versus nonaqueous), three studies,<sup>1,10,22</sup> the effect of different doses (400 µg versus 800 µg), and two studies,<sup>12,13</sup> the effect of different types of steroids.

### Effect of Short-term Intranasal Corticosteroids

#### Reduction in polyp size

Fourteen<sup>1,6,10-20,23</sup> out of 16 included studies compared intranasal

steroids to placebo for 2 to 4 weeks duration. Intranasal steroids showed a clear effect over placebo on polyp size reduction (RR= 3.00, 95% CI: 2.39, 3.77). There was no significant heterogeneity among the trials ( $X^2 = 19.72, p = 0.10$ , Figure 1).

#### Reduction in rhinitis symptoms score

Of the 16 RCTs, 12 reported the effect of steroids administered from 2 to 4 weeks on the overall rhinitis symptoms score. There was significant heterogeneity in the risk of reduction of symptoms ( $X^2=44.08, p < 0.01$ ). The pooled risk of rhinitis symptom reduction was RR = 2.56 (95% CI: 2.13, 3.08).

#### PNIF

PNIF, a continuous variable, was measured in 3 trials<sup>13,10,20</sup>. However, the trials did not report standard deviations or absolute values of test-statistics and  $p$ -values, which are required for pooling studies. The mean difference of PNIF between the steroid and placebo groups could not be calculated without this information.

### Effect of Long-term Use (4-12 weeks and >12 weeks) of Intranasal Corticosteroids

#### Reduction of polyp size, 4 to 12 weeks

Four<sup>10,11,13,14</sup> out of 16 studies showed the effect of intranasal steroids given for 4 to 12 weeks on the reduction of polyp size when combined. There was significant reduction in polyp size that favored steroids over placebo (RR=2.89; 95% CI: 1.99, 4.18). However, a significant heterogeneity across studies was noted ( $X^2 = 11.14, p = 0.01$ ).

#### Reduction of overall rhinitis symptoms, 4-12 weeks

The same four studies<sup>10,11,13,14</sup> reported the comparison of intranasal steroids and placebo in terms of the effect on rhinitis symptoms after 4-12 weeks. Fixed effect analysis demonstrated that intranasal corticosteroids have a beneficial effect over placebo on reduction in rhinitis symptoms (RR=1.64; 95% CI: 1.25, 2.14). There was no significant heterogeneity ( $X^2 = 0.73, p = 0.87$ , Figure 2).

#### Reduction of polyp size, >12 weeks

No study reported effects of treatment of >12 weeks on polyp size.

#### Reduction of overall rhinitis symptoms, >12 weeks

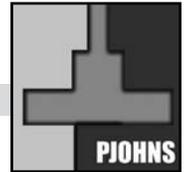
Two studies<sup>10,18</sup> (total n=182) were pooled and showed significant benefit with intranasal steroids versus placebo in reducing rhinitis symptoms when given >12 weeks (RR = 1.41; 95% CI: 1.05, 1.91). Tests for heterogeneity showed the studies were homogeneous and comparable ( $X^2 = 0.81, p = 0.44$ ). However, one study<sup>19</sup> had a lower CI value of < 1 showing no statistically significant effect when analyzed singly (Fig 3).

In summary, the use of intranasal steroids for a longer period of 4-12 weeks and >12 weeks significantly reduced the overall rhinitis symptoms. Studies on polyp size reduction for 4-12 weeks were heterogeneous.

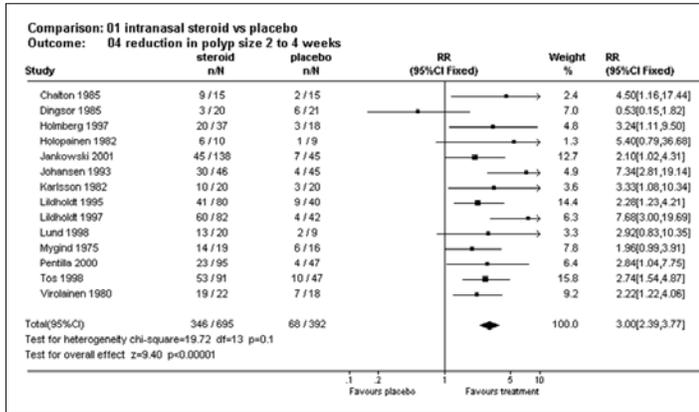
#### Medication Side Effects of Intranasal Steroids

The three most common side effects reported in the 16 randomized controlled trials included were found to be epistaxis or bloody discharge, nasal itchiness and throat irritation.

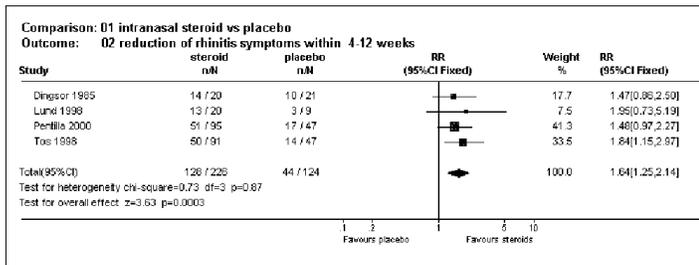
**Epistaxis:** Seven studies reported epistaxis as an adverse effect of intranasal steroids. The risk of epistaxis with the use of intranasal



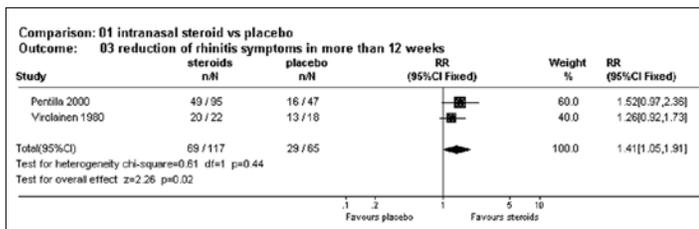
**Fig 1. Reduction of Polyp Size Score, 2 to 4 weeks**



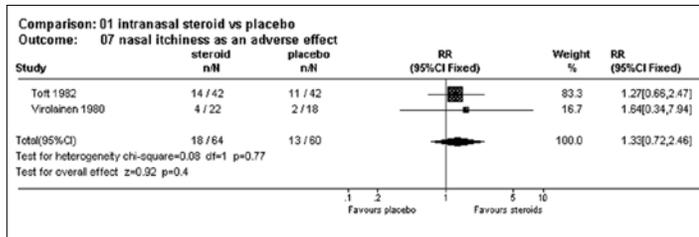
**Fig 2. Reduction of Rhinitis Symptoms, 4 to 12 weeks**



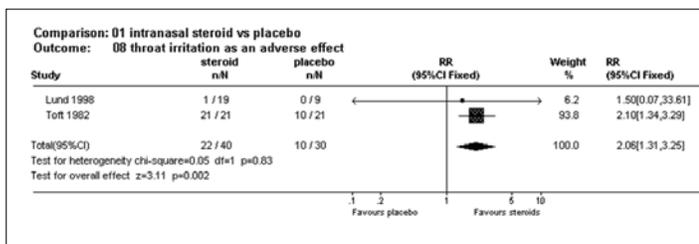
**Fig 3. Reduction of Rhinitis Symptoms, more than 12 weeks**



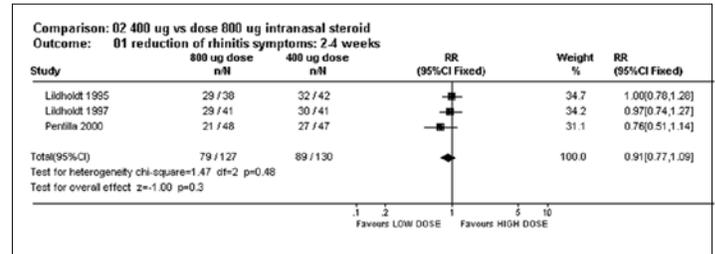
**Fig 4. Nasal Itchiness**



**Fig 5. Throat Irritation**



**Fig 6. Reduction of Rhinitis Symptoms, 400 µg vs. 800µg**



steroids compared to placebo was statistically significant (RR=1.95; 95% CI: 1.37, 2.77). However, this finding is inconclusive because it was noted when pooling the studies heterogeneity ( $\chi^2 = 18.57, p < 0.006$ ).

**Nasal itchiness:** When the two studies<sup>18,21</sup> that reported nasal itchiness as an adverse effect were combined ( $\chi^2 = 0.08, p = 0.77$ ), the results showed that the risk of nasal itchiness did not significantly differ between intranasal steroids and placebo (RR= 1.33; 95% CI: 0.72, 2.45, Fig 4).

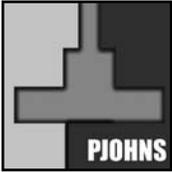
**Throat Irritation:** On the other hand, the risk of throat irritation was greater in patients treated with intranasal corticosteroids than those in placebo (RR = 2.06; 95% CI: 1.31, 3.25). The effect size of the two studies<sup>13,21</sup> were noted to be homogeneous ( $\chi^2 = 0.05, p = 0.83$ , Fig 5).

In summary, the side effect which was significantly greater with the use of intranasal steroids was throat irritation. Nasal itchiness was not significantly different from intranasal steroids as compared to placebo.

**Comparison of 400 µg vs. 800 µg Dose of Intranasal Steroids:** The two different types of intranasal steroids, budesonide and fluticasone were found to have no difference in drug bioavailability, with terminal plasma half life of three hours. The dose delivered per nasal spray actuation was 64 µg/actuation for budesonide and 50 µg/actuation for fluticasone. The dose of intranasal steroids given is determined by the number of sprays delivered into the nasal cavity and the average dose given at 200 to 400 µg, with a maximum high dose of 800 µg per day. Two RCTs<sup>12,13</sup> compared budesonide 400 µg and fluticasone 400 µg on its effect in reduction of polyp size and rhinitis symptoms and showed no significant difference. Comparison of three studies<sup>1,10,15</sup> showed the following results after fixed effect analysis.

**Reduction of polyp size, dose effect:** Three studies<sup>1,10,15</sup> were pooled comparing the 800 µg and 400 µg dose of intranasal steroids on reduction of polyp size which showed RR=1.14 (95% CI: 0.78, 1.66). A test of heterogeneity showed the studies were not comparable ( $\chi^2 = 6.12, p = 0.01$ ) and therefore no conclusions could be made.

**Reduction of rhinitis symptoms, dose effect:** Three studies<sup>1,10,15</sup> were combined to show the effect of dose on rhinitis symptoms with use of intranasal steroids for 2 to 4 weeks duration. Two different



intranasal steroids were represented in the trials, namely budesonide and fluticasone.

There was no significant difference between the 400 µg and 800 µg dose of intranasal steroids on reduction of rhinitis symptoms (RR=0.91; 95% CI: 0.77, 1.09). A test of heterogeneity showed the studies were homogeneous and comparable ( $X^2=1.47, p = 0.48$ , Figure 6).

## DISCUSSION

The medical treatment of nasal polyps with intranasal corticosteroids has been studied extensively showing good clinical outcomes. Given the large quantity of information on intranasal steroids for nasal polyps, this systematic review sought to quantitatively analyze the effect of intranasal corticosteroids on polyp size and rhinitis symptoms. The review focused on the short-term (2 to 4 weeks) and long-term (4-12 weeks and >12 weeks) use of intranasal steroids to address clinician's queries on duration of therapy for optimal results. Since the use of intranasal steroids for nasal polyps in clinical practice has become common, the adverse effects of epistaxis, nasal itchiness and throat irritation were included in this review. The 400 µg and 800 µg (low versus high) dose of intranasal steroids was also compared to determine if greater benefits obtained with increased dose. A total of 16 RCTs were included in this meta-analysis.

**Interpretation of the Benefit of Treatment:** The short-term use of intranasal steroids for 2-4 weeks was significant in the reduction of polyp size, with three times the relative benefit compared to placebo. The anti-inflammatory effect of intranasal steroids immediately showed a response within the first four weeks of treatment for nasal polyps of all sizes.

The studies on long-term use of 4-12 weeks were not conclusive with regards effect on polyp size when analyzed together because they were not comparable following a test of heterogeneity. When sensitivity analysis was done, reduction of polyp size was more visible after four weeks of treatment in big compared to small polyps. Therefore, reduction of nasal polyp size may be achieved with short-term intranasal steroids in small polyps and long-term use for big polyps.

Overall rhinitis symptomatology is a summary of the different symptoms of nasal obstruction, rhinorrhea and sneezing. Overall rhinitis symptoms were significantly reduced by one and half times compared to placebo in all sizes of polyps only with intranasal steroids given over a long-term duration of 4-12 weeks and >12 weeks.

The summary effect on overall rhinitis symptoms for short-term use of 2-4 weeks was not conclusive because of heterogeneity. With sensitivity analysis, the studies with the following characteristics were comparable: small polyp size, date of publication after 1990, non-drug sponsored studies, and sample size < 50. With small polyps, summary effect drastically changed from 2.5 - 4 times benefit. However, for the rest of the factors, summary effect changed from 2.5 -1.5 times. The reduction in overall rhinitis symptoms was more apparent for small polyps compared to big polyps with 2-4 weeks use of intranasal steroids. Positive results for articles published after 1990 may be related to increased awareness of the advantages of intranasal steroids by researchers and clinicians. With these premises, the sensitivity analysis

done was just a theoretical exercise to find out with which factors the studies would be comparable. Still the final summary effect was that the reduction of overall rhinitis symptomatology was seen only for long-term intranasal steroid use over 4-12 weeks and >12 weeks, and not for short-term use of 2 -4 weeks.

The PNIF would have been a good objective measure of nasal obstruction. However, the studies could not be pooled for analysis because the standard deviations or variances were not available, leading to the decision to exclude this measure.

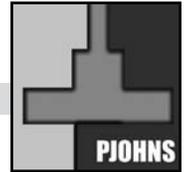
The summary effect showed that there was no significant difference in the reduction of rhinitis symptoms between 400 µg and 800 µg of intranasal steroids with results showing that effects were not dose-related. Reductions in rhinitis symptoms in many patients who use < 400 µg intranasal steroids suggest that dose may not really matter. Because of heterogeneity, the comparative effects of 400 and 800 µg doses on polyp size was also not conclusive.

**Adverse Effects of Treatment:** Significantly, of the three adverse effects included in this review, only throat irritation was most frequently seen with the use of intranasal steroids as compared to use of placebo. Compared to placebo, patients have twice the chance of more symptoms of throat irritation, which may mimic the postnasal drip experienced by patients with rhinitis. In clinical practice, this may be interpreted as postnasal drip or any after-taste from application of the intranasal steroids. Two studies that reported nasal itchiness showed that there was no difference between the treatment and the placebo groups.

Seven studies reported epistaxis but could not be pooled or analyzed because they were positive for heterogeneity. With sensitivity analysis for epistaxis, the studies with the following characteristics were comparable: 1) publications on or earlier than 1990, non-drug company-sponsored studies, small sample size (< 50) and the presence of small polyps. When all of these factors were considered, the studies became homogeneous but there was no significant difference in the frequency of epistaxis between the intranasal steroid and the placebo group. This meta-analysis showed that epistaxis may occur with the use of intranasal steroids or any non-medicated application to the nasal mucosa.

In conclusion, this meta-analysis of 16 randomized clinical trials on intranasal steroids for nasal polyps in adults showed that:

- There is a significant reduction of polyp size with short-term treatment of intranasal steroids at 2 to 4 weeks (RR = 3.0, 95% CI: 2.39, 3.77).
- There is a significant reduction of overall rhinitis symptoms with long-term treatment of intranasal steroids at 4 to 12 weeks (RR = 1.64, 95% CI: 1.25, 2.14) and at more than 12 weeks (RR=1.41, 95% CI: 1.05, 1.91).
- In two studies, throat irritation was reported more frequently with intranasal steroid use than with placebo (RR=2.06, 95% CI: 1.31, 3.25)
- There was no significant difference in nasal itchiness between both the intranasal steroid and placebo groups (RR=1.33, 95% CI: 0.72, 2.45).
- There was no significant difference in the use of 400 µg and 800 µg intranasal steroids in the reduction of overall rhinitis symptoms (RR = 0.91, 95% CI: 0.77, 1.09).



• The PNIF would have been a good objective way to measure nasal obstruction. However, the studies could not be pooled for analysis because of missing information either on the variance, the test-statistic or the *p*-value.

### Recommendations

**Implications for Practice:** This meta-analysis documented quantitative evidence to recommend intranasal steroid therapy use for nasal polyps in adults for a short duration of 2-4 weeks to reduce polyp size and 4-12 weeks and >12 weeks to reduce rhinitis symptoms. Adverse effects are minimal and should not inhibit the clinician from prescribing intranasal steroids when clinically warranted.

**Recommendations for Research:** Documentation of new and unusual adverse effects of long-term intranasal steroid administration such as fungal infection is recommended. The benefit of intranasal steroids in children should be looked into to check the reliability of reports of increased recurrence rate of polyps after surgical removal in children.

Following conclusion of this meta-analysis, the searches were re-run for primary studies up to October 2007 using the same strategies, yielding four studies that have since been published.<sup>24, 25, 26, 27</sup> These four studies should be subjected to the same criteria for inclusion in this review in order to compare their findings with ours.

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