Oral and intranasal steroid treatments improve nasal patency and paradoxically increase nasal nitric oxide in patients with severe nasal polyposis*

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Summary

Introduction: Recently, we demonstrated that acoustic rhinometry (AR) measurements correlated with nasal cavity volumes in patients with nasal polyposis (NP). The aim of the present study was to evaluate whether AR and nasal nitric oxide (nNO) are useful methods in monitoring and follow-up of medical treatment of NP.

Material and methods: Patients with severe nasal polyps were randomized into two groups after a 4-week steroid washout period (w0): a treatment group received oral prednisone for 2 weeks (w2) and intranasal budesonide for 12 weeks (w12) while the control group received no steroid treatment. Nasal volume (vol $_{0\text{-}6}$), minimum cross-sectional area (mCSA), nNO, peak nasal inspiratory flow (PNIF), nasal obstruction, and smell loss were evaluated.

Results: At w2, the treatment group showed a significant increase of vol 0-6 compared to w0 and the control group. The mCSA area also increased compared to w0 and the control group. At w12, the improvement in vol $_{0\text{-}6}$ and mCSA was maintained after intranasal steroids compared to w0. At w2, the treatment group showed a paradoxical increase of nNO compared to w0 and the control group. At w12, this increase was maintained by intranasal steroids.

Conclusion: Both oral and intranasal steroid treatments improve nasal patency and paradoxically increase nNO, by opening the ostiomeatal complex. This suggests that AR and nNO are useful methods in the monitoring and follow-up of patients with NP.

Key words: acoustic rhinometry, medical treatment, nasal polyposis, nitric oxide

Introduction

Nasal polyposis (NP) is an inflammatory condition of unknown aetiology, which is present in 2 - 4% of the European adult population [1,2]. NP is often associated with asthma and other respiratory diseases [3]. Smell loss and nasal obstruction are the most frequent complaints in patients with nasal polyps, often being the first symptoms of the disease and having a negative impact on quality of life [4-8].

Several objective tools have been used to evaluate nasal obstruction such as computed tomography (CT), magnetic resonance images (MRI), acoustic rhinometry (AR), rhinomanometry, and peak nasal inspiratory flow (PNIF). However, CT of the paranasal sinuses has become the method of choice for the radiological evaluation of NP and has a strong correlation with nasal endoscopy [4]. Paranasal sinus CT scan provides objective evidence for topographic diagnoses and is useful before endoscopic sinus surgery. It can also be used for staging of NP [1]. AR

is a technique that provides accurate measurements of nasal cavity geometry via analysis of reflected acoustic impulses. AR is a non-invasive, simple, rapid, inexpensive and reliable method that can be performed easily with minimal patient cooperation. The correlation between the outcomes found with rhinomanometry and AR and an individual's subjective sensation of nasal patency remains uncertain [9]. AR has been used for characterizing the geometry of the nasal cavity, for assessing the dimensions of nasal obstruction and for evaluating surgical results and patient response to medical treatment [10].

The measurement of nasal nitric oxide (nNO) concentrations has evoked interest as a non-invasive and simple diagnostic tool for upper and lower respiratory tract disorders. In the sinuses, nNO levels have been reported to be several-fold higher than in the nose. This has led to the suggestion that the paranasal sinuses are the main site for nNO production within the airways [11].

Although AR has been used to study different nasal conditions its accuracy in patients with NP remains unclear. Recently, we demonstrated that AR measurements, especially nasal volumes between 0 and 5 (vol $_{0\text{-}5}$), reflect reasonably well the nasal cavity volumes in patients with NP [12].
The aims of this study were: 1) to evaluate whether AR and nNO are useful methods in the monitoring and follow-up of medical treatment of nasal polys; and 2) to study correlations between AR with PNIF, CT scan, polyp size, symptoms and nNO.

Methods

Study population

Patients with moderate to severe nasal polyps (n = 62) were included in this prospective and randomized study (mean age was 49 ± 13 yr, ranging from 30 to 81 yr, 30% female). Among them 57% had asthma, while 26% had aspirin sensitivity. After a 4-week steroid washout period (w0) patients were randomized into two groups: treatment group (n = 46) received oral prednisone for 2 weeks (w2) (30 mg daily for 4 days, followed by progressive reduction of 5 mg every two days) and intranasal budesonide 400 µg twice a day for 12 weeks (w12); and control group (n = 16) received no steroid treatment. There were no differences between the two groups regarding age, gender, or disease severity. Approval for this study was obtained from the local Ethics Committee of our institution and a signed informed consent was obtained from all patients.

Inclusion and exclusion criteria

The diagnosis of NP was based on the EP^{3}OS criteria: nasal congestion in combination with nasal discharge, ± facial pain/pressure, ± reduction or loss of smell for more than 12 weeks, and presence of both nasal polyps by nasal endoscopy and mucosal changes within the ostiomeatal complex and/or paranasal sinuses by CT scan [1]. Neither intranasal steroids nor asthma treatment were modified during the study, and none of the patients received treatment with leukotriene antagonists. Patients with non-eosinophilic polyps were not included in this study.

Study design

AR, nNO, PNIF, paranasal sinus CT scan, nasal symptoms score, and nasal endoscopy were assessed in all NP patients included in the study. These tests were conducted without vasoconstrictor. One third of all patients (n = 18) were randomized to the control group, and 2 patients dropped out of the study. Owing to our ethics committee's concerns about keeping patients more than 6 weeks without known effective treatment, patients of the control group were not further evaluated. Among the patients included in the study, a total of 13 patients had had previous sinus surgery, but there were no differences between operated and non-operated patients.

Acoustic rhinometry

Nasal volume was measured by acoustic rhinometry (Acoustic rhinometer SER 2000 RhinoMetrics, Lynge, Denmark). All measurements were performed after a short period of acclimatization to minimize the effects of physical stress and temperature changes. The measurements were performed during a breathing pause while patients were in a sitting position. All AR measurements were repeated three times in order to ensure the reproducibility of the results. The default software settings were used for the parameters of most interest, which were the minimum cross-sectional area (mCSA) and nasal cavity volume from 0 to 6 cm (vol $_{0\text{–}6}$) from the end of the nosepiece [13]. Repeated measurements were performed and the mean of three values was recorded for mCSA and vol $_{0\text{-}6}$.

Nasal nitric oxide (nNO)

nNO determination was performed by chemiluminescence (SIR, System N6008 NO tracer, Madrid, Spain) following a standardized method and was repeated three times to ensure the reproducibility of the results [11]. The mean of three recordings was used as the estimate of the nNO level. The patient was asked to take a deep breath and to hold it to keep the soft palate closed while samples were taken from the nostril. This was confirmed by the absence of a CO_2 increase during sampling.

Peak nasal inspiratory flow (PNIF)

Youlten peak flow meter (In-Check®; Clement Clarke, Harlow, UK) was used to assess nasal resistance. PNIF measures were based on the manufacturer's recommendation. As such, participants used a facemask sealed around the nose and mouth, closed their mouth, and inhaled forcefully through the nose. For each assessment, 3 measurements were performed, the

maximal one of which was considered for evaluation.

Nasal symptoms

The intensity of nasal obstruction and loss of smell was scored as follows: 0, no symptom; 1, mild symptom; 2, moderate symptom; and 3, severe symptom.

Radiologic staging

A CT scan of paranasal sinuses was performed in all patients and was blindly staged by the same radiologist using the Lund-Mackay scoring system: 0, no opacity; 1, partial opacity; and 2, total opacity for each of the sinuses. In addition, the ostiomeatal complex was scored 0 for no obstruction or 2 when obstructed. The system has a bilateral total score of 24 [14].

Statistical analysis

The data are presented as mean ± SD (standard deviation). Nonparametric tests such as the Mann-Whitney *U* test, the Wilcoxon signed ranks test, and Kruskal-Wallis test were applied for data that did not follow a normal distribution. Pearson correlation coefficients were used to examine the association between AR and gender, age, nasal symptoms, nNO, PNIF, and CT scan. A p-value of less than 0.05 was considered statistically significant.

Results

Acoustic rhinometry

Before treatment, there were no significant differences between the treatment group and control. At w2, the treatment group showed a significant increase of vol $_{0\text{-}6}$ (21.5 ± 6.1; $p < 0.05$) compared to w0 (13.8 ± 5.4 cm^3) and to control group (11.2 ± 4.8 cm^3) (Figure 1). The mCSA area also increased (1.4 ± 0.3 cm^2; $p < 0.05$) compared to w0 (0.9 ± 0.4 cm^2) and to control group (0.7 ± 0.4 cm^2). At w12, the improvement in vol $_{0\text{-}6}$ (20.7 ± 6.9 cm^2; $p < 0.05$) and mCSA (1.3 ± 0.2 cm^2; $p < 0.05$) was maintained after intranasal steroids compared to w0 (Figure 2). Vol $_{0\text{-}6}$ and mCSA had an inverse correlation with nasal polyp size before treatment ($r = -0.63$; $p < 0.05$ and $r = -0.72$; $p < 0.05$, respectively) and after treatment ($r = -0.45$; $p < 0.05$ and $r = -0.52$; $p < 0.05$, respectively).

Nasal nitric oxide (nNO)

Before treatment, there were no significant differences between the treatment group and control. At w2, the treatment group showed a paradoxical significant increase of nNO (671 ± 411 ppb; $p < 0.05$) compared to w0 (439 ± 262 ppb) and to control group (420 ± 97 ppb). While at w12, this increase was maintained by intranasal steroids (635 ± 320 ppb; $p < 0.05$) (Figure 3). At w2, there was a direct correlation between nNO and vol $_{0\text{-}6}$ ($r = 0.61$; $p < 0.05$).

Peak nasal inspiratory flow (PNIF)

Before treatment, there were no significant differences between the treatment group and control. At w2, the treatment group showed a significant increase of PNIF values (138 ± 36 l/min) compared to w0 (79 ± 43 l/min) and to control group (93 ± 24 l/min) while intranasal steroids maintained this increase (131 ± 40 l/min) at w12 (Figure 4). After treatment there was a direct correlation between PNIF and vol $_{0\text{-}6}$ ($r = 0.46$; $p < 0.05$).

Nasal symptoms

Patients scored the loss of sense of smell as the most intense complaint (2.6 ± 0.6) followed by nasal obstruction (2.5 ± 0.7). Oral steroids improved ($p < 0.05$) nasal obstruction (1.2 ± 0.8) and sense of smell (1.6 ± 0.6), while intranasal steroids (w12) maintained the improvement only on nasal obstruction (1.4 ± 0.6) at w12. There was an inverse correlation between vol $_{0\text{-}6}$ and nasal obstruction ($r = -0.8$; $p < 0.05$) and sense of smell score ($r = -0.7$; $p < 0.05$). After treatment, sense of smell has an inverse correlation with nNO ($r = -0.45$; $p < 0.05$)

CT scan score

Before treatment, the total CT scan score was 18.3 ± 4.7 for all nasal polyp patients, with no difference between treatment and control groups. At w12, oral and intranasal steroid treatment resulted in a significant reduction of the CT scan score (15.1 ± 4.2, $p < 0.05$) compared to w0. Before treatment, the CT scan score had an inverse correlation with vol $_{0\text{-}6}$ ($r = -0.73$; $p < 0.05$) and a direct correlation with nasal obstruction ($r = 0.41$; $p < 0.05$) and sense of smell ($r = 0.54$; $p < 0.05$). After treatment, there was inverse correlation between the CT scan of the anterior ethmoid and vol $_{0\text{-}6}$ ($r = -0.46$; $p < 0.05$) and nNO ($r = -0.61$; $p < 0.05$).

No significant differences on vol $_{0\text{-}6}$, mCSA, nNO, PNIF, and polyp size were found at w0, w2 and w12 between males and females, asthmatic and non-asthmatic, aspirin-tolerant and aspirin–sensitive patients, or between treatment and control groups.

Discussion

The main findings of our study are: 1) both oral and intranasal steroid treatments reduce nasal patency and paradoxically increase nNO by opening the ostiomeatal complex, suggesting that AR and nNO are useful methods in monitoring and following-up patients with NP; and 2) nasal patency correlates inversely with nasal polyp size and CT scan, suggesting that AR may be a useful objective method in monitoring response to medical treatment, and, in combination with endoscopy it may be cheaper, easier and less prone to risk than CT scan.

Muñoz-Cano et al., [12] evaluated 29 patients diagnosed with NP by nasal endoscopy. They studied the accuracy of AR compared with paranasal sinuses CT scan in the diagnosis and follow up of

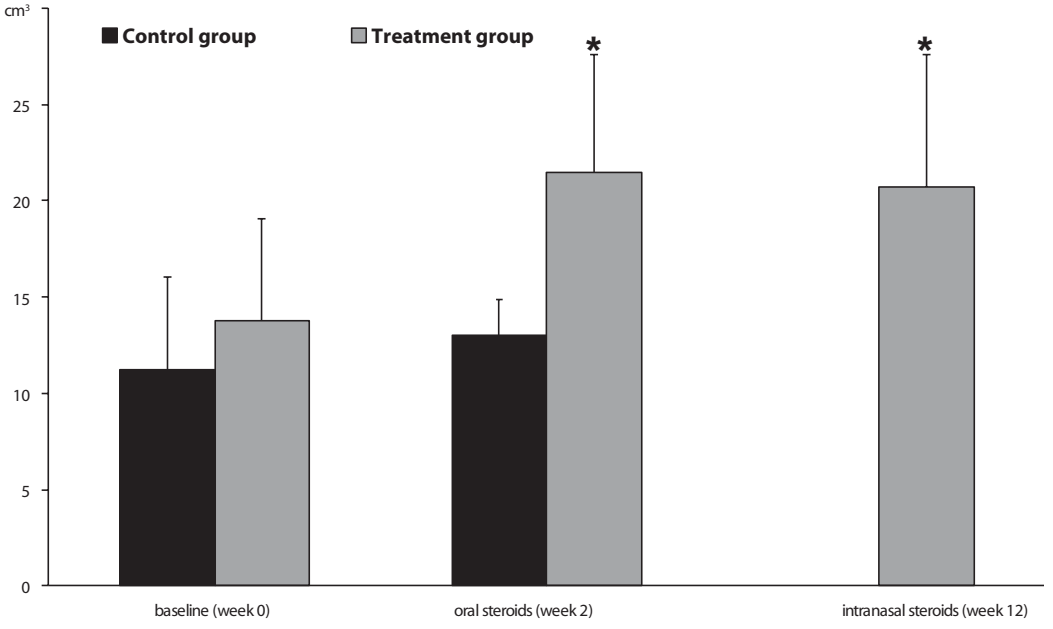

Figure 1. Acoustic rhinometry (vol $_{0\text{-}6}$). Effect of oral (week 2) and intranasal (week 12) steroids compared to week 0. * $p < 0.05$, weeks 2 and week 12 compared to week 0.

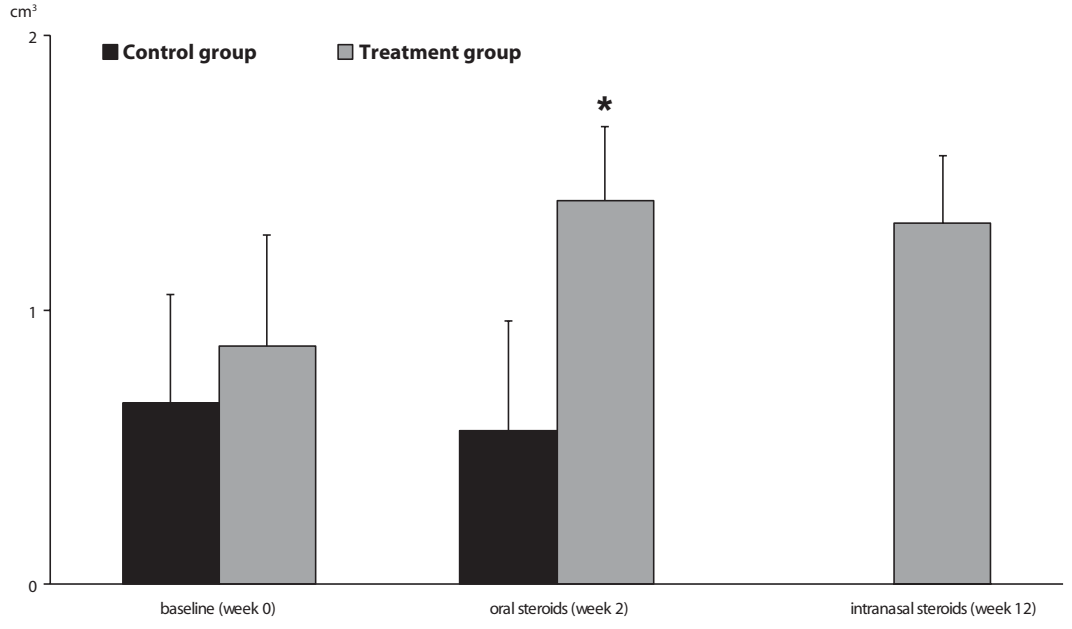

Figure 2. Acoustic rhinometry (minimum cross-sectional area). Effect of oral (week 2) and intranasal (week 12) steroids compared to week 0. * $p < 0.05$, weeks 2 and week 12 compared to week 0.

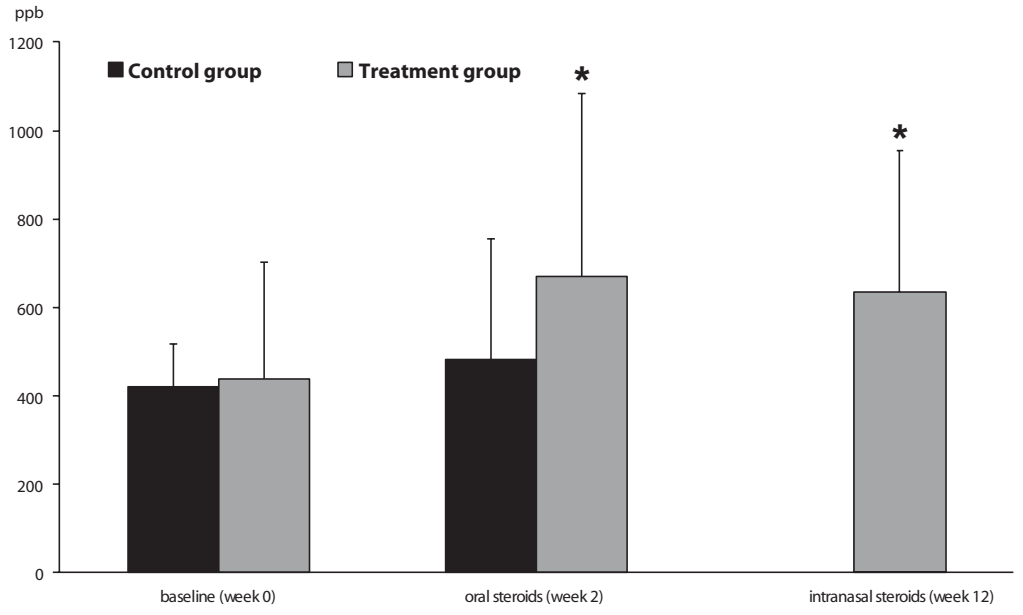

Figure 3. Nasal nitric oxide. Effect of oral (week 2) and intranasal (week 12) steroids compared to week 0. * $p < 0.05$, weeks 2 and week 12 compared to week 0.

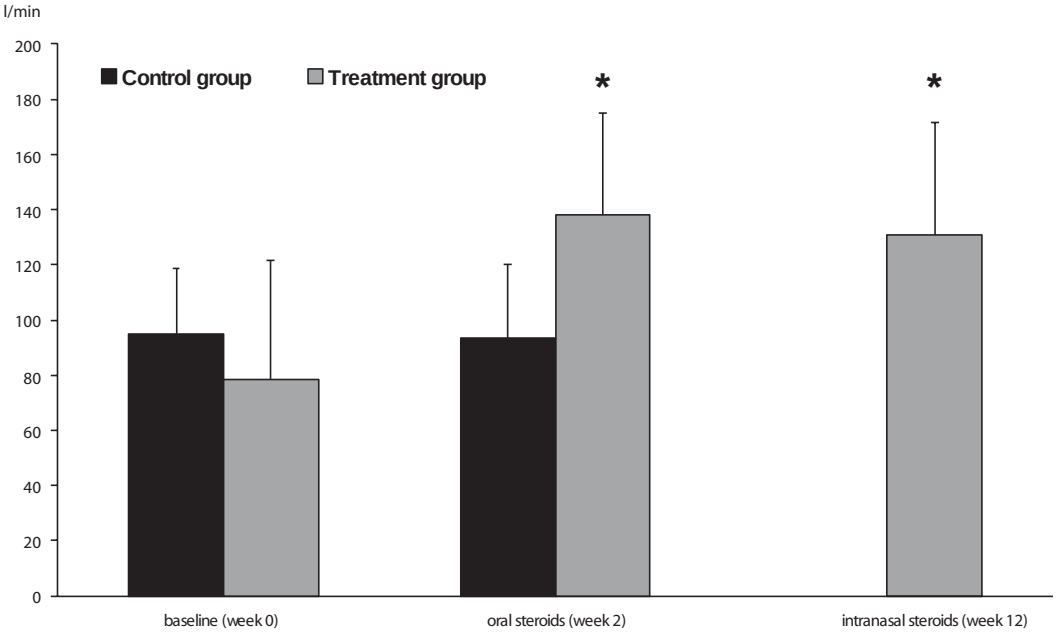

Figure 4. Peak nasal inspiratory flow. Effect of oral (week 2) and intranasal (week 12) steroids compared to week 0. * $p < 0.05$, weeks 2 and week 12 compared to week 0.

nasal polyps. They concluded that AR measurement accurately reflects the nasal cavity volumes with a better assessment of the anterior chamber. Kjaergaard et al., [15] conducted a large cross sectional study including 2,536 consecutive adult patients who were evaluated for chronic nasal or sleep-related complaints. Using the nasal congestion index to measure subjective nasal obstruction and AR objective nasal obstruction, they found a highly significant association between nasal congestion index, mCSA and nasal cavity volume confirmed by linear and logistic regression.

Elbrond et al., [16] used AR, PNIF and nasal index questionnaire to evaluate the effect of intramuscular steroid injection in eight patients with recurrent NP. The authors demonstrated a significant relationship between these three parameters before and after systemic treatment with steroids. They concluded that AR provided an accurate and objective method for measuring the geometry of the nasal cavity before and after treatment for processes which block the nasal cavity. Ragab et al., [17] compared the medical (12-week course of erythromycin, alkaline nasal douche, and intranasal corticosteroid preparations) and surgical treatment (endoscopic sinus surgery) of polypoid and nonpolypoid chronic rhinosinusitis (n = 90). Almost all the subjective and objective parameters improved significantly in both groups, with no significant difference being found between the medical and surgical groups, except for the total nasal volume, in which the surgical treatment demonstrated greater changes.

Akarcay et al., [18] investigated the objective and subjective outcomes in NP with (n = 21) or without asthma and allergy (n = 12) after surgery. Recovery was statistically significant in all observed evaluations for endoscopic and radiologic staging, nasal obstruction, and sense of smell compared with the first evaluation in all patients regardless of the subgroups. Total nasal volumes measured by AR increased in all evaluations for both subgroups. O´Flynn [19] used AR to assess the change in nasal cavity volume following intra-nasal polypectomy in 20 subjects. He obtained a significant correlation comparing the volumes of the polyps removed surgically with the volume change recorded by AR. Tosun et al., [20] evaluated the impact of endoscopic sinus surgery with polipectomy on sleep-related breathing disorders in 27 patients with chronic nasal obstruction for more than 6 months and at least 50% of nasal obstruction of each nasal passage due to nasal polyps on endoscopic examination. They used AR to assess the cross sectional area and total nasal volume, and their results showed a significant increase in both parameters comparing pre- and postoperative time. Papp et al., [21] compared nasal air conditioning in patients with chronic rhinosinusitis and NP with healthy control subjects without nasal pathologic conditions. They studied 25 patients and assessed intranasal volume of the nasal cavity (22 and 54 mm from the nasal entrance), and results revealed a significant increase comparing pre- and postoperative values.

nNO is produced in the respiratory tract, with a major contribution from the upper airways especially the maxillary sinuses [22]. Although NP is an inflammatory disease and we might expect high nNO levels, some studies have found a decrease in nNO [22]. This paradoxical finding may be explained by the fact that a complete obstruction of the ostiomeatal complex by nasal polyps prevents the release of nNO from maxillary sinuses to nasal cavities. Muñoz-Cano et al., [12] concluded that the correlation between nNO levels and volumes measured by AR was not statistically significant. Although the response of nNO in our study is paradoxical, it could provide a useful method for assessing response to treatment of NP as an indirect marker of the permeability of the ostiomeatal complex. Ragab et al., [24] investigated the response to montelukast as an add-on therapy to topical and inhaled corticosteroids in 44 patients with NP and asthma. AR and nNO levels did not change significantly in any group. However, correlations were seen between nNO levels and polyp scores, and between nNO levels and AR changes. Ragab et al., [25] studied 90 patients with NP treated either medically or surgically, with follow up at 6 and 12 months. They showed that nNO levels correlated inversely with CT scan changes. The percentage rise in nNO seen on both medical and surgical treatment correlated with changes in symptom scores, saccharin clearance time, and polyp size. There was no significant correlation with age, sex, smoking or allergy.

Conclusion

These results show that both oral and intranasal steroid treatments improve nasal patency and paradoxically increase nNO, by opening the ostiomeatal complex, suggesting that AR and nNO are useful methods in the monitoring and follow-up of patients with NP.

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