



Original research article

The effect of medical treatment on nasal exhaled nitric oxide (NO) in patients with persistent allergic rhinitis: A randomized control study

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ABSTRACT

Purpose: This study aimed to evaluate the role of nasal nitric oxide (NO) in the management of patients with persistent allergic rhinitis (PER).

Methods: It was a randomized and comparative study. The study subjects were classified as controls (healthy subjects) or patients with PER based on defined criteria. All clinical, functional and biological data were collected for analyzing. Nasal fractional exhaled nitric oxide (FENO) was measured by electroluminescence device. Patients with PER were randomized for treatment with antihistamine (ATH) combined with leukotriene receptor antagonists (LRA) or only with intranasal steroids (INS).

Results: During two years, 501 subjects were included: 234 control subjects and 267 patients with PER. The levels of nasal NO, total IgE, blood eosinophil counts, and apnea-hypopnea index (AHI) in patients with PER were higher than controls ($P < 0.001$; $P < 0.05$; $P < 0.05$; $P < 0.01$; respectively). There were statistically significant correlations between nasal NO, nasal peak flows, total IgE, and blood eosinophil counts in patients with PER ($R = -0.687$ and $P = 0.0012$; $R = -0.643$ and $P = 0.0018$; $R = 0.432$ and $P = 0.0024$; $R = 0.445$ and $P = 0.002$; respectively). After 6 months of treatment, patients treated with INS had greater improvement of clinical symptoms and reduction of nasal NO values than patients treated with ATH + LRA (985 ± 253 vs. 732 ± 298 ppb; $P < 0.05$).

Conclusion: Nasal NO measurement is a useful tool for the follow-up of patients with PER. It also helps clinicians to estimate the level of response to treatment in patients with PER.

1. Introduction

Allergic rhinitis (AR) is a very common disease worldwide. This disease affects more than 25% of population in the world and continues to increase [1]. AR is defined as an inflammatory and IgE-mediated disease, characterized by typical symptoms that include nasal congestion (blocked nose), rhinorrhea (runny nose), sneezing, and/or nasal itching. These symptoms occur when AR patients inhale airborne allergens (aeroallergens), such as animal hair or pollens. Depending on the triggering allergen and the frequency of symptoms, AR may be classified as seasonal (usually due to pollens), perennial (exposure to dust mites), or intermittent (episodic allergic environment) [2]. This classification helps physicians to have the most appropriate treatment strategies for patients with AR. The Allergic Rhinitis and its Impact on Asthma (ARIA) group proposed a new classification based on the

duration and severity of symptoms; AR is classified into the intermittent (IAR) or persistent (PER) according to the duration of symptoms [3]. Unfortunately, patients with PER due to an inadequate therapy may have the impairment of quality of life and loss of working days and productivity, or school attendance and learning performance for children [4,5].

The diagnosis of patients with PER is mainly based on clinical symptoms as described above and as recommended by many academic societies [2,6,7]. However, the paraclinical diagnosis of PER should be combined with different laboratory tests such as total IgE dosage, blood eosinophil count, or skin prick test (SPT) to evaluate the allergy status. Recently, an increase of evidence suggests that the measurement of nasal nitric oxide (NO) might be a useful tool for diagnosis of patients with AR. In these patients, NO is produced mainly from nasal epithelial and inflammatory cells, mediated by inducible nitric oxide synthase

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(iNOS), triggered by aeroallergens [8,9].

Currently, the treatment of patients with PER includes oral antihistamines (ATH), intra-nasal steroids (INS), or leukotriene-receptor antagonists (LRA) [2,10,11]. Although LRA is usually prescribed in AR with asthma in Western countries, in some Asian countries, this drug is preferred for treating PER due to its oral administration. In some other countries, the use of oral antihistamine is usually considered as the first line treatment of patients with PER. However, the therapy based on oral antihistamine has been reported as inadequate treatment for controlling the symptoms of patients with PER. In addition, there are few studies about the role of biomarkers used to predict the response to treatment of patients with AR, especially of those with PER. This study aimed to evaluate the role of nasal NO as a biomarker for evaluating the efficacy of treatment in patients with PER, who were treated with INS or ATH combined with LRA.

2. Patients and methods

2.1. Patients

Patients included in this study were pre-selected from three different centers and referred to the Clinical Research Center of LD Medical College for diagnosis with PER between March 2015 and March 2017. We included 520 subjects over 18 years of age in the present study, however, there were only 501 patients who completed 6 months of follow-up, including 234 control patients and 267 patients with PER. Patients with PER were randomized and treated with ATH + LRA (126 patients) or with INS alone (141 patients). The patients ($n = 19$) who were lost to follow-up included 16 patients treated with ATH + LRA and 3 patients treated with INS alone.

2.1.1. Inclusion criteria

Based on the ARIA guidelines [3], patients with allergic symptoms (nasal congestion, runny nose, nasal itching, or sneezing) lasting more than 4 days per week and more than 4 consecutive weeks were classified into the PER group. They were divided into mild and moderate/severe PER according to the severity of the symptoms. Patients with symptoms present but not troublesome (causing sleep disturbance, impairment of daily activities/leisure and/or sport, impairment of work) were classified as mild PER; those with one or more symptoms that were troublesome were classified as moderate/severe PER.

All study patients (control and PER patients) were evaluated using the Score for Allergic Rhinitis (SFAR) [12], including the following eight components: 1) nasal symptoms in the past year (sneezing, runny nose, and nasal congestion); 2) nasal symptoms accompanied by itchy watery eyes (rhinoconjunctivitis); 3) months of the year in which the nasal symptoms occur; 4) triggers of nasal symptoms (pollens and house dust); 5) perceived allergic status; 6) previous medical diagnosis of allergy; 7) previous positive tests of allergy; and 8) familial history of allergy.

The Visual Analogue Scale (VAS; 0–10 cm) was used to measure the severity of each symptom and the total severity of PER as defined by ARIA guidelines: mild: VAS = 0–3 cm; moderate: VAS = 3.1–7 cm; severe: VAS = 7.1–10 cm [3,13].

The Total Nasal Symptom Score (TNSS) was used to measure the severity of AR and it included the following five symptoms: nasal congestion, runny nose, nasal itching, sneezing, and difficult sleep. The symptoms were rated 0–3 for each symptom (none = 0, mild = 1, moderate = 2, severe = 3) and 0–15 for total score.

As the control group, we included healthy subjects without AR aged over 18 years old. They were excluded from the study if they had SFAR ≥ 1 .

2.1.2. Exclusion criteria

The following exclusion criteria were used in our study: acute or chronic cardio-respiratory diseases (acute myocardial infarction, severe

coronary disease, chronic heart failure, COPD), asthma, AR treated with oral corticosteroids, septal deviation or nasal polyp diagnosed by Ear-Nose-Throat (ENT) specialists, upper respiratory tract infection in the past 15 days. Patients who were unable to undergo the laboratory tests were also excluded from the study.

2.1.3. Ethical issues

The protocol of the study was approved by Lam Dong Medical College, Vietnam (approval number: CDYTL04.2015-NCKH) and signed written informed consent was obtained from all the study participants. The study was conducted in line with the principles of the 1964 Declaration of Helsinki with its later amendments.

2.2. Methods

2.2.1. Study design

It was a randomized and comparative study. The study subjects were classified as controls (healthy subjects) or uncontrolled PER who were then randomized and treated with antihistamine (ATH: desloratadine) combined with leukotriene receptor antagonist (LRA: montelukast), or with intranasal steroid alone (INS: fluticasone propionate) according to the inclusion criteria. The treatment with ATH + LRA or INS alone depended on the severity of PER at inclusion or on the patients' choice for oral or intranasal drug administration. They were followed-up for 6 months. All data of clinical characteristics and laboratory tests were collected for analyzing.

2.2.2. Laboratory techniques

All the following parameters were measured at admission in patients with PER and in the control subjects, and 6 months after the randomized treatment in those with PER.

We measured nasal peak inspiratory flow (PIF) and peak expiratory flow (PEF) by Mediflux Device (Mediflux, Bry sur Marne, France). We diagnosed normal or obstructive or restrictive ventilatory disorders by spirometry using Blue Spiro or Body Box 500 (Medisoft, Sorinnes, Belgium).

Nasal fractional exhaled nitric oxide (FENO) was measured with constant aspiratory flow using Hypair FeNO⁺ Device (Medisoft, Sorinnes, Belgium). In brief, first, patient connected a catheter to one of the nostrils. Next, the air from the nasal cavity was continuously aspirated and measured by NO electrochemical sensor. During the analysis, study subjects breathed continuously through an expiratory brake so that the velum was closed to prevent any contamination of nasal air with the air coming from the lower airways. The aspiration flow rate of 100 mL/s was used to measure nasal NO. The concentration of NO in the lower airways was measured with multiple flow rates for bronchial FENO alveolar concentrations of NO (CANO). The technique of nasal NO measurement was conducted according to manufacturer's instructions and as recommended by the ATS/ERS guidelines [14]. All the data were reported by Expair Software (Medisoft; Sorinnes, Belgium).

In- or out-laboratory overnight polysomnography (PSG) or respiratory polygraphy (RPG) was performed for each study subject using Alice PDx (Philips, USA) as described previously [15]. The recorded and analyzed parameters included apnea-hypopnea index (AHI), type of apnea (central apnea, obstructive apnea, or mixed apnea), snoring, oxygen saturation (SpO₂), and minimum SpO₂ (nadir SpO₂).

The SPT was done for all study subjects (Stallergenes; UK). For each test, the negative control was 0.9% saline solution, and the positive control was 1 mg/mL of histamine. Six respiratory allergens including house dust mites (*Dermatophagoides Pteronyssius* - Dp, *Dermatophagoides Farinae* - Df, *Blomia tropicalis* - Blo), dog and cat hairs, cockroaches, and mixed pollens were used for testing. The SPT was considered positive when the wheal size exceeded the negative control by 3 mm.

IgE concentration in peripheral blood was quantified by chemical luminescence technique (COBASC 501; Hitachi, Japan). Complete blood count with eosinophil value (%) was analyzed by automatic

Table 1
Clinical and functional characteristics of study patients.

Parameters	Control (n = 234)	PER (n = 267)	P
Age, years (mean $\pm$ SD)	37 $\pm$ 18	36 $\pm$ 17	NS
Gender, male - female ratio, (n)	1.2 (132/112)	1.2 (146/121)	NS
BMI, kg/m ² (mean $\pm$ SD)	21.5 $\pm$ 3.4	22.7 $\pm$ 3.5	NS
Smoking status			
Active smokers, %	32.6	31.7	NS
Former smokers, %	12.5	12.8	NS
Passive smokers, %	33.6	34.7	NS
SFAR assessment, (mean $\pm$ SD)	0	5 $\pm$ 2	–
AR symptoms*, %	0	100	–
Nasal congestion, %	–	87.2	–
Runny nose, %	–	83.1	–
Sneezing, %	–	72.2	–
Nasal itching, %	–	56.1	–
TNSS**, (mean $\pm$ SD)	–	11.8 $\pm$ 5.7	–
PER severity, VAS***, (mean $\pm$ SD)	–	7.6 $\pm$ 2.3	–
Skin prick test****, %	–	86.1	–
Pollens, %	–	69.2	–
House dust mites, %	–	67.0	–
Dog or cat hairs, %	–	64.0	–
Cockroaches, %	–	31.0	–
Nasal peak flows, L/min			
Nasal PIF, (mean $\pm$ SD)	143 $\pm$ 57	96 $\pm$ 32	< 0.001
Nasal PEF, (mean $\pm$ SD)	176 $\pm$ 52	126 $\pm$ 43	< 0.001
Exhaled NO, ppb			
Nasal NO, (mean $\pm$ SD)	547 $\pm$ 132	1789 $\pm$ 315	< 0.001
FENO, (mean $\pm$ SD)	12 $\pm$ 6	14 $\pm$ 5	NS
CANO, (mean $\pm$ SD)	4.3 $\pm$ 2.5	4.7 $\pm$ 2.2	NS
Spirometry testing, %			
FVC, (mean $\pm$ SD)	91 $\pm$ 8	89 $\pm$ 11	NS
FEV ₁ , (mean $\pm$ SD)	92 $\pm$ 11	91 $\pm$ 7	NS
FEV ₁ /FVC, (mean $\pm$ SD)	82 $\pm$ 9	87 $\pm$ 12	NS
Total IgE, UI/ μ L (mean $\pm$ SD)	215 $\pm$ 103	476 $\pm$ 132	< 0.05
Blood eosinophil counts, cells/ μ L (mean $\pm$ SD)	183 $\pm$ 84	347 $\pm$ 126	< 0.05
Sleep disorders			
Insomnia, %	6.4	37.4	< 0.01
Snoring, %	11.1	78.1	< 0.001
Difficult sleep, %	15.3	69.3	< 0.001
PSG/RPG			
AHI, events/hour (mean $\pm$ SD)	6 $\pm$ 3	17 $\pm$ 12	< 0.01
Mean SpO ₂ , % (mean $\pm$ SD)	93 $\pm$ 2	89 $\pm$ 6	< 0.05
Nadir SpO ₂ , % (mean $\pm$ SD)	87 $\pm$ 5	81 $\pm$ 7	< 0.05

PER: persistent allergic rhinitis; BMI: body mass index; SFAR: Score for Allergic Rhinitis; AR: allergic rhinitis; TNSS: total nasal symptom scores; VAS: visual analogue scales; PIF: peak inspiratory flow; PEF: peak expiratory flow; NO: nitric oxide; FENO: fractional exhaled nitric oxide; CANO: concentration of alveolar nitric oxide; ppb: part per billion; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; PSG: polysomnography; RPG: respiratory polygraphy; AHI: apnea-hypopnea index; *: having at least one symptom (blocked nose, runny nose, sneezing, and/or nasal itching); **: TNSS measured with 5 symptoms (nasal congestion, runny nose, nasal itching, sneezing, and difficult sleep) and rated from 0 to 3 for each symptom (none = 0, mild = 1, moderate = 2, and severe = 3) and 0–15 for total scores; ***: VAS rated from 0 to 10 cm for total severity of PER (mild: VAS = 0–3 cm; moderate: VAS = 3.1–7 cm; severe: VAS = 7.1–10 cm); ****: positive skin-test with at least one allergen; NS: no significant difference.

machines (XT-4000i-SYSMEX; Kope, Japan).

2.2.3. Statistical analyses

The SPSS 22.0 statistics software (Chicago, USA) was used to analyze all collected data. Categorical variables were presented as numbers or percentages; continuous parameters were presented as mean $\pm$ standard deviation (SD). Normal distribution was evaluated by Skewness-Kurtosis manner. The Mann–Whitney *U* test was used for pair comparison of mean between the two groups. Regression analysis was used to measure the correlation between the nasal FENO and quantitative variables with the correlation coefficient *R* of Pearson for normal

distribution. The *P*-value < 0.05 was considered as statistically significant.

3. Results

3.1. Clinical and functional characteristics of study patients

There were no significant differences between control subjects and patients with PER for age, male - female ratio, body mass index (BMI), and smoking status (Table 1). The mean of total nasal symptom scores (TNSS) was 11 $\pm$ 4. The mean severity of PER measured with VAS was 7.6 $\pm$ 2.3 cm (Table 1). At least one positive SPT was found in 86% of patients with PER, two positive SPT in 61.7% and three positive SPT in 28.8% of patients with PER. The level of nasal PIF and PEF of patients with PER was significantly lower than that of the control subjects (Table 1). The level of nasal FENO of PER patients was higher than of the control subjects (1789 $\pm$ 315 vs. 547 $\pm$ 132 ppb; *P* < 0.001; Table 1). Bronchial FENO and CANO were not different between the two groups (*P* > 0.05 and *P* > 0.05; respectively). The levels of total IgE and eosinophil counts in PER patients were higher than in the control subjects (476 $\pm$ 132 vs. 215 $\pm$ 103 UI/ μ L and 347 $\pm$ 126 vs. 183 $\pm$ 84 cells/ μ L; *P* < 0.05 and *P* < 0.05; respectively; Table 1). Obstructive sleep apnea (OSA) in patients with PER was more severe than in the control subjects (AHI = 17 $\pm$ 12 vs. 6 $\pm$ 3; *P* < 0.01; Table 1).

3.2. Correlation between nasal FENO, clinical, functional and biological characteristics

In the control subjects, there were no significant correlations between nasal FENO and BMI (*R* = 0.023; *P* = 0.086), nasal PIF/PEF (*R* = 0.056, *P* = 0.124; *R* = 0.105, *P* = 0.092; respectively). In these subjects, there were no significant correlations between nasal FENO, total IgE (*R* = 0.029; *P* = 0.187), and blood eosinophil counts (*R* = 0.089; *P* = 0.075). In patients with PER, there were the negative and linear significant correlations between nasal FENO and PIF/PEF (*R* = −0.687, *P* = 0.0012; *R* = −0.643, *P* = 0.0018; respectively). In these patients, the level of nasal FENO was also significantly correlated with total IgE and blood eosinophil counts (*R* = 0.432, *P* = 0.0024; *R* = 0.445, *P* = 0.002; respectively). There were no significant correlations between nasal NO, TNSS, and VAS in patients with PER (*R* = 0.187, *P* = 0.214; *R* = 0.134, *P* = 0.122; respectively). There were no significant correlations between nasal FENO, bronchial FENO, CANO, and AHI in the control subjects and in the patients with PER (data not shown).

3.3. Comparison of clinical, functional and biological characteristics of patients with PER at inclusion and after 6 months of treatment

The results after 6 months of treatment showed that clinical symptoms of patients with PER were significantly reduced after 6 months of treatment vs. at inclusion (*P* < 0.001; *P* < 0.01; Table 2). The levels of nasal PIF and PEF were significantly increased after 6 months (148 $\pm$ 41 vs. 96 $\pm$ 32 L/min, *P* < 0.01; 184 $\pm$ 47 vs. 126 $\pm$ 43 L/min, *P* < 0.01; respectively; Table 2). The level of nasal FENO was significantly decreased after treatment (794 $\pm$ 229 vs. 1789 $\pm$ 315 ppb; *P* < 0.01; Table 2). Also, the PER patients had a significant reduction of sleep disorders (snoring and insomnia) and severity of OSA, measured by AHI (8 $\pm$ 4 vs 17 $\pm$ 12; *P* < 0.01; Table 2).

3.4. Comparison of the treatment efficacy with ATH + LRA vs INS after 6 months

There were no significant differences between the study patients who had PER treated with ATH + LRA vs. INS for mean age, male -

Table 2

Comparison of clinical, functional and biological characteristics of patients with PER at inclusion and after 6 month of treatment (n = 267).

Parameters	PER at inclusion (n = 267)	PER after 6 months (n = 267)	P
Age, years (mean ± SD)	36 ± 17	36 ± 16	NS
Gender, male - female ratio, (n)	1.2 (146/121)	1.2 (146/121)	NS
BMI, kg/m ² (mean ± SD)	22.7 ± 3.5	22.5 ± 3.7	NS
Smoking status			
Active smokers, %	31.7	29.9	NS
Former smokers, %	12.8	13.8	NS
Passive smokers, %	34.7	34.0	NS
SFAR assessment, (mean ± SD)	5 ± 2	4 ± 2	NS
AR symptoms*, %	100	34.4	< 0.001
Nasal congestion, %	87.2	22.8	< 0.001
Runny nose, %	83.1	6.3	< 0.0001
Sneezing, %	72.2	24.7	< 0.001
Nasal itching, %	56.1	21.7	< 0.01
TNSS**, (mean ± SD)	11.8 ± 5.7	4.3 ± 2.6	< 0.05
PER severity, VAS***, (mean ± SD)	7.6 ± 2.3	2.4 ± 1.5	< 0.05
Nasal peak flows, L/min			
Nasal PIF, (mean ± SD)	96 ± 32	148 ± 41	< 0.01
Nasal PEF, (mean ± SD)	126 ± 43	184 ± 47	< 0.01
Exhaled NO, ppb			
Nasal NO, (mean ± SD)	1789 ± 315	794 ± 229	< 0.001
FENO, (mean ± SD)	14 ± 5	13 ± 7	NS
CANO, (mean ± SD)	4.7 ± 2.2	4.5 ± 1.8	NS
Spirometry testing, %			
FVC, (mean ± SD)	89 ± 11	88 ± 12	NS
FEV ₁ , (mean ± SD)	91 ± 7	90 ± 10	NS
FEV ₁ /FVC, (mean ± SD)	87 ± 12	88 ± 11	NS
Total IgE, UI/μL (mean ± SD)	476 ± 132	482 ± 119	NS
Blood eosinophil counts, cells/μL (mean ± SD)	347 ± 126	338 ± 114	NS
Sleep disorders			
Insomnia, %	37.4	12.3	< 0.01
Snoring, %	78.1	23.5	< 0.001
Difficult sleep, %	69.3	29.9	< 0.001
PSG/RPG			
AHI, events/hour (mean ± SD)	17 ± 12	8 ± 4	< 0.01
Mean SpO ₂ , % (mean ± SD)	89 ± 6	92 ± 5	< 0.05
Nadir SpO ₂ , % (mean ± SD)	81 ± 7	86 ± 6	< 0.05

PER: persistent allergic rhinitis; BMI: body mass index; SFAR: Score for Allergic Rhinitis; AR: allergic rhinitis; TNSS: total nasal symptoms scores; VAS: visual analogue scales; PIF: peak inspiratory flow; PEF: peak expiratory flow; NO: nitric oxide; FENO: fractional exhaled nitric oxide; CANO: concentration of alveolar nitric oxide; ppb: part per billion; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; PSG: polysomnography; RPG: respiratory polygraphy; AHI: apnea-hyponea index; *: having at least one symptom (blocked nose, runny nose, sneezing, and/or nasal itching); **: TNSS measured with 5 symptoms (nasal congestion, runny nose, nasal itching, sneezing, and difficult sleep) and rated from 0 to 3 for each symptom (none = 0, mild = 1, moderate = 2, and severe = 3) and 0–15 for total scores; ***: VAS rated from 0 to 10 cm for total severity of PER (mild: VAS = 0–3 cm; moderate: VAS = 3.1–7 cm; severe: VAS = 7.1–10 cm). NS: no significant difference.

female ratio, BMI, and smoking status (Table 3). The percentage of PER patients treated with INS having AR symptoms after 6 months was significantly lower than that in the patients treated with ATH + LRA (Table 3; Fig. 1). After 6 months of treatment, the levels of nasal PIF and PEF were significantly higher in patients treated with INS vs. ATH + LRA (158 ± 43 and 192 ± 46 L/min vs. 124 ± 36 and 167 ± 41 L/min; P < 0.01 and P < 0.05; respectively; Table 3). The reduction levels of nasal NO (Δ values) in patients treated with INS was significantly higher than in patients treated with ATH + LRA

Table 3

Comparison of treatment effect of study patients with PER after 6 months.

Parameters	PER treated with ATH + LRA (N = 126)	PER treated with INS (n = 141)	P
Age, years (mean ± SD)	37 ± 17	35 ± 15	NS
Gender, male - female ratio, (n)	1.3 (72/54)	1.1 (74/67)	NS
BMI, kg/m ² (mean ± SD)	22.7 ± 3.5	22.5 ± 3.7	NS
Smoking status			
Active smokers, %	28.5	31.2	NS
Former smokers, %	14.2	13.4	NS
Passive smokers, %	32.5	34.7	NS
AR symptom*, %	49.2	21.2	< 0.001
Nasal congestion, %	30.1	16.3	< 0.01
Runny nose, %	9.5	3.5	< 0.05
Sneezing, %	33.3	17.0	< 0.01
Nasal itching, %	30.9	13.4	< 0.01
TNSS, Δ values** (mean ± SD)	4.8 ± 2.7	7.3 ± 3.6	< 0.05
VAS, Δ values*** (mean ± SD)	2.7 ± 1.4	4.9 ± 2.5	< 0.05
Δ Values** of symptom improvement, %	51	79	< 0.01
Nasal peak flows, L/min			
Nasal PIF, Δ values*** (mean ± SD)	29 ± 12	58 ± 24	< 0.01
Nasal PEF, Δ values*** (mean ± SD)	45 ± 19	67 ± 25	< 0.05
Exhaled NO, ppb			
Nasal NO, Δ values** (mean ± SD)	732 ± 298	985 ± 253	< 0.05
FENO, (mean ± SD)	13 ± 8	13 ± 6	NS
CANO, (mean ± SD)	4.5 ± 1.9	4.8 ± 1.7	NS
Spirometry testing, %			
FVC, (mean ± SD)	89 ± 13	87 ± 11	NS
FEV ₁ , (mean ± SD)	89 ± 6	90 ± 9	NS
FEV ₁ /FVC, (mean ± SD)	88 ± 11	88 ± 10	NS
Total IgE, UI/μL (mean ± SD)	479 ± 117	488 ± 109	NS
Blood eosinophil counts, cells/μL (mean ± SD)	327 ± 118	349 ± 108	NS
Sleep disorders, %			
Insomnia, %	13.3	11.3	NS
Snoring, %	18.2	28.3	< 0.05
Difficult sleep, %	30.9	29.0	NS
PSG/PGR			
AHI, events/hour, Δ values** (mean ± SD)	7 ± 3	9 ± 2	< 0.05
Mean SpO ₂ , %	92 ± 4	91 ± 6	NS
Nadir SpO ₂ , %	85 ± 7	86 ± 5	NS

PER: persistent allergic rhinitis; ATH: antihistamines; LRA: leukotriene-receptor antagonists; INS: intra-nasal steroids; BMI: body mass index; AR: allergic rhinitis; TNSS: total nasal symptoms scores; VAS: visual analogue scales; PIF: peak inspiratory flow; PEF: peak expiratory flow; NO: nitric oxide; FENO: fractional exhaled nitric oxide; CANO: concentration of alveolar nitric oxide; ppb: part per billion; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; PSG: polysomnography; RPG: respiratory polygraphy; AHI: apnea-hyponea index; *: having at least one symptom (blocked nose, runny nose, sneezing, and/or nasal itching); **: having at least one symptom (blocked nose, runny nose, sneezing, and/or nasal itching); ***: differences from baseline at inclusion (reduced levels); ***: differences from baseline at inclusion (increased levels) NS: no significant difference.

(985 ± 253 vs. 732 ± 298 ppb; Table 3; Fig. 2). Although the percentage of patients treated with ATH + LRA who had been previously snoring was significantly lower than patients treated with INS (18% vs. 28%; P < 0.05; Table 3), the level of AHI in these patients was significantly higher after 6 months of treatment (11 ± 5 vs. 7 ± 3 times/hour; P < 0.01; Table 3).

4. Discussion

The results of our study show that the level of nasal NO, total IgE, blood eosinophil counts, and severity of OSA in patients with PER were significantly higher than in the control subjects; additionally, patients with PER treated by INS had greater improvement of clinical and

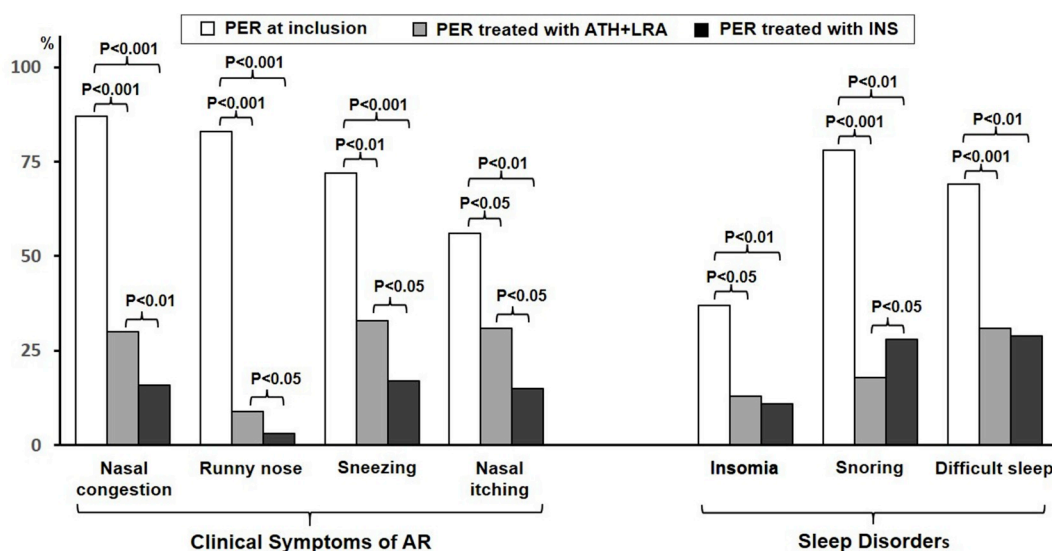


Fig. 1. Comparison of clinical symptoms in patients with PER at inclusion and after 6 months of treatment.

Abbreviations PER - persistent allergic rhinitis; ATH - antihistamine; LRA - leukotriene receptor agonist; INS - intranasal steroids.

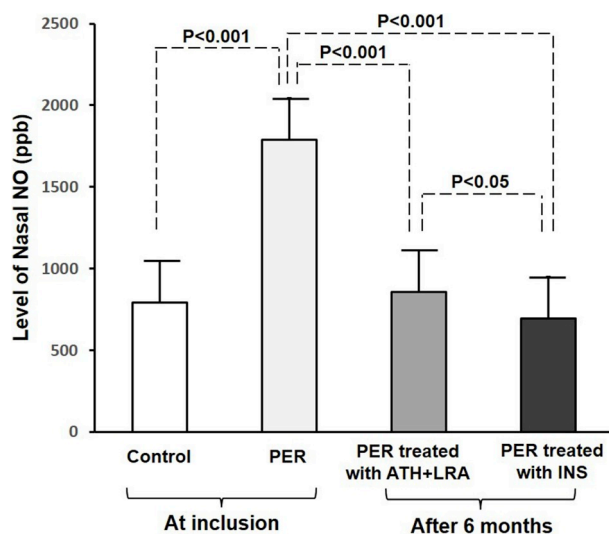


Fig. 2. Comparison of the level of nasal FENO at inclusion and after 6 months of treatment.

Abbreviations: PER - persistent allergic rhinitis; ATH - antihistamine; LRA - leukotriene receptor agonist; INS - intranasal steroids; ppb - part per billion.

functional parameters than those treated by ATH + LRA.

In the present study, all included patients with PER had the symptoms of AR although they had been previously treated with ATH as verified at inclusion. In these patients, the levels of biomarkers of AR, such as nasal NO, total IgE, or blood eosinophil count were significantly higher than in the control subjects (Table 1). In other studies, which analyzed patients with such allergic disorders as atopic dermatitis, conjunctivitis, or asthma [16–18], the results were the same as presented in our study, showing the levels of total IgE and blood eosinophil count significantly higher than in the healthy subjects. Previous studies also reported a correlation between IgE and eosinophil count with the severity of PER [19,20]. In the present study, all study participants with PER received an SPT with standardized allergen extracts to find out the specific aeroallergens as recommended by previous studies [21–23]. We performed the SPT at inclusion in all patients who had ATH treatment discontinued at least 2 weeks before the SPT to prevent the false negative result [24] and there was no significant correlation between the level of nasal NO and allergens (data not shown). In fact, in patients

with AR, the symptoms of disease are due to local reaction of the nose mediated by immunoallergic response via inflammatory cells when these patients are exposed to aeroallergens.

The role of nasal NO measurements in assessing the efficacy of nasal steroids and monitoring patients with AR was shown more than 20 years ago [25,26]. Recently, nasal NO measurement has been suggested for diagnosis of patients with AR [27–29]. Previous studies demonstrated that nasal NO was produced mainly in para-sinusal areas and nasal mucosal membranes [30,31]. Therefore, in patients with AR, nasal NO may be used as a biomarker of eosinophilic inflammation because nasal eosinophils displayed the best correlation with symptoms and inflammation in AR [29,32,33]. The stimulation effect of intranasal administration of eotaxin which increased nasal eosinophils and NO in patients with AR was described by Hanazawa et al. [34]. More recently, Takeno et al. [35] measured nasal NO in control subjects and AR patients by using an electrochemical analyzer, and stated that nasal NO may reflect persistent eosinophilic inflammation and may be a valid marker to estimate the severity of AR.

The result of our previous study also showed that the levels of nasal NO in AR patients with or without asthma were significantly higher than control subjects and the cut-off of nasal NO for diagnosis of AR (> 799 ppb) had very high sensitivity and specificity [29]. In the present study, the level of nasal NO in uncontrolled PER was significantly higher than that in the control subjects (Table 1). Interestingly, in patients with PER, the level of nasal NO was significantly correlated with nasal peak flows, total IgE, and blood eosinophil count. These results suggest that nasal NO may be used as a useful complementary test with additional information in patients with PER. Although, the results of the present study showed that patients with PER had more severe OSA than control subjects, there was no correlation between the level of nasal NO and AHI (data not shown).

In the present study, all patients with PER were treated with either ATH + LRA or INS after inclusion. There were no significant differences between the two groups for clinical and functional characteristics (Table 2). The results showed that the clinical symptoms, nasal peak flows, and nasal NO levels improved significantly after treatment (Table 2; Figs. 1–2). However, the levels of total IgE and blood eosinophil counts were not significantly different after treatment. This result suggests that together with clinical symptoms, the measurement of nasal NO might be performed as a useful tool for the follow-up of patients with PER. The present study showed that nasal NO was also a relevant biomarker of PER because it was not correlated and not

dependent on anthropometric characteristics. In comparison to patients with PER treated by ATH + LRA, patients treated with INS showed greater improvement in clinical and functional features after 6 months of treatment (Table 3). Interestingly, the results of the present study showed that INS had higher efficacy in relieving nasal itching than ATH + LRA in the study patients with PER. In the study by Weiner et al. [36] the authors showed that INS offered greater relief of nasal itching and total nasal symptoms vs. oral ATH and there was no difference between the two treatments for nasal discomfort and nasal resistance in patients with seasonal AR. In an evidence-based review of efficacy for nasal symptoms by class, Benninger et al. [37] confirmed that INS offered the greatest improvements in nasal symptoms in patients with seasonal AR and was effective for PER, but the data were of variable quality, and oral ATH may be equally effective for some patients. Wilson et al. [38] also demonstrated that LRA was as effective as ATH, but less effective than INS in improving symptoms in patients with seasonal AR.

Our present study showed that the treatment with ATH + LRA was more effective than with INS for snoring in the study patients. The effect of LRA in treatment of children with OSA has been demonstrated previously and suggested that it was related to a statistically significant reduction in the size of adenoid tissues after treatment with montelukast [39]. Recently, Yang et al. [40] showed that montelukast sodium combined with nasal spray of mometasone furoate in the treatment of OSA children had a better effect than each drug alone in significant improving snoring, apnea, and restless sleep. However, in adult with OSA related to PER, the effect of ATH + LRA on OSA symptoms has not been well studied. Currently, the use of INS for AR treatment is widely recommended by different international guidelines due to their superiority efficacy over other therapies and good safety record [2]. INS are very effective for the treatment of AR due to their potential anti-inflammatory properties [41–43]. Previous studies also demonstrated the effect of INS in the reduction of nasal symptoms, quality of life [44–46], and sleep disturbances [47,48] in patients with AR. In the present study, all patients treated with either ATH + LRA or INS had the improvement of insomnia, snoring, and OSA during sleep (Table 2). While patients treated with INS had more efficacy in reducing the severity of OSA, patients treated with ATH + LRA had more benefits in reducing snoring in study patients (Table 3).

4.1. Limitations of the study

Although the present study offers new information and results in the field of nasal NO measurement for the management of patients with PER, it has some limitations concerning the small number of study participants with short-term follow-up and the lack of evidence to demonstrate the significant correlation between nasal NO and nasal eosinophilia. Another limitation of the present study concerns the lack of placebo group to confirm objectively the significant effect of treatment. Moreover, the use of nasal NO for titration of treating patients with PER should be studied in long-term follow-up.

5. Conclusion

The measurement of nasal FENO is a useful method for follow-up of patients with AR, especially in patients with PER. Nasal FENO measurement may help physicians to estimate the level of response to treatment in patients with AR. However, more studies with a large number of subjects and long-term follow-up to evaluate the cost and benefits of nasal FENO measurement in patients with AR seems to be necessary.

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Declaration of competing interest

The authors declare no conflict of interests for this study.

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