Allergic Rhinitis in Children: A Randomized Clinical Trial Targeted at Symptoms

Nicola Mansi · Gabriele D'Agostino · Antonella Silvia Scirè ·
Giada Morpurgo · Dario Gregori · Achal Gulati ·
Valerio Damiani

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Abstract Allergic rhinitis (AR) underlies many symptoms and complications which severely affect children's quality of life. This two-arm study aimed at evaluate the efficacy and safety of the medical device Narivent[®] versus topical corticosteroids in the symptomatic management of allergic rhinitis in paediatric patients. A randomized study was conducted. Forty subjects with a diagnosis of allergic rhinitis were randomized to receive one puff of Narivent[®] into each nostril twice daily for 30 days (n = 20) or to receive one puff of topical intranasal corticosteroid into each nostril twice daily for 30 days (n = 20). In both treatment arms, severity of major symptoms related to AR, including nasal congestion, rhinorrhoea, sneezing and nasal itching, was assessed subjectively on a 0–100 mm visual analogue scale. Nasal congestion, rhinorrhoea and sneezing improved significantly after 30 days of treatment with Narivent[®]. Similarly, in topical steroids group severity of

all subjective symptoms decreased significantly. Narivent[®] appears to be efficacious in treating nasal congestion and other major symptoms in children with AR over a 30-day period, showing comparable results to intranasal corticosteroids therapy but with a better safety profile.

Keywords Intranasal corticosteroids · Osmotically-acting medical device · Anti-oedematous · Anti-inflammatory · Allergic rhinitis · Children

Introduction

Allergic rhinitis (AR), an antigen-mediated inflammation of the nasal mucosa that may extend into the paranasal sinuses, is one of the most common illnesses in childhood and adolescence, affecting 10–40 % of young people worldwide. Its prevalence among children has been significantly increasing over the last two decades, accompanied by a parallel increase in comorbidity such as asthma [1].

Though AR is considered as a mild disorder, often being regarded by parents as an irritation rather than as a disease, and frequently under diagnosed, misdiagnosed and mistreated [2], it imposes a significant burden to children's daily life, quality of sleep, school performance and social activities, as well as physical and emotional health [3, 4].

AR major symptoms typically include nasal obstruction and rhinorrhoea accompanied to sneezing, itchy nose, eyes and throat [4]. Nasal congestion is a hallmark of AR and is often the symptom patients find most troublesome and would like most to prevent [5, 6]. Furthermore, typical sleep-related problems seen in AR, such as sleep-disordered breathing, sleep apnoea, and snoring, are associated with nasal obstruction [7]. First generation antihistamines

N. Mansi · G. D'Agostino
S.C. di Otorinolaringoiatria della A.O.R.N. Santobono
Pausilipon di Napoli, Naples, Italy

A. S. Scirè · G. Morpurgo
Zeta Research Srl, Trieste, Italy

D. Gregori (✉)
Unit of Biostatistics, Epidemiology and Public Health,
Department of Cardiac, Thoracic and Vascular Sciences,
University of Padova, Via Loredan, 18, 35121 Padua, Italy
e-mail: dario.gregori@unipd.it

A. Gulati
E.N.T. Department, Maulana Azad Medical College
and LN, New Delhi, India

V. Damiani
ENT Department San Giovanni Addolorata Hospital,
Rome, Italy

are not recommended due to their sedative effect and the consequent impairment of psychomotor, cognitive and academic functions in children [8, 9]. Second generation antihistamines have allowed overcoming these adverse effects. They are the medication of choice in patients with mild intermittent AR, but their efficacy is poor in the management of more severe cases [8] and in treating perennial rhinitis, because symptoms, predominantly nasal obstruction, are not histamine mediated [2, 10], being therefore mostly a relief in the treatment of rhinorrhea, nasal itching and sneezing.

Topical nasal corticosteroids are commonly prescribed by pediatricians, rhinologists and allergologists. They act directly on the nasal mucosa and represent the most effective anti-inflammatory agents used for the treatment of pediatric allergic rhinitis [8, 11]. However, safety of these compounds remains controversial and main concerns derive from dose-related systemic adverse effects associated to long-term treatments, such as suppression of adrenocortical function, growth and bone metabolism [8, 11]. These concerns might not be implied in short term therapies, but researches focusing on children have often required high standards of safety [12].

Pharmacotherapy of AR in children requires, therefore, great attention to dosing and the avoidance of the many adverse effects related to standard therapies. That is why there is a growing need for alternative or adjuvant treatments for the relief of AR symptoms, allowing to reduce the amount of pharmacological therapy in paediatric field. Decongestants and immunotherapy, equally present varying levels of safety and tolerability issues in children [13]. The use of osmotically acting medical device has been proven as an efficient solution in the treatment of nasal congestion [14]. Nasal lubricant containing eucalyptol, glycyrrhizin and mannitol has shown osmotic, antioedematous and anti-inflammatory actions. Mannitol in fact exerts potent and fast anti-edema effects [15] and glycyrrhizin acts with anti-inflammatory properties [16].

The present study aimed at evaluate the efficacy and safety of the medical device Narivent® (DMG Italia Srl, Pomezia, Italy) versus intranasal corticosteroids therapy, in the management of allergic rhinitis symptoms in a paediatric population. Following clinical experience, the use of Narivent® was considered for the treatment of all symptoms of allergic rhinitis, broadening the knowledge of its action from its primary indication as decongestant, to a broader use as a safe alternative in symptoms control. Changes in visual analog scale (VAS) scores for major symptoms were assessed both through a comparative evaluation between Narivent® and topical corticosteroids and through a before-after evaluation in each treatment group.

Patients and Methods

Study Population

Forty patients, male and female, aged between 5 and 18 years old, with allergic rhinitis presenting at the Ear, Nose and Throat (ENT) Department of the Santobono Pausilipon Hospital, Naples, Italy were enrolled in the present study between February and May 2012.

Patients were excluded if they had a diagnosis of cystic fibrosis, presence of asthma episodes in the 30 days preceding the study, any acute upper respiratory tract infection or the presence of massive occlusive polyps in the sinus.

At enrolment, patients or their parents/legal representatives provided verbal and written informed consent to participate in the trial. The study was conducted in compliance with the requirements of the Santobono Pausilipon Hospital Institutional Review Board.

Study Design and Assessments

This was a single-centre, two-parallel group, randomized study. Patients were randomly divided into two groups and followed for 30 days: in one group subjects were treated with one puff of Narivent® into each nostril twice daily; in the control group patients received one puff of topical intranasal corticosteroid (mometasone furoate monohydrate) into each nostril twice daily.

The diagnosis of AR was based on the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria [17] and classified as follows: intermittent (symptoms lasting for less than 4 days/week or less than 4 consecutive weeks); persistent (symptoms lasting for more than 4 days/week and more than 4 consecutive weeks); mild (symptoms not interfering with daily activities); moderate-severe (symptoms impacting at least upon one or more items among sleep, daily activities, sport, leisure and school performance).

In both groups, patients were visited by the investigators at enrolment and after 30 days of treatment. A physical examination was conducted at the first visit through a complete ENT endoscopy. Turbinate hypertrophy was classified according to the examiner's personal experience as absent, mild (turbinates obstructing 1/3 of nasal fossae), moderate (turbinates obstructing 2/3 of nasal fossae) or severe (turbinates completely obstructing nasal fossae). Septal deviation was classified according to the examiner's personal experience as absent, mild (septum slightly deviated from baseline), moderate (septum markedly deviated from baseline) or severe (obstructing septum).

The Lund-Mackay scale was used to classify nasal polyps [18, 19]. Adenoid hypertrophy was classified as: absent, mild (slightly enlarged adenoids), moderate

(adenoids enlarged but not beyond tubal ostium) or severe (adenoids enlarged beyond tubal ostium) [20, 21].

The nasal mucosa was described as either normal, hyperaemic, pallid/livid or atrophic, and nasal secretions were described as either absent, haematic/purulent, pallid/serous, or mucous.

During each visit, AR major symptoms, including the subjective feeling of nasal obstruction, rhinorrhoea, sneezing and nasal itching, were assessed. Measurements of symptoms severity from the patient's perspective were assessed by a visual analog scale (VAS; 0–100 mm) [22], allowing subjects to rate their symptoms on a linear scale, where 0 corresponds to symptoms that are not troublesome at all and 100 corresponds to the most presumable troublesome symptoms [23, 24]. All adverse effects were recorded during the study.

Study Medical Device

According to the Directive 93/42/EEC, Narivent® is a class I medical device based on the application of rule 5 of annex IX.

Narivent® is a nasal lubricant spray which acts osmotically, carrying out anti-oedematous and anti-inflammatory effects. The presence of components like mannitol (a well-known osmotic agent) promotes the anti-oedematous action [25]. The anti-inflammatory activity derives from glycyrrhizin, a triterpene glycoside extracted from the roots of liquorice plant (*Glycyrrhiza glabra*) [26]. This compound has been proven to be the first direct inhibitor of the HMGB1 (high-mobility group box 1 protein), an intranuclear protein belonging to the alarmin family, which acts as a potent pro-inflammatory mediator when released in the extracellular environment [27]. Glycyrrhizin binds to high-mobility group box one protein by means of a mechanical interaction, promoting the inhibition of its immune-activating properties [28, 29].

Sample Size Calculation and Statistical Analysis

The primary outcome of the present study was symptoms' resolution (improvement in each symptom score from enrolment to week 4) as measured by the VAS. Sample size was computed with reference to the following scenario: a type I error of 0.05 and a power of 0.90. At this error level, 15 subjects are required to detect as significant a difference in VAS change rates over follow-up at least by two points (SD 1.5) after the administration of the treatment and between Narivent® and topical steroids groups. Assuming a drop-out rate of 30 %, 20 patients per group (total 40 patients) have been estimated as necessary for the conduct of the study. Continuous variables were always expressed as median and inter-quartile difference and categorical

variables as percentages and absolute numbers. Differences between symptoms felt before and after treatment with Narivent® were compared using Wilcoxon signed rank test and Chi square test with Yates correction whenever appropriate. Tests were performed using the R system [30].

Results

A total of 40 patients (twenty-one females and nineteen males) were enrolled in the study and median age was 9.6 years (I quartile: 6.9; III quartile: 12.3).

Demographic and disease characteristics of patients in both treatment groups are shown in Table 1. Regarding the type of diagnosis according to ARIA classification, in the whole study sample, 19 patients (49 %) suffered from intermittent rhinitis. Symptom severity was classified as mild in 18 patients (47 %), while 20 subjects (53 %) showed moderate–severe manifestations. Adenoid, nasal mucosa and nasal secretions were similarly distributed in the two groups. No significant differences between the two groups were retrieved (all $p > 0.05$).

Results from physical examination in both study groups at baseline are shown in Table 2. No significant difference was retrieved between the two arm at baseline (all $p > 0.05$).

Table 3 shows the subjective evaluation of symptoms before and after 30 days of treatment with Narivent®. Nasal congestion, rhinorrhoea and sneezing were all significantly decreased ($p < 0.001$) after treatment. As indicated by VAS score, nasal itching was improved although the effect was not statistically significant ($p > 0.05$).

Table 4 shows the subjective evaluation of symptoms before and after 30-day therapy with intranasal corticosteroids (INCs): all symptoms' evaluations were significantly improved following treatment ($p < 0.001$).

Table 5 shows the percentage reductions in VAS score for the major subjective symptoms of allergic rhinitis in each study group. For all symptoms, no significant differences were found between Narivent group and topical steroids group ($p > 0.05$).

During the study, 15 patients (38 %) reported mild adverse reactions (Table 6). Compliance with both treatments and the use of concomitant therapies are shown in Table 7.

Discussion

Allergic rhinitis is a widespread disease in children and adolescents [2, 10]. Although it is not a serious illness, AR is a clinically relevant condition because is a major cause of morbidity and a major risk factor for poor asthma control.

Table 1 Demographic and disease characteristics of patients in each treatment group

Variable	<i>N</i>	INCs group (<i>N</i> = 20)	Narivent group (<i>N</i> = 20)	Combined (<i>N</i> = 40)	Test statistics
Sex					
M	40	9 (45 %)	10 (50 %)	19 (48 %)	<i>p</i> = 0.752
F		11 (55 %)	10 (50 %)	21 (52 %)	
Age (years)	39	7.2 (6.0, 10.9)	9.6 (6.9, 12.3)	8.12 (6.1, 11.7)	<i>p</i> = 0.163
Allergic rhinitis					
Persistent	39	10 (50 %)	10 (53 %)	20 (51 %)	<i>p</i> = 0.869
Intermittent		10 (50 %)	9 (47 %)	19 (49 %)	
AR severity					
Moderate–severe	38	7 (35 %)	13 (72 %)	20 (53 %)	<i>p</i> = 0.022
Mild		13 (65 %)	5 (28 %)	18 (47 %)	
Main allergens					
Mites	40	4 (20 %)	3 (15 %)	7 (18 %)	<i>p</i> = 0.256
Mites/graminaceae/parietaria		0 (0 %)	1 (5 %)	1 (2 %)	
Alternaria		3 (15 %)	2 (10 %)	5 (12 %)	
Dermatophagoides farinae		0 (0 %)	1 (5 %)	1 (2 %)	
Dermatophagoides farinae/dermatophagoides pteronyssinus		0 (0 %)	2 (10 %)	2 (5 %)	
Graminaceae		5 (25 %)	1 (5 %)	6 (15 %)	
Graminaceae/parietaria		0 (0 %)	1 (5 %)	1 (2 %)	
Graminaceae mix		0 (0 %)	1 (5 %)	1 (2 %)	
Olive		2 (10 %)	5 (25 %)	7 (18 %)	
Parietaria		6 (30 %)	3 (15 %)	9 (22 %)	

Data are presented as number of patients for all variables, with percentages in brackets. Age is presented as median (interquartile range in brackets). *N* represents the number of patients on which data were statistically analysed for the selected variable. Combined refers to the all data recorded, without separation in groups

The traditional classification as perennial or seasonal, dependent on whether symptoms occur all year around or in relation to seasonal exposure to allergen [2, 4], has been recently sided and in some cases substituted by a functional classification based on symptom severity (mild/moderate–severe) and frequency (intermittent/persistent) and useful in decisions regarding treatment strategies called ARIA [31], adopted in 2001 by the World Health Organization, considering the high symptomatic burden of allergic rhinitis.

Nasal congestion is a prominent and troublesome manifestation of allergic rhinitis, along with rhinorrhea, sneezing, and pruritus of the eyes, nose, and throat [4]. Perception of nasal airflow is a subjective sensation and, by definition, difficult to quantify unless it is nearly complete [32]. Moreover, inconsistencies between subjective nasal obstruction and the appearance of the nasal cavities is common [32, 33, 34]. The visual analogue scale (VAS) offers a reproducible, quantifiable evaluation of patients' symptoms, which may provide more subtle information than simply asking whether the patient is better, the same, or worse [24]. In children suffering from allergic rhinitis, VAS has been found to represent a reliable tool, and scores

adequately correlate with severity of symptoms according to ARIA items [35]. The goal of the present study was therefore to assess symptomatology's improvements by mean of a subjective tool, able to define patients' statuses.

The therapeutic goal is the relief of subjective symptoms and improvement of objective measures. Between the available treatment options for pediatric allergic rhinitis, the newer oral antihistamines and intranasal corticosteroids are first-line treatments [8, 36].

Pharmacotherapy of AR in children is similar in many aspects to that in adults but requires attention to dosing and the avoidance of adverse effects.

Pharmacological strategies include a wide range of topical and oral decongestants, topical and oral antihistamines, anticholinergic agents, topical sodium cromoglycate, topical and systemic corticosteroids, leukotriene antagonists and a number of over the counter preparations [11]. Numerous preparations have been investigated for the symptomatic management of rhinitis, including isotonic/hypertonic saline, nasal douche, mucolytic agents/phyto-medical preparations, immuno-modulators/immunostimulants and bacterial lysate preparations, but substantial evidence for their benefit is lacking [37] And yet the most

Table 2 Physical examination at baseline in each treatment group

Variable	INCs Group (<i>N</i> = 20)	Narivent Group (<i>N</i> = 20)	Combined (<i>N</i> = 40)	Test statistic
Turbinate hypertrophy				
Absent	5 (25 %)	0 (0 %)	5 (12 %)	<i>p</i> = 0.068
Mild	14 (70 %)	16 (80 %)	30 (75 %)	
Moderate	1 (5 %)	3 (15 %)	4 (10 %)	
Severe	0 (0 %)	1 (5 %)	1 (2 %)	
Septal deviation				
Absent	16 (80 %)	19 (95 %)	35 (88 %)	<i>p</i> = 0.323
Mild	3 (15 %)	1 (5 %)	4 (10 %)	
Moderate	1 (5 %)	0 (0 %)	1 (2 %)	
Adenoid hypertrophy				
Absent	11 (55 %)	10 (50 %)	21 (52 %)	<i>p</i> = 0.551
Mild	8 (40 %)	9 (45 %)	17 (42 %)	
Moderate	1 (5 %)	0 (0 %)	1 (2 %)	
Severe	0 (0 %)	5 (1 %)	2 (1 %)	
Nasal polyposis	0 (0 %)	0 (0 %)	0 (0 %)	
Mucosa status				
Hyperemic	16 (80 %)	13 (65 %)	29 (72 %)	<i>p</i> = 0.079
Normal	2 (10 %)	0 (0 %)	2 (5 %)	
Pallid/livid	2 (10 %)	7 (35 %)	9 (22 %)	
Atrophy	0 (0 %)	0 (0 %)	0 (0 %)	
Type of secretion				
Absent	5 (25 %)	1 (5 %)	6 (15 %)	<i>p</i> = 0.14
Mucous	7 (35 %)	6 (30 %)	13 (32 %)	
Pallid-serum	8 (40 %)	13 (65 %)	21 (52 %)	
Haematic–purulent	0 (0 %)	0 (0 %)	0 (0 %)	

Data are presented as number of patients (with relative frequency as % in brackets) for all variables

Table 3 Visual analogue scale (VAS) scores of subjective symptoms' evaluation before and 30 days after treatment with Narivent®

Subjective symptoms (VAS ^b)	<i>N</i>	Before Narivent (<i>N</i> = 20)	After Narivent (<i>N</i> = 20)	Combined (<i>N</i> = 40)	Statistical significance ^a
Nasal obstruction	40	72.00 (64.50, 78.50)	15.00 (8.00, 21.00)	48.5 (15.0, 72.0)	<i>p</i> < 0.001
Rhinorrhea	40	59.50 (41.00, 77.00)	14.00 (6.50, 20.50)	31.00 (12.75, 58.25)	<i>p</i> < 0.001
Sneezing	40	31.00 (10.25, 41.00)	1.00 (0.00, 9.75)	10.00 (0.75, 33.50)	<i>p</i> < 0.001
Nasal itching	40	5.50 (0.75, 18.25)	1.00 (0.00, 6.50)	2.00 (0.00, 9.50)	NS

All data are presented as median value, with lower and upper quartile in brackets

NS not statistically significant (*p* > 0.05)

^a Comparison of variable distribution before and after treatment with INC and with Narivent® using Wilcoxon's signed rank test

^b Patients rated the perceived degree of obstruction on a scale of 0 ('symptom not troublesome at all') to 100 ('the most troublesome symptom imaginable')

effective proven strategy to treat nasal symptoms is represented by intranasal corticosteroids. They are the treatment of choice for persistent moderate–severe allergic rhinitis, even in children, as specifically indicated also from WHO manual for essential medicines, where the corticosteroid chlorpheniramine, (oral, 0.1 mg/kg/dose 6–8 hour) is specifically indicated at different posologies in children under 11 years old [38]. However, the use of topical

steroids in pediatric patients remains controversial because of their safety profile [10, 39]. The most frequent local adverse effects are epistaxis, nasal dryness, burning, and stinging [40], with the first two present also in this study, although epistaxis is usually due to the nozzle trauma to the nasal mucosa.

Taking into account the adverse effects related to standard therapies and long-term treatments and the paucity of

Table 4 Visual analogue scale (VAS) scores of subjective symptoms' evaluation before and 30 days after treatment with Intranasal Corticosteroids (INCs)^a

Subjective symptoms (VAS ^b)	N	Before INCs (N = 20)	After INCs (N = 20)	Combined (N = 40)	Statistical significance ^a
Nasal obstruction	38	54.50 (40.75, 62.00)	8.00 (6.25, 13.00)	21.50 (8.50, 55.75)	$p < 0.001$
Rhinorrhea	38	40.50 (24.00, 50.75)	5.00 (3.00, 10.25)	18.00 (5.50, 41.25)	$p < 0.001$
Sneezing	38	19.00 (9.75, 28.50)	1.00 (0.00, 6.00)	8.50 (0.50, 21.00)	$p < 0.001$
Nasal itching	38	8.50 (4.75, 12.50)	1.00 (0.00, 2.75)	4.50 (1.00, 10.00)	$p < 0.001$

All data are presented as median value, with lower and upper quartile in brackets

NS not statistically significant ($p > 0.05$)

^a Comparison of variable distribution before and after treatment with INC and with Narivent[®] using Wilcoxon's signed rank test

^b Patients rated the perceived degree of obstruction on a scale of 0 (complete patency) to 100 (complete stenosis)

Table 5 Percentage reduction in VAS scores for AR major subjective symptoms in each treatment group

Subjective symptoms (VAS)	N	INCs (N = 20) (%)	Narivent (N = 20) (%)	Combined (N = 40) (%)	Statistical significance ^a
Nasal obstruction	38	80.23	78.31	78.74	NS
Rhinorrhea	38	84.52	75.92	79.59	NS
Sneezing	36	90.47	96.15	93.31	NS
Nasal itching	35	84.52	27.77	74.69	NS

Data presented as median values of recorded percentage reductions

NS not statistically significant ($p > 0.05$)

^a Comparison of variable distribution before and after treatment with INC and with Narivent[®] using Wilcoxon's signed rank test

^b Patients rated the perceived degree of obstruction on a scale of 0 ('symptom not troublesome at all') to 100 ('the most troublesome symptom imaginable')

Table 6 Adverse reactions recorded in each study group

Variable	N	INCs (N = 20)	Narivent (N = 20)	Combined (N = 40)	Statistical significance ^a
Presence of adverse reactions	40	8 (40 %)	7 (35 %)	15 (38 %)	NS
Adverse reactions					
Epistaxis	15	6 (75 %)	1 (14 %)	7 (47 %)	$p = 0.051$
Nasal dryness		2 (25 %)	6 (86 %)	8 (53 %)	

Data are presented as absolute frequencies, with relative frequencies (%) in brackets

NS not statistically significant ($p > 0.05$)

^a Comparison of variable distribution before and after treatment with INC and with Narivent[®] using Wilcoxon's signed rank test

Table 7 Compliance with treatment and concomitant therapies in each study group

Variable	N	INCs (N = 20)	Narivent (N = 20)	Combined (N = 40)	Statistical significance ^a
Compliance					
High	40	15 (75 %)	7 (35 %)	22 (55 %)	$p = 0.028$
Fair		5 (25 %)	11 (55 %)	16 (40 %)	
Poor		0 (0 %)	2 (10 %)	2 (5 %)	
Concomitant treatments					
No therapy	40	0 (0 %)	16 (80 %)	16 (40 %)	$p < 0.001$
Antihistamine		20 (100 %)	2 (10 %)	22 (55 %)	$p < 0.001$
Hypertonic solution		4 (20 %)	0 (0 %)	4 (10 %)	$p = 0.035$

Data are presented as absolute frequencies, with relative frequencies (%) in brackets

NS not statistically significant ($p > 0.05$)

^a Comparison of variable distribution before and after treatment with INC and with Narivent[®] using Wilcoxon's signed rank test

evidence for the efficacy of symptomatic therapy, there is a growing need for alternative or co-adjuvant treatments to manage symptoms associated with AR in children. In this context, the role of medical devices is emerging thanks to their safety profile and the lack of severe side effects. Narivent® (DMG Italia Srl, Pomezia, Italy) is a medical device dispensing a nasal lubricant containing eucalyptol, glycyrrhizin and mannitol, that acts osmotically and has anti-oedematous and anti-inflammatory actions. The present study was conducted in order to verify whether treatment with Narivent®, compared with intranasal corticosteroids therapy, was effective in reducing nasal obstruction and other symptoms in children with allergic rhinitis.

Patients' perception of subjective nasal symptoms was assessed using a 0–100 mm VAS. Changes in VAS scores were assessed before and following a 30-day treatment period, and compared between the two study groups. In both arms, patients showing persistent allergic rhinitis, and moderate severe symptoms were equally distributed.

When considering concomitant treatments, in corticosteroids arm all patients were undergoing antihistamine treatment, while in Narivent®'s arm, only two were presently undergoing an antihistamine therapy. Taken that combined treatment of corticosteroids and antihistamine has been reported as showing an increased efficacy on nasal symptoms in patients [41–43], the higher presence was considered as acceptable for the purpose of the study.

Results demonstrated a significant improvement in all major symptoms of allergic rhinitis, including rhinorrhoea, sneezing and nasal obstruction following treatment in both groups, not showing a significant difference when comparing percentage reaction. Nasal itching improvement was recorded as significant only in the corticosteroids group. Although at baseline median VAS score in Narivent®'s group was higher than in the other arm, upper limits before and after showed percentage reductions comparable between the two groups, confirming the efficacy on subjective symptoms in the observational period.

When considering nasal obstruction, median absolute improvement, considered as the difference between median VAS scores pre and post treatment, was higher in Narivent®'s arm. Same considerations could be made also for sneezing.

In both treatment arms, no severe adverse events were reported by patients over the treatment period. The incidence of nasal dryness was higher in Narivent® group than in steroid group, despite no direct causal relationship can be related to the medical device content, as its active ingredients have a known mucolytic and lubricating action; therefore we can suppose the nasal dryness could be more probably connected with the mechanical insertion of the device in the nasal cavities. The same consideration could

be done for the epistaxis, which is usually mainly caused by the nozzle trauma, and that occurred less frequently in Narivent® group than in subjects treated with topical steroids group. Considering the contemporary use of antihistamines in all patients from corticosteroids arm, also the higher improvement in the median score of itching VAS could be explained within this study, that showed an overall better performance of Narivent® when considering symptoms' relief and occurrence of adverse events.

Final Remarks

Although the study period (30 days) was narrow, registered symptoms and side effects appeared to be in line with previous studies, allowing therefore to conclude on Narivent®'s effect. Even if in a small sample, this study provided evidence that in paediatric patients with allergic rhinitis Narivent® can improve nasal symptoms' control over a 30-day treatment and observational period, reaching in this time frame comparable results to those of intranasal corticosteroids therapy, but with less registered side effects (epistaxis).

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Conflict of interest A.S. Scirè and G. Morpurgo have on-going contracts with DMG Italia Srl for conducting clinical studies. The other authors have no conflicts of interest in relation to this article.

References

- Lunn M, Craig T (2011) Rhinitis and sleep. *Sleep Med Rev* 15(5):293–299
- Turner PJ, Kemp AS (2010) Allergic rhinitis in children. *J Paediatr Child Health* 48(4):302–310
- Westman M et al (2012) Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol* 129(2):403–408
- Kemp AS (2009) Allergic rhinitis. *Paediatr Respir Rev* 10(2):63–68
- Meltzer EO et al (2010) Treatment of congestion in upper respiratory diseases. *Int J Gen Med* 8(3):69–91
- Craig TJ, Sherkat A, Safae S (2010) Congestion and sleep impairment in allergic rhinitis. *Curr Allergy Asthma Rep* 10(2):113–121
- Sardana N, Craig TJ (2011) Congestion and sleep impairment in allergic rhinitis. *Asian Pac J Allergy Immunol* 29(4):297–306
- Baena-Cagnani CE (2004) Safety and tolerability of treatments for allergic rhinitis in children. *Drug Saf* 27:883–898
- Hardjojo A et al (2011) Rhinitis in children less than 6 years of age: current knowledge and challenges. *Asia Pac Allergy* 1(3):115–122
- Greiner AN et al (2011) Allergic rhinitis. *Lancet* 378(9809):2112–2122
- Al Sayyad JJ et al (2007) Topical nasal steroids for intermittent and persistent allergic rhinitis in children. *Cochrane Database Syst Rev* 1:CD003163

12. Aberer W et al (2003) Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 58(9):854–863
13. Scadding G (2008) Optimal management of nasal congestion caused by allergic rhinitis in children: safety and efficacy of medical treatments. *Paediatr Drugs* 10(3):151–162
14. Damiani V et al (2012) A single-centre, before-after study of the short- and long-term efficacy of Narivent(R) in the treatment of nasal congestion. *J Int Med Res* 40(5):1931–1941
15. Cavone L et al (2012) Topical mannitol reduces inflammatory edema in a rat model of arthritis. *Pharmacology* 89(1–2):18–21
16. Mollica L et al (2007) Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. *Chem Biol* 14(4):431–441
17. Brozek JL et al (2010) Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 126(3):466–476
18. Lund VJ, Mackay IS (1993) Staging in rhinosinusitis. *Rhinology* 31(4):183–184
19. Lund VJ, Scadding GK (1994) Objective assessment of endoscopic sinus surgery in the management of chronic rhinosinusitis: an update. *J Laryngol Otol* 108(9):749–753
20. Saedi B et al (2011) Diagnostic efficacy of different methods in the assessment of adenoid hypertrophy. *Am J Otolaryngol* 32(2):147–151
21. Cassano P et al (2003) Adenoid tissue rhinopharyngeal obstruction grading based on fiber endoscopic findings: a novel approach to therapeutic management. *Int J Pediatr Otorhinolaryngol* 67(12):1303–1309
22. Krouse J et al (2010) Diagnostic strategies in nasal congestion. *Int J Gen Med* 8(3):59–67
23. Passali D et al (1999) Alterations of nasal mucociliary transport in patients with hypertrophy of the inferior turbinates, deviations of the nasal septum and chronic sinusitis. *Eur Arch Otorhinolaryngol* 256(7):335–337
24. Ciprandi G et al (2009) Visual analog scale (VAS) and nasal obstruction in persistent allergic rhinitis. *Otolaryngol Head Neck Surg* 141:527–529
25. Sweetman SC (2007) Martindale. The extra pharmacopoeia. 35 edn. Pharmaceutical Press, London
26. Asl MN, Hosseinzadeh H (2008) Review of pharmacological effects of *Glycyrrhiza* sp. and its bioactive compounds. *Phytother Res* 22(6):709–724
27. Bianchi ME, Manfredi AA (2007) High-mobility group box 1 (HMGB1) protein at the crossroads between innate and adaptive immunity. *Immunol Rev* 220:35–46
28. Mollica L et al (2007) Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. *Chem Biol* 14(4):431–441
29. Cavone L et al (2011) 18 β -Glycyrrhetic acid inhibits immune activation triggered by HMGB1, a pro-inflammatory protein found in the tear fluid during conjunctivitis and blepharitis. *Ocul Immunol Inflamm* 19(3):180–185
30. R Development Core Team (2012) A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
31. Bousquet J et al (2008) Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(Suppl 86):8–160
32. André RF et al (2009) Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. *Clin Otolaryngol* 34(6):518–525
33. van Spronsen E et al (2008) Evidence-based recommendations regarding the differential diagnosis and assessment of nasal congestion: using the new GRADE system. *Allergy* 63(7):820–833
34. Kim CS et al (1998) Correlation between nasal obstruction symptoms and objective parameters of acoustic rhinometry and rhinomanometry. *Auris Nasus Larynx* 25(1):45–48
35. Jáuregui I et al (2011) Validation of ARIA (Allergic Rhinitis and its Impact on Asthma) classification in a pediatric population: the PEDRIAL study. *Pediatr Allergy Immunol* 22(4):388–392
36. Kakumanu S, Glass C, Craig T (2002) Poor sleep and daytime somnolence in allergic rhinitis: significance of nasal congestion. *Am J Respir Med* 1(3):195–200
37. Fokkens W et al (2007) European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology* 20(Suppl):1–136
38. WHO, WHO Model List of Essential Medicines for Children. 2013(April 2013)
39. Brozek JL et al (2010) Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 126(3):466–476
40. Sastre J, Mosges R (2012) Local and systemic safety of intranasal corticosteroids. *J Investig Allergol Clin Immunol* 22(1):1–12
41. Backhouse CI, Finnamore VP, Gosden CW (1986) Treatment of seasonal allergic rhinitis with flunisolide and terfenadine. *J Int Med Res* 14(1):35–41
42. Mullol J et al (2011) Mometasone and desloratadine additive effect on eosinophil survival and cytokine secretion from epithelial cells. *Respir Res* 12:23
43. Uzzaman A, Story R (2012) Chapter 5: allergic rhinitis. *Allergy Asthma Proc* 33(Suppl 1):S15–S18