Send Orders of Reprints at Reprints@benthamscience.org

A Before-after Assessment of the Efficacy of Narivent® in the Treatment of Symptoms Associated with Allergic Rhinitis in a Paediatric Population

Nicola Mansi[1], Gabriele D'Agostino[1], Antonella Silvia Scirè[2], Giada Morpurgo[2], Dario Gregori[3], Valerio Damiani[4,*]

[1]*S.C. di Otorinolaringoiatria della A.O.R.N. Santobono Pausilipon di Napoli, Italy*

[2]*Zeta Research Srl, Trieste, Italy*

[3]*Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy*

[4] *ENT Department San Giovanni Addolorata Hospital, Rome, Italy*

Abstract: *Rationale and aim:* Allergic rhinitis (AR) is a common disorder that affects people of all ages, peaking in childhood and in the teenage years. Although AR is not a serious disease, it is clinically relevant because underlies many symptoms and complications which severely affect children's quality of life.

The aim of this study was to evaluate the clinical effectiveness of Narivent®, an osmotically acting medical device with anti-oedematous and anti-inflammatory effects, in the treatment of symptoms associated with allergic rhinitis in a paediatric population.

Methods: A single-centre prospective study with a pre-post design was conducted with consecutive enrolment in an Italian Otolaryngology Department of 20 both genders children with allergic rhinitis.

Patients received 1 puff of Narivent® into each nostril 2 times a day over the course of 4 weeks. The severity of major symptoms associated with AR, such as nasal congestion, rhinorrhoea, sneezing and nasal itching, was assessed subjectively as measured by a 0 to 10 visual analogue scale (VAS).

Differences in subjective severity measures before and after treatment were compared using Paired-Sample Wilcoxon Signed Rank Test.

Results: Nasal congestion, rhinorrhoea and sneezing significantly improve after treatment ($p<0.001$).

Conclusion: Study results confirm the efficacy of Narivent® in the treatment of nasal congestion and other major symptoms in children with AR over a 4 weeks period.

Keywords: Paediatric allergic rhinitis, osmotically acting medical device, anti-oedematous activity, anti-inflammatory activity.

INTRODUCTION

Inflammatory disorders of the upper respiratory tract are very common diseases, with high prevalence recorded in industrialised nations. Allergic rhinitis (AR), in particular, represents a global health problem affecting up to 40% of the general population [1, 2].

AR is an antigen-mediated inflammation of the nasal mucosa that may extend into the paranasal sinuses and, along with asthma, is the most common chronic disorder in childhood and adolescence. Its prevalence in children is estimated to be 10–40% and appears to be increasing throughout the world [3, 4].

*Address correspondence to this author at the ENT Department San Giovanni Addolorata Hospital, Via dell'Amba Aradam, 9, 00186 Rome - Italy; Tel: +39 06 7705428; Fax: +390677053253;
E-mail: valeriodamiani76@gmail.com

AR is often considered as a mild disorder. It may be in fact regarded by parents as an irritation rather than as a significant disease and consequently to be ignored, underdiagnosed, misdiagnosed (with symptoms frequently attributed to a recurrent cold) and mistreated [4].

However, many studies have shown that allergic rhinitis has a deleterious impact upon children's daily life, quality of sleep, school performance and participation in social activities, as well as physical and emotional health [5, 6].

AR is characterized by symptoms of sneezing and nasal itching with obstruction and mucosal discharge, caused by an IgE-mediated reaction, and traditionally is classified as either perennial (PAR) or seasonal ('hay fever'), dependent on whether symptoms occur throughout the year or in relation to seasonal exposure to allergen [4, 6].

Seasonal AR is a disease particularly of teenagers and young adults and typical allergens include tree/grass pollens and fungal spores. On the contrary, perennial rhinitis with

1875-1814/12

the prominent symptom of nasal blockage is more common in primary and preschool age children and allergens usually implicated include the house dust mite (HDM) (e.g. Dermatophagoides pteronyssinus and Dermatophagoides farinaeae) and animal dander [4]. The pattern of rhinitis (seasonal or perennial) also depends by the climatic environment (temperate or tropical) [6].

Initial allergen exposure in susceptible subjects results in the production of IgE antibodies, which become fixed to cells such as mast cells, a process known as sensitisation. Subsequent exposure causes the release of inflammatory mediators (such as histamine, bradykinin, prostaglandins, leukotrienes) generating an immediate, IgE-dependent allergic response and leading to increased nasal obstruction, tissue oedema and production of secretions.

Ongoing allergen exposure induces nasal airway hyperresponsiveness (NAHR), which is a hallmark of AR and can be defined as an increased nasal response to a normal stimulus resulting in sneezing, nasal congestion and secretion, either one of these symptoms or in various combinations [7]. Most of patients with AR also experience a late phase reaction 6-12 h after exposure, related histologically to an influx of inflammatory cells (including eosinophils, neutrophils and T-lymphocytes) to the nasal airways, where they release a variety of mediators that further exacerbate symptoms [4, 8].

Nasal congestion is therefore a prominent manifestation of allergic rhinitis and is often the symptom patients find most troublesome and would like most to prevent [9, 10]. Furthermore, typical sleep-related problems seen in AR, such as sleep-disordered breathing, sleep apnea, and snoring, are associated with nasal obstruction [11].

Other complications of AR in children include the exacerbation of asthma, deviations in facial growth, reduction of sense of smell (hyposmia), incisor protrusion, malocclusion, nasal polyps, sinusitis and middle ear effusion/hearing loss [12].

As a consequence of the importance of symptoms related to AR, an alternative functional classification has been proposed in 2001 by the World Health Organization based on symptom severity (mild/moderate-severe) and frequency (intermittent/persistent) and useful in decisions regarding therapy to treat allergic rhinitis [6].

The goal of current treatments is to manage the subjective symptoms and to improve objective measures of the disease. Therapies for allergic rhinitis include topical corticosteroids, sedating and non-sedating antihistamines, topical cromolyn sodium (sodium cromoglycate), decongestants, immunotherapy and topical ipratropium bromide. Of the available treatment options for paediatric allergic rhinitis, the newer oral antihistamines and intranasal corticosteroids are first-line treatments [13, 14].

First-generation antihistamines may cause cardiotoxicity, sedation and impairment of psychomotor, cognitive and academic functions in children, whereas the newer antihistamines (developed to be more specific for the histamine H1 receptor) have allowed overcoming these adverse effects. They are the medication of choice in patients with mild intermittent allergic rhinitis, but are poorly effective in the management of more severe cases and their effect on nasal congestion is relatively modest [13].

Intranasal corticosteroids are the most effective anti-inflammatory agents used for the treatment of paediatric allergic rhinitis, but the safety of these compounds remains controversial, implicating long-term treatments and dose-related systemic effects, such as suppression of adrenocortical function, growth and bone metabolism [13].

Other treatments, such as decongestants and immunotherapy, present varying levels of safety and tolerability issues in children [15].

The pharmacotherapy of AR in children requires therefore great attention to dosing and the avoidance of the numerous adverse effects related to standard therapies. That is why there is a growing need for alternative or co-adjuvant treatments capable of relieving symptoms associated with allergic rhinitis in children, allowing a reduction in the amount of pharmacological therapy.

The present study was conducted in order to evaluate the safety and the clinical effectiveness of Narivent®, an osmotically acting medical device with anti-oedematous and anti-inflammatory effects, in the management of symptoms associated with allergic rhinitis in a paediatric population.

Nasal obstruction, rhinorrhea, sneezing and nasal itching, were assessed subjectively before and after the treatment. The visual analog scale (VAS) was used to understanding symptom severity from the patient's perspective [16]. This tool allows patients to rate their symptoms on a linear scale, where 0 corresponds to symptoms that are not troublesome at all and 10 is the most troublesome symptom imaginable [17].

METHODS

Study Design

A single-centre prospective study with a pre-post design was conducted in the Department of Otorhinolaryngology at the A.O.R.N. Santobono Pausilipon Hospital (Napoli, Italy) with consecutive enrolment of 20 patients of both genders, aged between 5 and 18 years old, with persistent or intermittent allergic rhinitis. Exclusion criteria were a diagnosis of cystic fibrosis, a diagnosis of Kartagener syndrome, the presence of concomitant chronic rhinologic diseases, any acute upper respiratory infections, the presence of massive occlusive polyps in the sinus and the concurrent use of corticosteroids.

At study enrolment, patients' parents or tutors were asked for verbal and written informed consent. Study was conducted in compliance with the requirements of the local Institutional Review Board.

Study Conduct

In accordance with the study protocol, patients received 1 puff of Narivent® into each nostril 2 times a day over the course of 4 weeks.

Patients were visited by the investigators twice during the study period, at the enrolment and after 1 month.

A physical examination was conducted at the first visit through a complete ENT endoscopy. Data were collected as follows:

- Turbinate hypertrophy was classified according to the examiner's personal experience as absent, good (turbinates obstructing 1/3 of nasal fossae), fair (turbinates obstructing 2/3 of nasal fossae) or poor (turbinates completely obstructing nasal fossae).
- Septal deviation was classified according to the examiner's personal experience as absent, good (septum slightly deviated from baseline), fair (septum significantly deviated from baseline) or poor (obstructing septum).
- Nasal polyps were classified according to the Lund-Mackay scale [18, 19].
- Adenoid hypertrophy was classified as absent, good (slightly increased adenoids), fair (increased adenoids but not beyond tubal ostium) or poor (adenoids beyond tubal ostium) [20, 21].
- Nasal mucosa was classified by the examiner (only one possible answer) as: normal, hyperaemic, pallid/livid or atrophic.
- Nasal secretions were classified by the examiner (only one possible answer) as: absent, haematic/purulent, pallid/serous or mucous.

During each visit a VAS was used to quantify the subjective feeling of nasal obstruction, rhinorrhea, sneezing and nasal itching [22]. The subjective symptom score was obtained with a visual analogue scale modified from Eccles' model [23]. Patients rated the perceived degree of their obstruction on a scale of 0 (complete patency) to 10 (complete stenosis).

Adverse effect were also recorded. Study was conducted in compliance with the requirements of the local Institutional Review Board.

Medical Device Description

According to the Directive 93/42/EEC on medical devices and subsequent amendments, Narivent® belongs to class I according to the application of the rule 5 of annex IX.

Narivent® is a nasal spray which acts osmotically with anti-oedematous and anti-inflammatory effects and lubricant properties.

It is indicated to decrease nasal congestion caused by turbinate hypertrophy, vasomotor rhinopathies, and in the treatment of oedema associated with inflammatory conditions in rhino-sinus non-occlusive polyposis and adenoid pathology.

Narivent® is also indicated in the postoperative management of rhino-sinus diseases and in the treatment and prophylaxis of postoperative recurrence of nasal polyps.

The anti-oedematous action of this medical device derives from the high concentration of mannitol, which is known in the medical field to carry out a wide osmotic activity [24], whereas the anti-inflammatory action is due to the presence of glycyrrhizin, a glucosidic triterpene extracted from the roots of the liquorice plant. Glycyrrhizin is a natural anti-inflammatory and is the first direct inhibitor of the intranuclear protein HMGB1 (High-Mobility Group Box 1 protein), which may be considered a cytokine acting as a potent pro-inflammatory mediator when released in the extracellular environment [25, 26].

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 0.80. At this error level, 15 subjects are required to detect as significant a change in VAS of 2 points (SD 2.5) after the administration of the treatment. Assuming a drop-out rate of 30%, 20 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 Paired-Sample Wilcoxon Signed Rank Test. Tests were performed using the R system [27].

RESULTS

Ten males and ten females were enrolled. Median age was 9.6 years (I quartile: 6.9; III quartile: 12.3). In Table **1** the description of the study population, the type of diagnosis, the main causes of allergic sensitisation based on skin prick test results, and previous therapies eventually used are reported.

With regard to the type of diagnosis based on symptoms frequency, at the enrolment 53% (10) of patients reported persistent allergic rhinitis, while the remaining patients were diagnosed with intermittent allergic rhinitis (47%; 9). One missing data was recorded.

The severity of symptoms was judged moderate-severe in 13 patients (72%) and mild in the other cases (28%; 6). Two missing data were recorded.

Table **1** also shows the results of the physical examination of the sample, regarding the concomitant presence of turbinate hypertrophy, nasal septal deviation, adenoid hypertrophy and nasal polyposis, mucosa status and the type of nasal secretion observed in patients.

Table **2** reports the level of compliance with the treatment, the adverse reactions recorded and concurrent therapies.

Table **3** shows the subjective evaluation of symptoms before and after the therapy: nasal obstruction, rhinorrhea and sneezing significantly decrease ($p<0.001$) after the treatment with Narivent®.

DISCUSSION

Allergic rhinitis (AR), an inflammatory disorder of nasal mucosa characterised by itching, sneezing, rhinorrhoea and nasal congestion, is a widespread disease in children and adolescents [4, 8]. Although AR is not a serious illness, it is clinically relevant because represents a major risk factor for poor asthma control and affects negatively upon quality of life, being a major cause of morbidity that includes interference with usual daily activities, school performance and impaired sleep quality [28].

Table 1. Study Population's Characteristics. Numbers are I Quartile / Median/III Quartile. Type of Diagnosis Based on Symptoms Frequency (Missing Data: 1/20) and Severity (Missing Data: 2/20) / Causes of Allergic Sensitisation Based on Prick test Results / Previous Pharmacotherapies / Physical Examination

		N	Summary Statistics (N=20)
Gender	M	20	50% (10)
	F		50% (10)
Age[yrs]		20	6.885695/9.583847/12.277207
Allergic rhinitis (AR)	Persistent	19	53% (10)
	Intermittent		47% (9)
AR severity	Moderate-severe	18	72% (13)
	Mild		28% (5)
Predominant allergic sensitisation (based on skin prick test)	Mites	20	15% (3)
	Mites/Graminaceae/Parietaria		5% (1)
	Alternaria		10% (2)
	Dermatophagoides farinaeae		5% (1)
	Dermatophagoides farinaeae/ Dermato-phagoides pteronyssinus		10% (2)
	Graminaceae		5% (1)
	Graminaceae/Parietaria		5% (1)
	Graminaceae mix		5% (1)
	Olive		25% (5)
	Parietaria		15% (3)
Previous therapies	No therapy	20	25% (5)
	Nasal corticosteroids		65% (13)
	Systemic corticosteroids		10% (2)
	Antihistamine		30% (6)
Physical Examination			
Turbinate hypertrophy	Absent	20	0% (0)
	Good		80% (16)
	Fair		15% (3)
	Poor		5% (1)
Septal deviation	Absent	20	95% (19)
	Good		5% (1)
	Fair		0% (0)
	Poor		0% (0)
Adenoid hypertrophy	Absent	20	50% (10)
	Good		45% (9)
	Fair		0% (0)
	Poor		5% (1)
Nasal polyposis	I	20	0%(0)
	II		0%(0)
	III		0%(0)
Mucosa status	Normal	20	0% (0)
	Hyperemic		65% (13)
	Pallid/livid		35% (7)

Table 1. contd…

		N	Summary Statistics (N=20)
	Atrophyc		0%
Type of secretion	Absent	20	5%(1)
	Haematic-purulent		0% (0)
	Pallid-serum		65% (13)
	Mucous		30% (6)

*Classification according to the Lund-Mackay scale

Table 2. Compliance with the Treatment / Adverse Reactions / Concurrent treatments (missing data: 2/20)

		N	Summary Statistics (N=20)
Compliance	High	20	35% (7)
	Fair		55% (11)
	Poor		10% (2)
Presence of adverse reactions	None	20	65% (13)
	Epistaxis		5% (1)
	Nasal dryness		30% (6)
Concurrent treatments	No therapy	18	88% (16)
	Nasal corticosteroid		0% (0)
	Antihistamine		12% (2)
	Hypertonic solution		0% (0)

Table 3. VAS Score Rating Relative to Symptoms' Subjective Evaluation before and after Treatment. Numbers are I Quartile/Median/III Quartile. P-value Refers to a Significantly Different Distribution of each given Variable before and after Treatment with Narivent®

Subjective Symtoms (VAS)	Pre (N=20)	Post (N=20)	Combined (N=40)	Test
				Statistic
Nasal obstruction	64.5/72.0/78.5	8.0/15.0/21.0	15.0/48.5/72.0	P<0.001
Rhinorrhea	41.00/59.5077.00	6.50/14.00/20.50	12.75/31.00/58.25	P<0.001
Sneezing	10.25/31.00/41.00	0.00/ 1.00/ 9.75	0.75/10.00/33.50	P<0.001
Nasal itching	0.75/5.50/18.25	0.00/ 1.00/ 6.50	0.00/2.00/9.50	P=0.182

AR underlies many relevant complications including conjunctivitis, sinusitis, otitis media due to Eustachian tube obstruction and hypertrophy with prominence of adenoidal and tonsillar tissue caused by chronic inflammation. These complications may be also associated with reduced appetite, delayed growth and obstructive sleep apnoea, as well as fatigue and mood changes [15].

Nasal congestion is a prominent and troublesome symptom of allergic rhinitis and, taking into account the pervasiveness of this condition along with other upper respiratory disorders, represents a highly prevalent problem [29].

The complaint of a blocked nose is a multifactorial and complex clinical problem. The perception of nasal airflow is a subjective sensation and is therefore, by definition, difficult to quantify. Moreover, inconsistency between subjective nasal obstruction and the appearance of the nasal cavities is not uncommon [30-32].

Objective methods to assess the nasal airway include nasal endoscopy, rhinomanometry and rhinometry (which assess nasal airflow), exhaled nitric oxide (a marker of inflammation and/or nasal polyposis) and cytological evaluation (nasal smear, lavage and biopsy) [4].

However, even though lacking in objectivity, a patient's subjective sensation of nasal blockage, assessed by validated questionnaires or visual analogue scales, seems to offer the most valuable information concerning the degree of nasal obstruction [30].

In fact, questionnaires, symptom scoring systems and particularly VAS are all tolls capable of determining subjective changes in perceived congestion severity, offering a

reproducible and quantifiable evaluation of patients' symptoms [30-32].

The pharmacological therapy of AR in children is similar in many aspects to that in adults but requires attention to dosing and the avoidance of adverse effects. Numerous options exist and, because of the burden of symptomatology, the focus of treatment revolves around symptoms and their improvement. Complete allergen avoidance should completely stop or result in reduced symptoms of allergic rhinitis, but the degree of avoidance required may prove difficult or impossible to attain [4, 8].

Careful assessment of nasal symptoms allows for the most appropriate therapeutic options to be chosen and for this purpose the most effective treatment is represented by intranasal corticosteroids. Although topical corticosteroids are the treatment of choice for persistent moderate-severe allergic rhinitis, even in children, the use is controversial because of their safety profile [8, 2].

In opposition with pharmacotherapy which provides symptom suppression, the aim of immunotherapy is to alter the immune system representing a cure for AR. However, the benefits of immunotherapy in house dust mite-induced rhinitis and asthma remain uncertain [8].

Antihistamines reduce rhinorrhoea and sneeze but they are of limited benefit in rhinitis caused by house dust mite and other perennial allergens, where the predominant symptom is nasal obstruction which is not histamine mediated. In addition, they frequently cause adverse effects, such as somnolence, impaired cognitive functioning, restlessness, insomnia and anticholinergic effects, such as dry mouth and blurred vision [4, 8].

Systemic and topical nasal decongestants are very effective in relieving nasal congestion but are generally not recommended because of safety concerns. Decongestants, particularly oral agents, are associated with insomnia, irritability and poor school performance, and may induce cardiac events in some children [8].

Considering the numerous side effects related to standard therapies and long-term treatments, there is a growing need for alternative or co-adjuvant treatments capable of relieving symptoms associated with AR in children and not involving major side effects.

Narivent® is a medical device which acts osmotically, carrying out anti-oedematous, anti-inflammatory and lubricant effects thanks to the presence of components such as mannitol and glycyrrhizin.

This pre-post study aimed to assess if the treatment with Narivent® is effective in reducing nasal obstruction and other major symptoms in children with allergic rhinitis. Patients' perception of nasal symptoms was evaluated using the VAS.

After the treatment a significant improvement in nasal congestion with a subjective sensation of reduced nasal resistance was found.

Our results also showed a relevant control of other predominant symptoms of allergic rhinitis, including rhinorrhoea, sneezing and nasal itching.

No severe adverse effects were reported by patients over the treatment period and the compliance with the product was generally assessed as high.

Final Remarks

This study provides evidence that in paediatric patients with allergic rhinitis Narivent® can improve nasal symptoms' control over a long period of time, demonstrating its efficacy even when used as unique therapeutic approach for the management of symptomatology.

ACKNOWLEDGEMENTS AND CONFLICT OF INTERESTS

The authors are deeply thankful to DMG Italia for providing Narivent® free of charge for the conduct of the study.

Authors Antonella Silvia Scirè and Giada Morpurgo have ongoing contracts with DMG Italia for conducting clinical studies.

The other authors of the above manuscript declared no conflict of interest.

REFERENCES

[1] Lunn M, Craig T. Rhinitis and sleep. Sleep Med Rev 2011; 15(5): 293-9.

[2] Brozek JL, Bousquet J, Baens Caqnani CE, *et al*.: Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010; 126(3): 466-76.

[3] de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. Thorax 2012; 67(7): 582-7.

[4] Turner PJ, Kemp AS. Allergic rhinitis in children. J Paediatr Child Health 2012; 48(4): 302-10.

[5] Westman M, Stjärne P, Asarnoj A, *et al.* Natural course and comorbidities of allergic and nonallergic rhinitis in children. J Allergy Clin Immunol 2012; 129(2): 403-8.

[6] Kemp AS. Allergic rhinitis. Paediatr Respir Rev 2009; 10(2): 63-8.

[7] Bousquet J, Khaltaev N, Cruz AA, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008; 63(Suppl 86): 8-160.

[8] Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet 2011; 378(9809): 2112-22.

[9] Meltzer EO, Caballero F, Fromer LM, Krouse JH, Scadding G. Treatment of congestion in upper respiratory diseases. Int J Gen Med 2010; 8(3): 69-91.

[10] Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. Curr Allergy Asthma Rep 2010; 10(2): 113-21.

[11] Sardana N, Craig TJ. Congestion and sleep impairment in allergic rhinitis. Asian Pac J Allergy Immunol 2011; 29(4): 297-306.

[12] DeGuzman DA, Bettcher CM, VanHarrison R, *et al.* Allergic Rhinitis: Guidelines for clinical care. University of Michigan Health Systems. Available at: http://cme.med.umich.edu/pdf-/guideline/allergic07.pdf updated October 2007.

[13] Baena-Cagnani CE. Safety and tolerability of treatments for allergic rhinitis in children. Drug Saf 2004; 27: 883-98.

[14] Kakumanu S, Glass C. Poor sleep and daytime somnolence in allergic rhinitis: significance of nasal congestion. Am J Respir Med 2002; 1(3): 195-200.

[15] Scadding G. Optimal management of nasal congestion caused by allergic rhinitis in children: safety and efficacy of medical treatments. Paediatr Drugs 2008; 10(3): 151-62.

[16] Krouse J, Lund V, Fokkens W, Meltzer EO. Diagnostic strategies in nasal congestion. Int J Gen Med 2010; 8(3): 59 - 67.

[17] Passali D, Ferri R, Becchini G, Passali GC, Bellussi L. Alterations of nasal mucociliary transport in patients with hypertrophy of the inferior turbinates, deviations of the nasal septum and chronic sinusitis. Eur Arch Otorhinolaryngol 1999; 256(7): 335-7.

[18] Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology 1993; 31(4): 183-4.
[19] Lund VJ, Scadding GK. Objective assessment of endoscopic sinus surgery in the management of chronic rhinosinusitis: an update. J Laryngol Otol 1994; 108(9): 749-53.
[20] Saedi B, Sadeghi M, Mojtahed M, Mahboubi H. Diagnostic efficacy of different methods in the assessment of adenoid hypertrophy. Am J Otolaryngol 2011; 32(2): 147-51.
[21] Cassano P, Gelardi M, Cassano M, Fiorella ML, Fiorella R. Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: a novel approach to therapeutic management. Int J Pediatr Otorhinolaryngol 2003; 67(12): 1303-9.
[22] Ciprandi G, Mora F, Cassano M, Gallina AM, Mora R. Visual analog scale (VAS) and nasal obstruction in persistent allergic rhinitis. Otolaryngol Head Neck Surg 2009; 141: 527-9.
[23] Eccles R. Nasal airway resistance and nasal sensation of airflow. Rhinol Suppl 1992; 14: 86-90.
[24] Sweetman SC. Martindale. The Extra Pharmacopoeia. Thirty-five ed. London: Pharmaceutical Press 2007.
[25] Asl MN, Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp.and its bioactive compounds. Phytother Res 2008; 22(6): 709-24.
[26] Cavone L, Muzzi M, Mencucci R, *et al.* 18 -glycyrrhetic acid inhibits immune activation triggered by HMGB1, a pro-inflammatory protein found in the tear fluid during conjunctivitis and blepharitis. Ocul Immunol Inflamm 2011; 19(3): 180-5.
[27] R Development Core Team R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing 2012.
[28] Walker SM, Clark AT, Dixon TA, *et al.* BSACI guidelines. Immunotherapy for allergic rhinitis. Clin Exp Allergy 2011; 41: 1177-200.
[29] Naclerio RM, Bachert C, Baraniuk JN. Pathophysiology of nasal congestion. Int J Gen Med 2010; 8(3): 47-57.
[30] André RF, Vuyk HD, Ahmed A, Graamans K, Nolst TGJ. Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. Clin Otolaryngol 2009; 34(6): 518-25.
[31] van Spronsen E, Ingels KJ, Jansen AH, Graamans K, Fokkens WJ. Evidence-based recommendations regarding the differential diagnosis and assessment of nasal congestion: using the new GRADE system. Allergy 2008; 63(7): 820-33.
[32] Kim CS, Moon BK, Jung DH, Min YG. Correlation between nasal obstruction symptoms and objective parameters of acoustic rhinometry and rhinomanometry. Auris Nasus Larynx 1998; 25(1): 45-8.

Received: August 08, 2012 Revised: August 15, 2012 Accepted: August 17, 2012