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Short-term Efficacy of Narivent® in the Treatment of Nasal Congestion

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Abstract: *Rationale and aim:* Nasal congestion is a common symptom in rhinologic diseases such as rhinosinusitis, nasal polyposis and adenoid pathology. Although various pharmacotherapy options exist, no agent is universally efficacious. The aim of this study was to evaluate the efficacy of Narivent®, an osmotically acting medical device with anti-oedematous and anti-inflammatory effects, in a short-term (7days) treatment.

Methods: A single-centre prospective study with a pre-post design was conducted with consecutive enrolment in an Italian Otolaryngology Department of 36 both genders patients with nasal congestion. Patients received 2 puffs of Narivent® into each nostril 2 times a day over the course of 1 week. The severity of symptoms was assessed subjectively as measured by a 0 to 10 visual analogue scale (VAS) and the presence/absence of symptoms and signs. Differences in subjective and objective severity measures before and after treatment were compared using Paired-Sample Wilcoxon Signed Rank Test.

Results: A significant improvement after treatment ($p<0.001$) has been recorded for the main subjective symptoms and objective signs (overall symptom burden, nasal congestion, cephalea, turbinates hypertrophy, normal mucosa status).

Conclusion: Study results confirm the efficacy of Narivent® in treating nasal congestion over a 1 week period.

Keywords: nasal congestion, osmotically acting medical device, anti-oedematous activity, anti-inflammatory activity.

INTRODUCTION

Nasal congestion, which may be best described as a feeling of blockage, fullness, or restricted airflow, is a common presenting complaint of rhinopathies such as rhinosinusitis, nasal polyposis and adenoid pathology. Other primary symptoms of these conditions are reduction/loss of smell, rhinorrhea, facial pain or pressure and headache [1-4].

Reversible nasal congestion is usually caused by mucosal inflammation and secretions, while obstruction (often used as synonymous with congestion) usually refers to irreversible blockage and to a fixed or relatively constant congestion. It may be due to occlusion (e.g.: nasal polyps), anatomical variation (e.g.: septal deformity, turbinate hypertrophy) or, rarely, neoplasm [2].

It has a complex pathophysiology that involves neural, vascular, and inflammatory elements [5]. It is associated with inflammation of the nasal epithelium and the generation of inflammatory mediators that cause dilatation of nasal blood vessels [6].

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Mucosal inflammation therefore underlies many of the specific and interrelated factors that contribute to nasal congestion, as well as other symptoms of both allergic rhinitis and rhinosinusitis [7]. A wide range of biologically active agents (e.g.: histamine, tumour necrosis factor-α, interleukins, cell adhesion molecules) and cell types contribute to inflammation, which can manifest as venous engorgement, increased nasal secretions and tissue swelling/oedema, ultimately leading to impaired airflow and the sensation of nasal congestion [7].

Diagnostic tools commonly used to assess the nasal airway are 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) [8]. Anterior rhinoscopy is limited in its evaluation of the entire nasal cavity and therefore complete and thorough examination using nasal endoscopy is advocated. In addition, the Lund–Mackay system of scoring nasal endoscopy findings is the only system regarding mucosal thickening (oedema) [9].

Beyond the objective measurements, the perception of nasal airflow is a subjective sensation and is therefore, by definition, hard to quantify unless it is nearly complete In clinical practice consequently, it is often difficult to assess the relative importance of individual factors contributing to nasal obstruction and to decide on the therapy most likely to be effective in restoring satisfactory nasal breathing [10].

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Moreover, inconsistency between subjective nasal obstruction and the appearance of the nasal cavities is not uncommon and there has always been controversy about the relationship between the subjective assessment of nasal obstruction and the objective measurement of nasal airway obstruction using rhinomanometry [11].

Even so, efforts are continuously being made to improve the ability to 'objectively' measure nasal patency [10].

Regarding the subjective symptomatology, questionnaires, VAS and the various symptom scoring systems are all capable of determining subjective changes in perceived congestion severity. Moreover therapeutic intervention is always aimed at relieving subjective complaints and therefore subjective parameters are necessary [9].

For this purpose, the Visual Analogue Scale (VAS) offers a reproducible, quantifiable evaluation of patients' symptoms, which may provide more subtle information than simply asking if the patient is better, the same or worse [12, 13].

Nasal congestion can impact upon quality of life (QoL) and affect work/school productivity and the ability to perform daily activities. Furthermore, nasal congestion can disturb sleep and impaired sleep can cause daytime somnolence, decreased alertness, increased accident rates and reduced work efficiency, and may lead to irritability and depression [14].

Symptoms in chronic and acute rhinopathies are very similar but they may vary in intensity, with more intense symptoms in acute pathologies [15].

Treatments for relief of nasal congestion may be considered as environmental control measures, medical therapy and surgical intervention. Standard conservative treatment for acute conditions, such as acute rhinosinusitis with or without nasal polyposis, is based on oral antibiotics (for severe cases), topical corticosteroids, topical steroid and oral antibiotic combined, oral corticosteroid (to reduce pain in severe cases); decongestants are used for symptomatic relief [15].

Although various pharmacotherapy options exist, no agent is universally efficacious, and there is a paucity of data supporting commonly used symptomatic therapies [1].

The present study was conducted in order to evaluate the safety and the clinical effectiveness of Narivent®, which is an osmotically acting medical device with anti-oedematous and anti-inflammatory effects, in patients with rhinosinusitis, nasal polyposis and adenoid pathology in a short term treatment. Nasal obstruction was assessed both subjectively and objectively. A well-established approach, a visual analogue scale (VAS), was used to understanding symptom severity from the patient's perspective [16]. The VAS 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 ENT Department at the San Giovanni Addolorata Hospital, (Rome, Italy) with consecutive enrolment of 36 patients of both genders with nasal congestion caused by mucus catarrhal rhinosinusitis, turbinate hypertrophy vasomotor rhinopathies, rhino-sinus non-occlusive polyposis, or adenoid pathology. Patients were excluded if they had: a diagnosis of cystic fibrosis; the presence of asthma episodes in the 30 days preceding the study; any acute upper respiratory tract infections; the presence of massive occlusive polyps in the sinus; used nasal or oral corticosteroids or decongestants during the 4 weeks preceding the study; or used antileukotrienes or antihistamines during the previous week.

At study enrolment, patients were asked for their verbal and written informed consent.

In accordance with the study protocol, patients received 2 puffs of Narivent® into each nostril 2 times a day over the course of one week. Patients were visited by the investigators twice during the study period, at enrolment and after 1 week.

A physical examination was conducted at every 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 [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). Likewise, VAS was used for other symptoms. Adverse effects 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 medical devices applying the rule 5 of annex IX.

Table 1. Study Population's Characteristics. Numbers are I Quartile/Median/III Quartile

		N	Summary Statistics (N=36)
Age:		36	32.75/42.00/58.25
Gender:	M	36	58% (21)
	F		42% (15)
Diagnosis:	Polyposis	36	17% (6)
	Hypertrophic rhinopathy		17% (6)
	Adenoid hypertrophy		3% (1)
	Turbinate hypertrophy		42% (15)
	Mucus-catarrhal rhinopathy		22% (8)
Septal deviation:	Absent	35	17% (6)
	Good		72% (26)
	Fair		11% (4)
Nasal polyposis*:	Absent	35	86% (31)
	I		0% (0)
	II		8% (3)
	III		6% (2)

*Classification according to the Lund-Mackay scale

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 particularly 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 outcomes of the present study were symptom resolution (improvement in each symptom score from enrolment to week 1) and improvement in overall symptom burden (as measured by the overall 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, 34 subjects are required to detect as significant a change in VAS of 2 points (SD 3) after the administration of the treatment. Assuming a drop-out rate of 5%, 36 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

Twenty-one males and 15 females were enrolled. Median age was 42 years (I quartile: 32.75; III quartile: 58.25). At enrolment 17% (6) of the patients reported hypertrophic rhinopathy, 3% (1) adenoid hypertrophy, 22% (8) mucus-catarrhal rhinopathy, 17% (6) polyposis and 42% (15) turbinate hypertrophy (see Table **1**).

One patient was lost to follow-up because of the presence of paradoxical nasal obstruction. Therefore, statistical analysis was performed on 35 patients rather than 36.

Table **2** shows the subjective evaluation of symptoms before and after treatment: all symptoms decreased, above all with respect to nasal obstruction and cephalea ($p<0.001$). The overall symptom burden before and after is also reported.

At the physical examination (Table **3**), a relevant improvement in turbinate hypertrophy and in mucosa status (see Fig. **1**) and a significant decrease in secretion were recorded (see Fig. **2**) after the treatment.

Palatability of Narivent® was considered as Good by 83% (29) of the patients, Fair by 11% (4) and Poor by 6% (2) of them. No patients reported an unsatisfactory palatabil ity judgement. Compliance was High in 83% (29) of the patients,

Table 2. VAS Score Rating and 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®.

		N	Pre	Post	Combined	p-value
VAS		35	7.275/7.550/7.925	2.100/2.600/3.450	2.600/6.300/7.550	<0.001
Nasal Congestion:	Absent	35	0% (0)	6% (2)	3% (2)	<0.001
	Good		0% (0)	83% (29)	41% (29)	
	Fair		31% (11)	11% (4)	21% (15)	
	Poor		69% (25)	0% (0)	35% (25)	
Cephalea:	Absent	35	17% (6)	51% (18)	34% (24)	<0.001
	Good		44% (16)	46% (16)	45% (32)	
	Fair		36% (13)	3% (1)	20% (14)	
	Poor		3% (1)	0% (0)	1% (1)	
Rhinorrhea:	Absent	35	31% (11)	51% (18)	41% (29)	0.095
	Good		50% (18)	46% (16)	48% (34)	
	Fair		17% (6)	3% (1)	10% (7)	
	Poor		3% (1)	0% (0)	1% (1)	
Rhino-pharyngeal exudates:	Absent	35	47% (17)	69% (24)	58% (41)	0.062
	Good		36% (13)	31% (11)	34% (24)	
	Fair		11% (4)	0% (0)	6% (4)	
	Poor		6% (2)	0% (0)	3% (2)	
Pain:	Absent	35	78% (28)	89% (31)	83% (59)	0.281
	Good		17% (6)	11% (4)	14% (10)	
	Fair		6% (2)	0% (0)	3% (2)	
Hyposmia:	Absent	35	39% (14)	51% (18)	45% (32)	0.078
	Good		36% (13)	43% (15)	39% (28)	
	Fair		17% (6)	0% (0)	8% (6)	
	Poor		8% (3)	6% (2)	7% (5)	

Table 3. Physical Examination Results 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®

		N	Pre (N=36)	Post (N=36)	Combined (N=72)	p-value
Turbinate hypertrophy:	Absent	35	0% (0)	11% (4)	6% (4)	<0.001
	Good		17% (6)	74% (26)	45% (32)	
	Fair		22% (8)	14% (5)	18% (13)	
	Poor		61% (22)	0% (0)	31% (22)	
Adenoid hypertrophy:	Absent	35	97% (35)	97% (34)	97% (69)	0.368
	Fair		0% (0)	3% (1)	1% (1)	
	Poor		3% (1)	0% (0)	1% (1)	
Mucosa status	Normal	35	11% (4)	68% (23)	39% (27)	<0.001
	Hyperemic		64% (23)	23% (8)	44% (31)	<0.001
	Pallid/livid		25% (9)	20% (7)	23% (16)	0.614
	Atrophyc		0% (0)	3% (1)	1% (1)	0.307
Type of secretion	Absent	35	28% (10)	60% (21)	44% (31)	0.006
	Haematic- purulent		3% (1)	0% (0)	1% (1)	0.321
	Pallid-serum		25% (9)	20% (7)	23% (16)	0.614
	Mucous		47% (17)	23% (8)	35% (25)	0.032

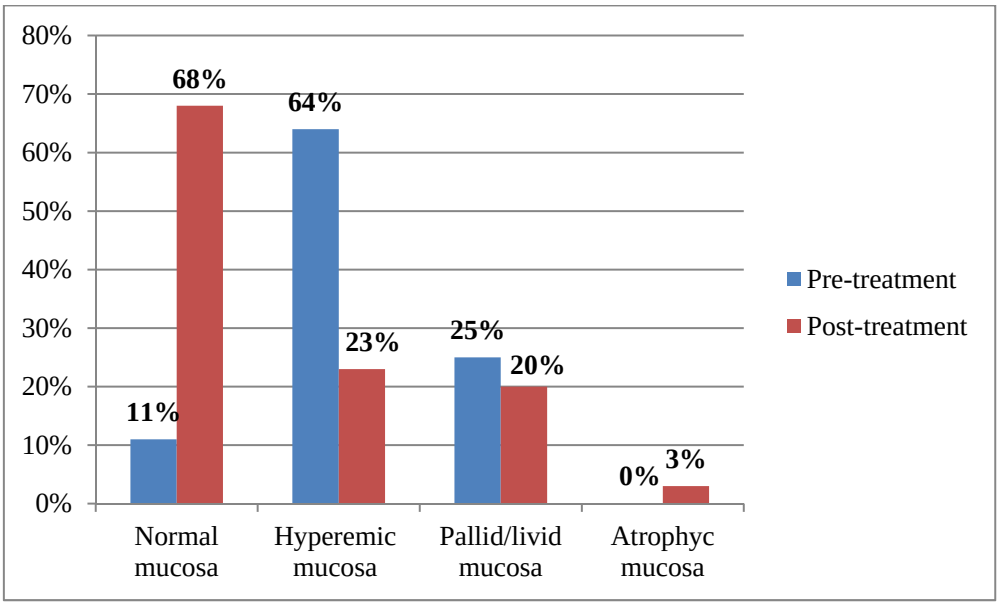

Fig. (1). Nasal mucosa status before and after the treatment. Differences are statistically significant ($p<0.05$) for pre-post comparisons in normal and hyperemic mucosa.

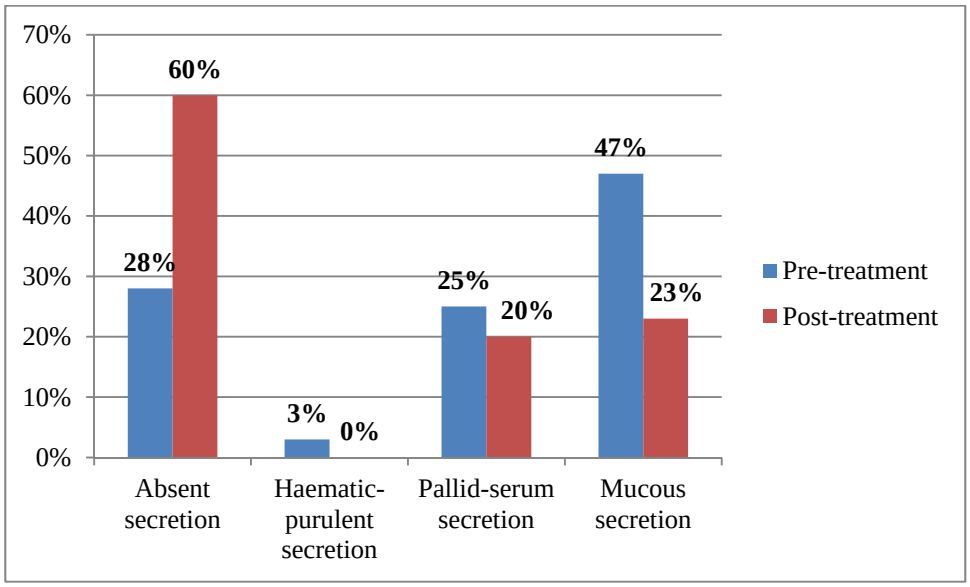

Fig. (2). Type of nasal secretion before and after the treatment. Differences are statistically significant ($p<0.05$) for pre-post comparisons in absent and mucous secretion.

Fair in 11% (4) and Poor in 6% (2). No adverse effects were reported by patients receiving the treatment.

DISCUSSION

Nasal congestion is one of the most common complaints dealt with in otorhinolaryngology. Among the pathologies responsible for general complete and continued or occasional nasal obstruction, specific and aspecific vasomotor rhinitis are the conditions with greater epidemiological impact [28].

Nasal congestion is often the predominant symptom in the upper respiratory tract disorders and the pervasiveness of these conditions has lead nasal congestion to become a highly prevalent problem [7].

The negative effects of nasal congestion impact a person's physical as well as emotional functioning. It influences quality of life (QoL) of patients, having negative impact on daily activities, causing sleep disturbances as well as promoting daytime sleepiness, fatigue and reduction of work/school productivity [2, 29, 30].

Taking into account the high prevalence, as well as the significant social and economic burden of nasal congestion, this symptom should be a key consideration in the treatment of patients with rhinologic disease [2]. Since mucosal inflammation is the central pathophysiological mechanism leading to nasal congestion in common upper respiratory diseases, and it is responsible of venous engorgement, in-

creased nasal secretions, and tissue swelling/oedema that ultimately impairs airflow and cause the sensation of nasal blockage, the development of pharmacologic therapies for congestion has been guided by the need to oppose vasodilatation, reducing nasal airway resistance and thus facilitating nose breathing [7, 28].

A variety of pharmacologic therapies is available for the treatment of nasal congestion in common upper respiratory diseases and it is often a focus of treatment [1]. In the majority of acute conditions of rhinitis associated with infection, over the counter treatment can provide symptom relief [6]. Intranasal corticosteroids have potent and broad anti-inflammatory activities. They have proven to be more effective than other classes of agents for the relief of congestion in controlled clinical trials, but they do not reduce mean nasal congestion scores to normal levels, nor do they effectively reduce congestion in every patient [1].

Decongestants are sympathomimetic drugs, employed as systemic or topical products, which act by constricting capacitance vessels in the turbinates. They produce a decrease in subjective symptoms and nasal airway resistance, but side effects including systemic effects such as elevated blood pressure, tachycardia, palpitations, restlessness, insomnia, anxiety, tremors, and hypersensitivity reactions and topical effects such as burning, stinging, sneezing, or local irritation are frequently seen in treated patients suffering from chronic nasal congestion [1, 6, 28, 31-33].

The adverse event profile of topical and oral decongestants limits their usefulness in allergic rhinitis and the evidence supporting the utility of these drugs for relief of congestion associated with non-allergic/vasomotor rhinitis, rhinosinusitis, or nasal polyposis is very limited [1]. Many types of preparations have also been investigated to treat symptoms associated with these conditions, but substantial evidence for their benefit is poor. These medications include antral washings, isotonic/hypertonic saline as nasal douche, antihistamines (in allergic conditions), antimycotics, mucolytic agents/phytomedical preparations, immunomodulators/immunostimulants and bacterial lysate preparations [3].

Due to the many adverse effects related to standard therapies and long-term treatments and on account of the paucity of evidence for the efficacy of symptomatological therapy, there is a growing need for alternative or co-adjuvant treatments capable of relieving symptoms associated with upper respiratory conditions and not involving major side effects.

Narivent® belongs to the medical devices category and it is a nasal lubricant which acts osmotically with anti-oedematous and anti-inflammatory action thanks to the presence of components such as eucalyptol, glycyrrhizin and mannitol. This pre-post study was conducted in order to verify if the treatment with Narivent® is effective in reducing nasal congestion and other symptoms associated with mucus-catarrhal rhinosinusitis, turbinate hypertrophy, vasomotor rhinopathies, rhino-sinus non-occlusive polyposis, adenoid pathology. Patients' perception of nasal symptoms and objective testing of nasal obstruction were both assessed. Our results showed a significant improvement in symptoms after treatment, demonstrating that the action is not limited to a subjective sensation of increased nasal air flow, but corresponds to an objective reduction in nasal resistance. In fact, a reduction in the main subjective symptoms, such as sensation of nasal congestion and cephalea, was found.

The overall subjective assessment of the sensation of nasal obstruction made by patients through the VAS also showed a relevant reduction after the treatment period. Moreover, an improvement in the sensation of decreased sense of smell was evidenced.

Physical examination of patients treated with Narivent® demonstrated an improvement achieving the best results in mucosa status, in turbinate hypertrophy and in production of nasal secretion.

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

FINAL REMARKS

This study therefore provides evidence that in patients with mucus-catarrhal rhinosinusitis, turbinate hypertrophy, vasomotor rhinopathies, rhino-sinus non-occlusive polyposis, adenoid pathology and in the treatment of oedema associated with acute rhinosinusal inflammatory conditions, Narivent® can improve nasal symptom control in a short-term treatment.

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

The other authors have no conflict of interest in relation to this article.

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