

# Long-term Efficacy of Narivent<sup>®</sup> in the Treatment of Nasal Congestion

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**Abstract:** *Rationale and aim:* Nasal congestion is a common symptom in allergic and non-allergic rhinitis, rhinosinusitis and nasal polyposis. Although various pharmacotherapy options exist, no agent is universally efficacious. The aim of this study was to evaluate the clinical effectiveness efficacy of Narivent<sup>®</sup>, which is an osmotically acting medical device with anti-oedematous and anti-inflammatory effects, in a long-term (30 days) treatment.

*Methods:* A single-centre prospective study with a pre-post design was conducted with consecutive enrolment in an Italian Otolaryngology Department of 56 both genders patients with persistent nasal congestion.

Patients received 2 puffs of Narivent<sup>®</sup> into each nostril 2 times a day over the course of 4 weeks. 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, cephalgia, rhinorrhea, hyposmia, turbinates hypertrophy, mucosa status).

*Conclusion:* Study results confirm the efficacy of Narivent<sup>®</sup> in treating nasal congestion over a 4 weeks period.

**Keywords:** Persistent nasal congestion, Osmotically acting medical device, Anti-oedematous activity, Anti-inflammatory activity.

## INTRODUCTION

Nasal congestion is a cardinal symptom of upper airway disorders, such as allergic and non allergic rhinitis, viral or bacterial rhinitis, rhinosinusitis and nasal polyposis [1-4]. It can be defined as an objective restriction of nasal cavity airflow and its characterization is an important part of the diagnosis, as well as the target of the treatment of these illnesses [5].

The pathophysiology of congestion involves neural, vascular, and inflammatory elements [6]. It is associated with the inflammation of the nasal epithelium which underlies many of the specific and interrelated factors that contribute to congestion and other symptoms of both allergic rhinitis and rhinosinusitis [7, 8]. A wide range of biologically active agents (e.g.: histamine, tumour necrosis factor- $\alpha$ , interleukins, cell adhesion molecules) and cell types contribute to inflammation, which can manifest as dilatation of nasal

blood vessels, increased secretions and tissue swelling /oedema, ultimately leading to impaired airflow thorough nasal cavities [8].

Although congestion and obstruction are often used as synonymous, it is important to highlight that reversible nasal congestion is caused by mucosal inflammation and secretions, while obstruction refers to irreversible or constant blockage which may be due to mechanical factors, including occlusion (e.g.: nasal polyps), anatomical variation (e.g.: septal deformity, turbinate hypertrophy) or, rarely, tumors or granulomas [2, 9].

Common upper respiratory tract diseases are also described by other primary symptoms, including rhinorrhea, sneezing, nasal itching, reduction/loss of smell, facial pain or pressure and headache, even if patients generally identify nasal congestion as the most bothersome symptom [1-4].

The complaint of a blocked nose is therefore a complex clinical problem involving mucosal, structural, and even psychological factors. In clinical practice, it is frequently difficult to assess and quantify the subjective sensation of nasal airflow and to decide on the therapy most likely to be effective in restoring satisfactory nasal breathing [10].

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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) [9, 11].

A complete and thorough examination using nasal endoscopy provides intense illumination and magnification of the nasal passages and is indicated especially for patients who experience chronic or recurrent acute rhinosinusitis symptoms, or those with suspected nasal polyposis [9]. In addition, the Lund–Mackay system of scoring nasal endoscopy findings is the only system regarding mucosal thickening (oedema) [12].

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

However, available tools for the subjective evaluation, such as questionnaires, the Visual Analogue Scale (VAS) and 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 essential [12].

For this purpose, 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 [14, 15].

Nasal congestion severely impacts upon quality of life (QoL) of patients suffering from chronic upper respiratory disorders and affects their ability to perform daily activities. Furthermore, when this symptom is poorly-controlled may contribute to sleep loss or disturbance and cause daytime somnolence, decreased alertness, increased accident rates and reduced work/school productivity [16].

Treatment strategies for relief nasal congestion may be considered as environmental control measures (e.g.: allergen avoidance in allergic rhinitis), pharmacologic therapy and surgical intervention. Standard conservative treatment for chronic conditions, such as chronic rhinosinusitis with or without nasal polyposis, is based on short or long-term antibiotics and topical steroids with the addition of decongestants - mostly in a short term regimen and for the acute attack itself [3].

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<sup>®</sup>, an osmotically acting medical device with anti-oedematous and anti-inflammatory effects, in the treatment of nasal congestion associated with chronic upper airway disorders. Nasal obstruction was assessed both subjectively and objectively.

To understanding symptom severity from patient's perspective a visual analogue scale (VAS), which is a well-

established approach, was used [17]. 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 imaginable [18].

## 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 56 patients of both genders with persistent nasal congestion caused by allergic or non-allergic rhinitis, turbinate hypertrophy and sinus non-occlusive polyposis. 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 infections; the presence of massive occlusive polyps in the sinus; used nasal or oral corticosteroids or decongestants during the four 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<sup>®</sup> 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 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 [19, 20].
- Adenoid hypertrophy was classified as absent, good (slightly increased adenoids), fair (increased adenoids but not beyond tubal ostium) or poor (adenoids beyond tubal ostium) [21, 22].
- 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, itching and dryness [23]. The subjective symptom score was obtained with a visual analogue scale modified from Eccles'

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

		N	Summary Statistics (N=56)
Age		56	34.75/48.50/59.00
Gender	M	56	50% (28)
	F		50% (28)
Rhinosinusitis	Rhinosinusitis	56	25% (14)
	Rhinosinusitis reactivation		4% (2)
	Allergic rhinitis		4% (2)
	Vasomotor rhinitis		18% (10)
	Turbinate hypertrophy		29% (16)
	Polyposis		21% (12)
Septal deviation	Absent	55	23% (13)
	Good		61% (34)
	Fair		14% (8)
	Poor		2% (1)
Nasal polyposis*	Absent	55	77% (43)
	I		2% (1)
	II		7% (4)
	III		14% (8)

\*Classification according to the Lund-Mackay scale

model [24]. 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 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 medical devices based on 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 post operative 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 [25], whereas the anti-inflammatory action is due particularly 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 as a cytokine and acts as a potent pro-inflammatory mediator when released in the extracellular environment [26, 27].

**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 4) 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, 51 subjects are required to detect as significant a change in VAS of 2 points (SD 4.5) after the administration of the treatment. Assuming a drop-out rate of 10%, 56 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 [28].

**RESULTS**

Twenty-eight males and 28 females were enrolled. Median age was 48.5 years (I quartile: 34.75; III quartile: 59). At the enrolment twenty-five per cent (14) of the patients reported rhinosinusitis, 4% (2) reactivation of rhinosinusitis, 4% (2) allergic rhinitis with positive clinical history for allergy and positive prick test results to Dermatophagoides pteronyssinus (Dpt), 18% (10) vasomotor rhinitis, 21% (12) polyposis and 29% (16) turbinate hypertrophy (Table 1).

**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 Variables before and after Treatment with Narivent®.**

		N	Pre (N=56)	Post (N=56)	Combined (N=112)	p-Value
VAS		55	6.080/7.080/8.050	2.000/3.010/3.545	3.015/6.010/7.085	<0.001
Nasal Congestion	Absent	55	0% (0)	13% (7)	6% (7)	<0.001
	Good		0% (0)	67% (37)	33% (37)	
	Fair		29% (16)	15% (8)	22% (24)	
	Poor		71% (40)	5% (3)	39% (43)	
Cephalaea	Absent	55	5% (3)	49% (27)	27% (30)	<0.001
	Good		29% (16)	40% (22)	34% (38)	
	Fair		50% (28)	11% (6)	31% (34)	
	Poor		16% (9)	0% (0)	8% (9)	
Rhinorrhea	Absent	55	32% (18)	64% (35)	48% (53)	<0.001
	Good		27% (15)	35% (19)	31% (34)	
	Fair		36% (20)	2% (1)	19% (21)	
	Poor		5% (3)	0% (0)	3% (3)	
Rhino-pharyngeal exudate	Absent	55	70% (39)	85% (47)	77% (86)	0.038
	Good		21% (12)	15% (8)	18% (20)	
	Fair		9% (5)	0% (0)	5% (5)	
	Poor		0% (0)	0% (0)	0% (0)	
Pain	Absent	55	82% (46)	95% (52)	88% (98)	0.147
	Good		11% (6)	5% (3)	8% (9)	
	Fair		5% (3)	0% (0)	3% (3)	
	Poor		2% (1)	0% (0)	1% (1)	
Hyposmia	Absent	55	4% (2)	33% (18)	18% (20)	<0.001
	Good		32% (18)	56% (31)	44% (49)	
	Fair		50% (28)	9% (5)	30% (33)	
	Poor		14% (8)	2% (1)	8% (9)	

One patient was lost to follow-up because of the presence of paradoxical nasal obstruction. Therefore, the statistical analysis was performed on 55 patients rather than 56.

Table 2 shows the subjective evaluation of symptoms before and after treatment: nasal obstruction, cephalaea and rhinorrhea significantly decrease ( $p<0.001$ ) after the treatment and a significant improvement in reduced sense of smell was also observed ( $p<0.001$ ). The overall symptom burden before and after is also reported.

At the physical examination (Table 3), a significant improvement in turbinate hypertrophy ( $p<0.001$ ) and in the overall condition of the mucosa were observed (Fig. 1). A relevant decrease in secretion production was also recorded (Fig. 2).

Palatability of Narivent® was considered as Good by 73% (40) of the patients and as Fair by 27% (15) of them. No patients reported an unsatisfactory palatability judgement. Compliance was High in 75% (41) of the patients, Fair

in 20% (11) and Poor in 5% (3). No adverse effects were reported by patients receiving the treatment.

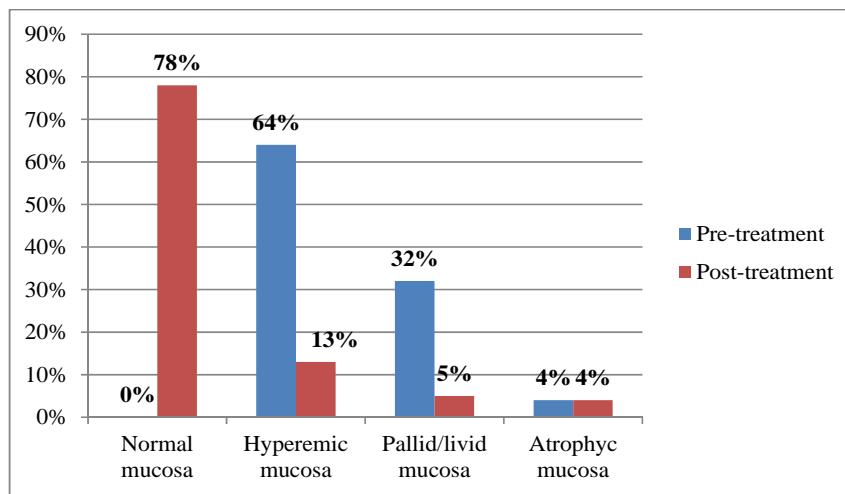
## DISCUSSION

Nasal congestion is a prevalent symptom of upper airway diseases and 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 [29]. The pervasiveness of allergic rhinitis and rhinosinusitis has caused congestion to become a highly prevalent problem; however, it is important to note that the perception of congestion in chronic rhinosinusitis can also be caused by polyps extruding into the nasal airway, producing a physical obstruction in the nostril [8].

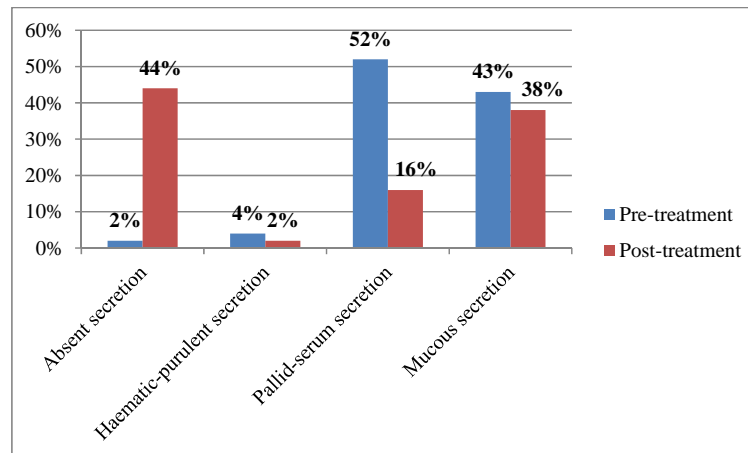
Patients diagnosed with these upper respiratory conditions identify congestion as the most common and typically the most troublesome symptom. The negative effects of

**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 Variables before and after Treatment with Narivent®.**

		N	Pre (N=56)	Post (N=56)	Combined (N=112)	p-Value
Turbinate hypertrophy	Absent	55	0% (0)	7% (4)	4% (4)	<0.001
	Good		9% (5)	71% (39)	40% (44)	
	Fair		36% (20)	18% (10)	27% (30)	
	Poor		55% (31)	4% (2)	30% (33)	
Adenoid hypertrophy		55	0% (0)	2% (1)	1% (1)	0.319
Mucosa status	Normal	55	0% (0)	78% (43)	39% (43)	<0.001
	Hyperemic		64% (36)	13% (7)	39% (43)	<0.001
	Pallid/livid		32% (18)	5% (3)	19% (21)	<0.001
	Atrophyc		4% (2)	4% (2)	4% (4)	0.985
Type of secretion	Absent	55	2% (1)	44% (24)	23% (25)	<0.001
	Haematic-purulent		4% (2)	2% (1)	3% (3)	0.569
	Pallid-serum		52% (29)	16% (9)	34% (38)	<0.001
	Mucous		43% (24)	38% (21)	41% (45)	0.616



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

nasal congestion are far reaching and impact a person's physical as well as emotional functioning. A persistent symptom of congestion, in fact, influences the quality of life (QoL) of patients, having negative impacts on daytime functioning and sleep. Persistent nasal congestion can cause sleep-disordered breathing and sleep fragmentation, reducing sleep time and quality as well as promoting daytime sleepiness and fatigue [2, 30, 31].

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].

The central pathophysiological mechanism of nasal congestion in common upper respiratory diseases is the inflammation of nasal mucosa, which can manifest as dilatation of nasal blood vessels, increased secretions and tissue swelling/oedema. That is why the development of pharmacologic therapies for congestion in these diseases aims at opposing vasodilatation, reducing nasal airway resistance and thus facilitating nasal breathing [8, 29].

A variety of pharmacologic therapies are available for the treatment of nasal congestion in common upper respiratory diseases and it is often a focus of treatment. The most extensively evaluated therapies include antihistamines, decongestants, leukotriene receptor antagonists, and intranasal corticosteroids [1].

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 patients with chronic nasal congestion treated [1, 7, 29, 32, 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 these conditions and not involving major side effects.

Narivent<sup>®</sup> 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<sup>®</sup>, is effective in reducing nasal obstruction and other symptoms associated with chronic rhinosinusitis, allergic rhinitis, turbinate hypertrophy, sinus non-occlusive polyposis or vasomotor rhinopathies. 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, cephalgia, rhinorrhea and an improvement in decreased sense of smell were 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.

A physical examination of patients treated with Narivent<sup>®</sup> showed an improvement of the general conditions, achieving the best results in mucosa status, in turbinate hypertrophy and in secretion production.

No 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 therefore provides evidence that, in patients with nasal turbinate hypertrophy and specific (allergic rhinitis) or non-specific vasomotor rhinitis, and in the treatment of oedema associated with chronic rhinosinusal inflammatory conditions, Narivent<sup>®</sup> can improve nasal symptoms control over a long period of time.

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

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