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ORIGINAL STUDY

The nasal congestion relevance and a novel suggestion to prevent and treat it

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ABSTRACT

BACKGROUND. Nasal congestion is a common symptom in allergic and non-allergic rhinitis, rhinosinusitis and nasal polyps. Although several options exist, no drug is overall efficacious. The aim of this study was to evaluate the clinical effectiveness of a medical device, containing dipotasssium glycyrrhizinate, which is an osmotically acting substance with anti-edema and anti-inflammation effects specifically against the pro-inflammatory High Mobility Group Box 1 (HMGB1) protein.

MATERIAL AND METHODS. A multicenter prospective study with a pre-post design has been performed in 8 Italian ENT Departments, consecutively enrolling 161 both genders patients affected by persistent nasal congestion. Patients received 2 puff of dipotassium glycyrrhizinate into each nostril two times a day over the course of four weeks. The severity of symptoms was assessed subjectively, as measured by a 0 to 5 visual analog scale (VAS), and objectively through endoscopic assessment, active anterior rhinomanometry (AAR), and by mean of the evaluation of mucociliary transport times (MCTt). Differences in subjective and objective severity measures before and after treatment were compared using Paired-Sample Wilcoxon Signed Rank Test.

RESULTS. All evaluated symptoms and all objective scores improved after treatment: the improvement was statistically significant ($p<0.001$).

CONCLUSION. The study results confirm the efficacy of dipotassium glycyrrhizinate in treating nasal congestion.

KEYWORDS: nasal congestion, Dipotasssium Glycyrrhizinate, VAS, AAR, nasal MCTt

INTRODUCTION

Nasal congestion, which may be best described as a feeling of blockage, fullness or restricted airflow, is a common symptom in allergic and non-allergic rhinitis, rhinosinusitis and nasal polyps[1]. Mucosal inflammation underlies many of the specific and interrelated factors that contribute to nasal congestion, as well as other symptoms of both allergic rhinitis and rhinosinusitis[2]. A wide range of biologically

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active agents (eg, histamine, tumor necrosis factor-α, interleukins, cell adhesion molecules) and cell types contribute to inflammation, which can give rise to venous engorgement, increased nasal secretions and tissue swelling/edema, ultimately leading to impaired airflow and to the sensation of nasal congestion[2].

High Mobility Group Box 1 (HMGB1), an evolutionarily ancient protein, is released as a result of loss of membrane integrity upon necrosis of nucleated cells (including neutrophils) and by activated leukocytes. There is increasing evidence that HMGB1 could contribute to the pathogenesis of chronic inflammatory diseases, including allergic and non-allergic rhinitis, rhinosinusitis and nasal polyps.

Nasal congestion can impact 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 it also may lead to irritability and depression[3].

Although several options of medical therapy exist, no agent can be considered overall efficacious, and there is a paucity of data supporting commonly used symptomatic drugs[4].

The present study was conducted in order to evaluate the safety and the clinical effectiveness of a solution containing dipotassium glycyrrhizinate, which is an osmotically acting substance with anti-edema and anti-inflammatory effects.

Glycyrrhizin and its derivative dipotassium glycyrrhizinate, is a natural anti-inflammatory and antiviral triterpene inhibiting HMGB1 protein chemo-attractant and mitogenic activities, and has a weak inhibitory effect on its intranuclear DNA binding function[5].

High Mobility Group Box 1 (HMGB1), an evolutionarily ancient protein which acts predominantly as a deoxyribonucleic acid (DNA)-binding protein with "alarmin" activity, has the dual capacity to recruit and to activate inflammatory cells, including dendritic cells (DCs). Alarmins are usually constitutively present in cells, such as leukocytes and epithelial cells, as components of the granules, cytoplasm, and nucleus. They are endogenous peptides that are released in host defence against danger signals and, therefore, can be considered as a subset of damage associated molecular patterns (DAMPs)[6,7]. HMGB1 is ubiquitously expressed in the nuclear compartment of eukaryotic cells functioning as a transcriptional regulator via interaction of its A-box and B-box subunits with DNA. Therefore, quiescent macrophages/monocytes constitutively express HMGB1 and maintain an intracellular "pool" of HMGB1, predominantly in the nucleus. After stimulation with exogenous bacterial products such as endotoxin, or with endogenous pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ, cultures of macrophages, monocytes, and pituicytes actively release HMGB1[8]. In addition, HMGB1 can be released passively from necrotic or damaged cells. However, HMGB1 is not released by apoptotic cells, which disintegrate themselves without setting off an inflammatory response[9]. Therefore, HMGB1 is released as a result of loss of membrane integrity upon necrosis of nucleated cells (including neutrophils) and by activated leukocytes. As an extracellular protein, HMGB1 has pleomorphic effects including activation of NF-kB, diffuse endothelial activation, hepatocellulary injury, epithelial leak and systemic activation of inflammatory cells[10]. HMGB1 activates inflammatory cells through interactions between receptor for advanced glycation end-products (RAGE) or toll-like receptor (TLR) -2 and -4[8]. Receptor binding leads to activation of the transcription factors nuclear factor-kappa B, inducing the transcription of multiple pro-inflammatory genes. Upon (co-) activation with HMGB1, macrophages produce pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, macrophage inflammatory protein-1α and MIP-2β[9]. HMGB1 acts as an alarmin because it induces both migration and activation of DCs and it enhances antigen-specific immune responses that favour Th1 polarization[10]. There is increasing evidence that HMGB1 contributes to the pathogenesis of chronic inflammatory diseases[11,12] including allergic and non-allergic rhinitis, rhinosinusitis and nasal polyps.

The solution of dipotassium glycyrrhizinate is classified and marketed in our Country as "medical device" according to the European Community (EC) 93/42 directive which states: "medical device" means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

MATERIAL AND METHODS

Study design

A multicentre prospective study with a pre-post design has been performed in 8 Italian Otorhinolaryngology Departments, consecutively enrolling 161 both genders patients affected by persistent nasal congestion, caused by allergic or non-allergic rhinitis, turbinate hypertrophy or nasal, not occlusive,

polyposis (1st degree according to Lund-McKay grading system).

Exclusion criteria were acute upper respiratory infections, massive occlusive polyps, septal deviations and the use of nasal or oral corticosteroids during the four preceding weeks, or the use of decongestants, antileukotrienes and 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 puff of our drug into each nostril two times a day over the course of four weeks

During each visit a VAS[13] was used to quantify the subjective feeling of nasal obstruction, rhinorrhea, itching and dryness. The subjective symptom score was obtained with a visual analogue scale modified from Eccles' model[14]. Patients rated the perceived degree of their obstruction on a scale of 0 (complete patency) to 5 (complete stenosis). Likewise, VAS was used for other symptoms. Moreover, Lund-McKay nasal endoscopy scoring, nasal polyps assessing, mucosa edema, ostiomeatal obstruction and turbinate hypertrophy were recorded; furthermore, nasal airflow resistances were measured by active anterior rhinomanometry, according with validated criteria and MCT times were measured with an inert, colour tracer (charcoal powder) mixed with 3% saccharine[15].

Adverse effects were also recorded. The study protocol received ethical approval from the Ethics Committees.

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 sum of all the symptom scores). Sample size has been computed with reference to the following scenario: a type I error of 0.05 and a power of 0.80. At this error levels, 129 subjects were needed to detect as significant a change in inspiratory nasal airflow resistances of 0.05 (SD 0.20) after the administration of the treatment. Assuming a drop-out rate of 20%, 160 patients have been estimated as necessary for the study conduction. 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 dipotasssium glycyrrhizinate and differences recorded in objective measures were compared using Paired-Sample Wilcoxon Signed Rank Test.

RESULTS

Eighty-eight males and 73 females were enrolled. The median age was 40 years (I quartile: 29; III quartile: 54). Comparing symptoms subjective evaluation before and after treatment, the statistical analysis pointed out that nasal obstruction, rhinorrhea and itching significantly decrease after the treatment ($p<0.001$) (Table 1). Overall symptom burden before and after is also reported. Similar results have been obtained comparing Endoscopic scoring, AAR and MCTt measurements before and after treatment (Table 2).

Adverse effects were not reported by patients receiving the treatment.

DISCUSSIONS

Nasal congestion is one of the most common complaints dealt with in otorhinolaryngology. Among the pathologies responsible for more or less complete and continued nasal obstruction, specific and non-specific vasomotor rhinitis have the greater epidemiological impact[16]. The pervasiveness of allergic rhinitis and rhinosinusitis has caused congestion to

Table 1
VAS score rating symptoms 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 dipotasssium glycyrrhizinate

	Before (N=161)	After (N=161)	p
Nasal obstruction	2/3/3	1/1/2	<0.001
Rhinorrhea	1/2/2	0/1/1	<0.001
Itching	1/1/2	0/0/1	<0.001
Dryness	0/0/0	0/0/0	0.307
Overall symptom burden	5/5/7	2/3/4	<0.001

Table 2
Objective measures assessing nasal obstruction. Numbers are I quartile/Median/III quartile. P-value refers to a significantly different distribution of each given variables before and after treatment with dipotasssium glycyrrhizinate

	Before (N=161)	After (N=161)	p
Nasal endoscopic assessment			
Turbinate hypertrophy	1/2/2	0/1/1	<0.001
Oedema	1/2/2	0/1/1	<0.001
Ostiomeatal obstruction	0/0/1	0/0/0	0.008
Polyp	0/0/0	0/0/0	0.216
AAR			
Inspiration	0.2300/0.3500/0.5100	0.1800/0.2376/0.3400	<0.001
Expiration	0.220/0.297/0.465	0.180/0.220/0.340	<0.001
MCTt	16/18/20	14/16/19	<0.001

become a highly prevalent problem[2], 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[2].

The main underlying cause of nasal congestion in common upper airway disorders in adults is inflammation, which usually is responsible for venous engorgement, increased nasal secretions and tissue swelling/edema.

The development of drugs for these diseases has been guided by the need to oppose vasodilation, reducing nasal airway resistance and thus facilitating nose breathing[2,16].

Decongestants are sympathomimetic drugs that constrict capacitance vessels in the turbinates and decrease nasal congestion. Systemic and nasal decongestants administered as aqueous spray, drops or dry powder, tablets or capsules are available. Side effects of systemic and topical decongestants, including systemic effects, such as elevated blood pressure, tachycardia, palpitations, arrhythmia, restlessness, insomnia, anxiety, tremors, psychological disturbances, hypersensitivity reactions, and topical effects, such as burning, stinging, sneezing, or local irritation, are frequently seen in patients with chronic nasal congestion. These observations lead to an increasing demand of alternative treatments[16-18].

For that reason, this pre-post study has been conducted in order to verify if the treatment with dipotasssium glycyrrhizinate which controlling the HMGB1 quantity may be effective in reducing nasal obstruction due to chronic inflammation.

Patient's perception of nasal symptoms and objective testing of nasal obstruction have been both assessed. Rhinorrhea and itching, significantly decrease after the treatment ($p<0.001$) (Table 1). Similar results have been obtained comparing Endoscopic scoring, AAR and MCTt measurements before and after treatment (Table 2).

Our results show a significant improvement in symptoms and objective measures after treatment, demonstrating that the action is not limited to a subjective sensation of increased nasal air flow, but it correspond to an objective reduction in nasal resistance. This study provides therefore the preliminary evidence that in patients affected by nasal turbinate hypertrophy and by specific (allergic rhinitis) or non-specific vasomotor rhinitis dipotasssium glycyrrhizinate can be used as a valid alternative to systemic and topical decongestants.

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