Glycyrrhetic Acid Exerts Positive Effects on Nasal Symptoms and Asthma Control in Allergic Children

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Abstract

Objective: Allergic rhinitis and asthma share an immunoglobulin E-mediated inflammatory reaction following exposure to the causal allergen. Asthma control is associated with rhinitis control. Glycyrrhetic acid is extracted from the licorice and has an anti-inflammatory property. Mannitol is an anti-edema molecule. A medical device contains these components. This study evaluated the medical device efficacy on symptoms and asthma control in children with allergic rhinitis and mild controlled asthma.

Methods: The children took 2 puffs of the medical device for each nostril twice a day for 4 weeks. Symptom severity was evaluated considering the total symptom score and nasal obstruction. Symptom perception was assessed by children and doctors using the visual analog scale. Asthma severity and control were also evaluated. Parents judged the efficacy.

Results: The study included 38 children: 18 (47.4%) females and 20 (52.6%) males; the mean age was 10.2 (±2.15) years. The treatment significantly reduced the severity of all symptoms, including nasal obstruction ($P < .001$). Both children and doctors perceived a reduction of symptom intensity ($P < .001$). Parents judged the treatment as effective. Asthma remained mild and controlled.

Conclusions: This pilot study, conducted in clinical practice, showed that intranasal glycyrrhetic acid plus mannitol could reduce nasal symptoms, including obstruction, and maintain asthma control. Therefore, this multicomponent medical device could represent a potential option in children with allergic rhinitis and mild controlled asthma.

Keywords: Allergic rhinitis, asthma, control, symptoms, glycyrrhetic acid, mannitol

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INTRODUCTION

A type 2 inflammation characterizes allergic rhinitis (AR); pathogenic mechanisms include a dysfunction of allergen-specific T regulatory cells, T helper 2 cell prevalence, and nasal eosinophilic inflammation.[1] Also, AR is frequently associated with asthma.[2] Both diseases share airway allergic inflammation, but the symptoms are different. In particular, type 2 nasal inflammation elicits local symptoms, including itching, sneezing, watery rhinorrhea, and nasal obstruction. Remarkably, nasal obstruction severity reflects the intensity of the inflammatory reaction.[3] Nasal obstruction is an annoying symptom associated with nasal discomfort, impaired smell, broken sleep, and significant impairment of quality of life and daily activities.[4]

Type 2 inflammation is the primary pathophysiological event leading to AR symptoms; consequently, anti-inflammatory drugs represent a first-line therapy.[5] Topical corticosteroids are the most potent anti-inflammatory drugs and, consequently, widely prescribed with effective and safe results.[6,7] However, although their safety is substantially fair, the parents of children with AR are commonly reluctant to use intranasal corticosteroids to care for their children.[8] Parents would prefer alternative options to intranasal corticosteroids. In this regard, glycyrrhizin is derived from the licorice (*Glycyrrhiza glabra*) and has anti-inflammatory property by blocking extracellular high mobility group protein box 1 (HMGB1), an alarmin molecule priming inflammatory events.[9] Glycyrrhetic acid (GlyAc) is the active principle of glycyrrhizin. Glycyrrhetic acid has no cytotoxicity, even at high concentrations, and good pharmacological tolerance.[10] In addition, there is evidence that GlyAc *in vitro* reduces the release of HMGB1 from cultured eosinophils and increases eosinophilic apoptosis; also *in vivo* it diminishes the HMGB1 in AR children.[11] The anti-inflammatory

activity also improved mucociliary clearance in patients with nasal polyps.[12] Moreover, GlyAC relieved nasal symptoms in children with AR and adults with nasal congestion.[13,14]

Glycyrrhetic acid is a component of a medical device (MD), containing mannitol, with anti-edema osmotic activity. This multicomponent medical device (MMD) significantly improved nasal endoscopic signs, symptoms' perception, and nasal airflow in adult patients suffering from allergic rhinitis.[15]

On the other side, there is evidence that uncontrolled AR may affect asthma concerning symptoms and function.[16] Therefore, the present study investigated the possible effects of this MMD on nasal symptoms and asthma control in children with AR and mild asthma.

METHODS

The present study was retrospective. The Ethics Committee of the Istituto G. Gaslini of Genoa approved the procedure (code number: 22253/2017); and parents signed the informed consent. The study included consecutive children with AR and mild controlled asthma. Allergic rhinitis diagnosis was performed according to validated criteria.[17] Briefly, nasal symptom history had to be consistent with documented sensitization, and allergic symptoms should occur after exposure to the sensitizing allergen. Asthma was diagnosed according to the Global INitiative for Asthma (GINA) guidelines.[18] The definition of mild asthma and controlled asthma are in detail reported in GINA guidelines.[18]

Inclusion criteria were: (i) age range between 6 and 13 years, (ii) both genders, (iii) AR diagnosis, (iv) asthma diagnosis, (v) presence of mild asthma, and (vi) controlled asthma. Exclusion criteria were: (i) presence of concomitant chronic nasal diseases, (ii) any acute upper and lower respiratory tract infection, (iii) presence of massive occlusive nasal polyposis, (iv) diagnosis of cystic fibrosis or Kartagener's syndrome, (v) immune diseases and/or immunodeficiency (congenital or acquired), (vi) clinical conditions (systemic diseases or other) that may interfere with the evaluation of the safety and efficacy of the products under investigation, and (vii) concomitant treatments able to interfere with the interpretation of results.

The primary endpoint was to demonstrate the efficacy of the MMD in reducing symptom intensity. Secondary endpoints were to evaluate the perception of symptom intensity assessed by patients and doctors and the perception of treatment efficacy perceived by parents. A visual analog scale assessed these perceptions. The scale ranged from 0 (no symptom) to 10 (the most severe symptom) for symptom severity. For the efficacy by parents, the scale ranged from 0 (no efficacy) to 10 (the best effectiveness). In addition, asthma severity and control were assessed considering the criteria established by GINA guidelines.[18]

Main Points

- *Allergic rhinitis and asthma are frequently associated. Both diseases share type 2 inflammation. Asthma control is the goal of asthma management.*
- *Glycyrrhetic acid exerts many actions, including to dampen inflammation.*
- *The present study showed that glycyrrhetic acid improved nasal symptoms and maintained the asthma control in children with allergic rhinitis and comorbid asthma.*

Patients took the multicomponent device: 2 puffs for nostril twice a day for 4 weeks. The patients were evaluated at baseline and after 28 days.

Statistical Analysis

As appropriate, descriptive data were summarized as mean with SD, median with interquartile range, or count with percentage. Comparison of severity of each symptom between the pre- and post-treatment was assessed by Wilcoxon signed-rank test (scores from 0 to 4) or marginal homogeneity test (grade from absent to severe). *P*-values below .05 were considered statistically significant. The analyses were performed using Statistical Package for Social Sciences Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The study retrospectively included 38 children: 18 (47.4%) females and 20 (52.6%) males; the mean age was 10.2 (±2.15) years. Moreover, 20 children were polysensitized, and 18 were monosensitized to house dust mites.

Table 1 reports the clinical data collected before and after treatment.

The asthma grade remained mild in all subjects. Likewise, asthma stayed controlled in all children.

The treatment significantly reduced the intensity of the total symptom score, including nasal obstruction ($P < .001$).

In addition, the treatment significantly affected the perception of symptom severity, measured both by children and by doctors ($P < .001$ for both). The parents judged the therapy as effective as the median value was 7.

The compliance was good in all patients. The tolerability was good in 92% of patients. No clinically relevant adverse events were reported.

Table 1. Symptoms and Perceptions Over Time

			P
T5SS score			
	Pre-treatment	9.0 (8.0-11.0)	<.001
	Post-treatment	6.0 (5.0-7.0)	
Nasal obstruction			
	Pre-treatment	2.0 (2.0-3.0)	<.001
	Post-treatment	1.0 (1.0-2.0)	
VAS by children			
	Pre-treatment	7.3 (6.5-8.0)	<.001
	Post-treatment	5.5 (4.2-6.5)	
VAS by doctors			
	Pre-treatment	7.0 (5.5-7.5)	<.001
	Post-treatment	4.8 (4.0-5.5)	
VAS by parents			
	Post-treatment	7.0 (6.5-7.5)	

Results are expressed as median with interquartile range. The change in symptoms scores among patients after the treatment was assessed with Wilcoxon signed-rank test. VAS, visual analog scale.

DISCUSSION

Allergic rhinitis and asthma share a type 2 inflammation that in turn elicits signs, symptoms, and dysfunction in AR and asthmatic patients. Therefore, topical corticosteroids are an effective therapeutic option for both diseases. Namely, both inhaled and intranasal corticosteroids improve symptoms and function of the nose and bronchi. The international guidelines also report that topical corticosteroids are usually safe.[17,18] Nevertheless, many parents are wary of long-lasting use for possible adverse events. This assumption is even stronger when intranasal and inhaled corticosteroids are used simultaneously. In this regard, GlyAc could represent an attractive alternative to corticosteroids as there is evidence that it is effective and safe.[10-14] The anti-inflammatory mechanism of action depends on the steroid-like conformation of GlyAc. Thus, this similarity explains the efficacy in relieving symptoms. In particular, GlyAc significantly reduced the severity of nasal obstruction: a symptom closely related to allergic inflammation.[3]

Asthma control is the primary goal of asthma therapy. Therefore, topical anti-inflammatory drugs are the key to achieving this. In this context, control of allergic rhinitis may contribute to maintaining asthma control.[19] A preliminary study showed that the MMD containing GlyAc and mannitol was equivalent to mometasone furoate nasal spray in inducing AR symptom control.[15]

The present retrospective study was designed to investigate the efficacy of this MMD in relieving AR symptoms and maintaining controlled asthma in children with AR and mild controlled asthma.

The findings underscored the effectiveness of this product in reducing symptom severity of all symptoms, mainly concerning nasal obstruction. The intensity of symptoms was actually reduced by one-third when assessed objectively, particularly the intensity of nasal obstruction was halved. Concordantly, the subjective perception of symptoms was reduced by about a quarter when assessed by patients and by about 30% when assessed by doctors.

Although a control group was not included, being a retrospective study, these results still had clinical relevance, as the so-called placebo effect usually corresponds to values of 20%-30%.[20] This outcome was also consistent with the positive parents' perception of efficacy.

These findings likely depend on the double activity of the MD: the anti-inflammatory effect due to GlyAc and the anti-edema activity due to mannitol.[21]

However, this study had some limitations: (i) the open and retrospective design, (ii) the relatively limited number of enrolled subjects, (iii) the lack of biological parameters' assessment, and (iv) the mono-center design. For these reasons, the findings should be considered preliminary; indeed, other studies with robust methodology are required to confirm these outcomes.

CONCLUSION

This retrospective study, conducted in clinical practice, demonstrated that intranasal GlyAc plus mannitol improved nasal symptoms and maintained asthma control significantly. Therefore, this MMD could represent a potential option in children with allergic rhinitis and mild controlled asthma.

Ethics Committee Approval: The study was approved by the Ethical Review Committee of Istituto G. Gaslini of Genoa (code number: 22253/2017) on March 22, 2017.

Informed Consent: Written informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no competing interest.

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