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Brief report

Resveratrol plus carboxymethyl-β-glucan reduces nasal symptoms in children with pollen-induced allergic rhinitis

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Abstract

Objective:
Allergic rhinitis (AR) is caused by an IgE-mediated inflammatory reaction consequent to the exposure to causal allergen. Resveratrol is a natural non-flavonoid polyphenol, exerting anti-inflammatory activity; β-glucan is a polysaccharide with immuno-modulatory properties. Thus, this study aimed to investigate whether these combined compounds are able of relieving nasal symptoms in children with AR due to pollen allergy.

Research design and methods:
The present study was conducted as placebo-controlled, double-blinded, and randomized. Globally, 68 children (36 males; mean age 7.9 years) were treated with resveratrol plus β-glucan or placebo (the diluent of active drug) two sprays (100 μL/spray) in each nostril three times/day for 2 months. Nasal symptoms, including itching, sneezing, rhinorrhea, and obstruction, were assessed at baseline and after treatment. Use of rescue medication, such as cetirizine syrup, was also evaluated.

Clinical trial registration:
ClinicalTrials.gov ID NCT02130440.

Results:
Children treated with active drug achieved a significant reduction in all nasal symptoms: itching ($p = 0.0001$), sneezing ($p = 0.0009$), rhinorrhea ($p = 0.009$), and obstruction (0.002) as well as antihistamine use ($p = 0.003$). Placebo did not affect nasal complaints and cetirizine use. The intergroup analysis showed that active treatment was significantly superior to placebo about reduction of AR symptoms and rescue medication use.

Conclusions:
The present preliminary study firstly showed that intranasal resveratrol plus carboxymethyl-β-glucan is capable of significantly improving nasal symptoms in children with pollen-induced AR.

Introduction

Allergic rhinitis (AR) is a very common atopic disorder that affects up to 40% of the pediatric population[1,2]. AR is caused by an IgE-mediated inflammatory reaction consequent to exposure to the causal allergen. Allergy is sustained by a functional defect of allergen-specific T regulatory cells allowing T helper 2 (Th2) cell polarization. Th2 cells produce interleukins, including IL-4, IL-5, and IL-13, driving allergic inflammation. In addition, Th2-cytokines up-regulate endothelial and epithelial expression of adhesion molecules

(for example ICAM-1), ligands of other molecules (e.g. LFA-1 expressed by leukocytes), so promoting eosinophil mucosal infiltration. Allergic inflammation causes typical AR symptom occurrence, such as itching, sneezing, rhinorrhea, nasal obstruction and impaired quality of life in children[3]. The main AR medications are antihistamines and intranasal corticosteroids, which are effective, but may have adverse events. For this reason, the number of people is growing who prefer to use complementary medicine, such as herbal medicine[4].

Resveratrol (*trans*-3,4,5-trihydroxystilbene) is a natural non-flavonoid polyphenol and belongs to a subclass of stilbenes. It is found in various fruits and vegetables and it is abundant in grape skin; it functions as a phytoalexin (a class of vegetal antibiotics) so protecting the plant from environmental stress or infections. Resveratrol is well known in Chinese and Japanese medicine, using a root of *Polygonum cuspidatum*. Resveratrol exerts anti-inflammatory activity[5]. The anti-inflammatory effects of resveratrol depend on the inhibition of transcription factor NF-kB, mainly via Ik-B kinase[6]. NF-kB activation regulates several pro-inflammatory proteins, such as IL-8, GM-CSF, COX2, and inducible nitric oxide synthase. This mechanism may be compared to the anti-inflammatory activity provided by steroids[7]. In addition, resveratrol is capable of inhibiting viral replication[8]. In particular, a very recent study showed that resveratrol reduced the replication of rhinovirus (RV) on nasal epithelial cells and the RV-dependent expression of ICAM-1, which is also the main RV receptor[9]. Resveratrol provided anti-inflammatory and anti-asthmatic effects in a mouse model of allergic asthma, as it significantly reduced IL-4 and IL-5 in plasma and bronchoalveolar lavage fluid, and suppressed bronchial hyperreactivity, lung eosinophilia, and mucus hypersecretion[10]. Moreover, resveratrol may prevent experimental eosinophilic rhinosinusitis, as it decreases the degree of eosinophilic infiltration and subepithelial fibrosis with potency similar to that of dexamethasone[11]. This study also showed that high doses of resveratrol decreased IL-4, IL-5, prostaglandin D and leukotriene C_4 synthase genes expression as well as 5-lypoxygenase production. In addition, resveratrol increases mucociliary transport and reduces inflammation in the sinunasal epithelium[12].

On the other hand, β-glucan is a polysaccharide, defined as a biological response modifier because it has many immuno-modulatory properties, including stimulation of phagocytosis by professional phagocytes, direct activation of NK cells and cytokine release[13]. Intranasal administration of glucans has been demonstrated to be capable of exerting anti-inflammatory effects in a mouse model: intranasal chitin plus β-glucan increased IgM levels[14], intranasal zymosan induced increase of secretory IgA and serum IgM mediated by activated dendritic cells[15], and intranasal chitosan induced increase of IgG[16]. Human studies were conducted in children with common cold[17] or allergic rhinitis[18], but glucan was combined with other compounds and evaluation was based on clinical parameters alone.

Previously, it has been reported that resveratrol combined with β-glucan exerted relevant *in vitro* synergistic effects on immune system[19,20]. Recently, the combination of resveratrol plus β-glucan has become available as an intranasal spray. As there are no human studies available on this issue, the present double-blind, placebo-controlled and randomized study aimed to investigate whether intranasal resveratrol plus carboxymethyl-β-glucan is capable of relieving nasal symptoms in children with AR due to pollen allergy.

Patients and methods

The present study was conducted as prospective, double-blinded, placebo-controlled and randomized. Globally, 68 children (36 males; mean age 7.9 ± 1.7 years) were enrolled. They attended the Pediatrics Department of the Second University of Naples suffering from AR. AR diagnosis was performed, according to validated criteria[21], if nasal symptom history was consistent with documented sensitization, such as positive skin prick test, to the *Parietaria* allergen, i.e. allergic symptoms had to occur only during the pollen season.

Inclusion criteria were: i) age range 4–17 years; ii) diagnosis of AR due to *Parietaria officinalis* pollen; iii) presence of nasal symptoms for at least 1 month, documented by a run-in period; iv) written informed consent signed by parents. Exclusion criteria were: i) concomitant comorbidities, including respiratory infections; ii) chronic illnesses; iii) continuous use of medications (antihistamines and corticosteroids) in the last 4 weeks.

Patients were randomly (1:1 ratio) subdivided in two groups: placebo-treated (Group A) and actively treated (Group B). Active medication was an isotonic solution containing resveratrol 0.05% (extracted by *Polygonum cuspidatum*) and carboxymethyl-β-glucan 0.33%. Placebo was an isotonic solution, such as the diluent of active drug. Patients were instructed to spray two sprays (100 µL/spray) for nostril three times/day for 2 months. Nasal symptoms (itching, sneezing, rhinorrhea, and obstruction) were scored using a four-point scale (0 = no symptom; 1 = mild; 2 = moderate; 3 = severe). It is noteworthy that this score is the preferred one in clinical trials on AR[22]. Symptoms were assessed during the visits: at baseline (after one run-in month) and after treatment. Cetirizine syrup (1 drop/3Kg/bw) was permitted as rescue medication during both run-in and treatment periods; its symptomatic use was recorded on a diary card. Adverse events were as usual recorded.

The study was performed during the *Parietaria* pollen season. The study protocol was approved by the Ethics Committee of the Second University of Naples. The study was registered at ClinicalTrials.gov ID NCT02130440.

Statistical analysis

The sample size was calculated by log-rank test with power at 90% and α error at 5%: 30 subjects per arm were considered sufficient. Randomization was performed in blocks following the Wichmann–Hill model.

Data were reported as means, standard deviation and 95% confidence interval. The Mann–Whitney test was used as a non-parametric counterpart, paired data were compared using the Wilcoxon test. A p value less than 0.05 was considered statistically significant. A statistical software program (StatSoft Italia s.r.l. 2005, Statistica, Vigonza, Italy) was used for all the analyses.

Results

Globally, 68 children were recruited and 65 completed the study (36 males; mean age 7.9 years, range between 5.8 and 12.5 years). The reason for drop-out cases was poor adherence to treatment (<80%). The adherence rate was 89% ±4 of prescribed doses. Both treatments were well tolerated and no significant adverse events were reported.

At baseline, symptom severity and antihistamine use were similar in the two groups, so the groups were homogeneous (Figures 1 and 2). Actively treated children reported a significant reduction in all nasal symptoms: itching ($p = 0.0001$), sneezing ($p = 0.0009$), rhinorrhea ($p = 0.009$), and obstruction (0.002) as well as cetirizine use ($p = 0.003$) after the 2 month treatment. Placebo did not affect nasal complaints and cetirizine use. The intergroup analysis showed that active treatment was superior to placebo in reducing AR symptoms itching ($p = 0.0001$), sneezing ($p = 0.0009$), rhinorrhea ($p = 0.009$), and obstruction (0.002) as well as rescue medication use ($p = 0.001$).

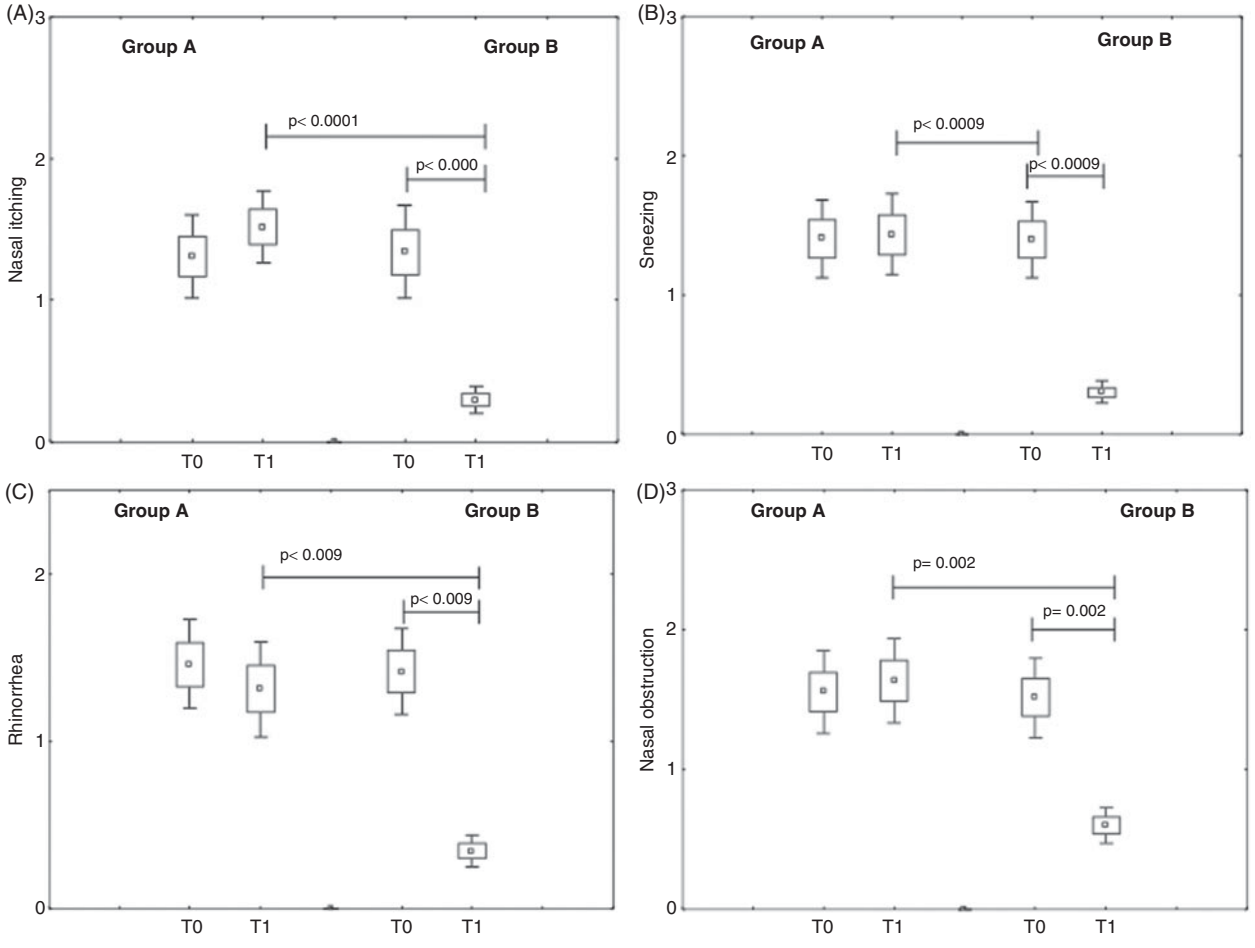

Figure 1. Mean (central box) ± standard error (box) and 95% CI (bars) of nasal symptom severity in Groups A (placebo) and B (active treatment) assessed before (T0) and after (T1) treatment. A = itching; B = sneezing; C = rhinorrhea; D = obstruction.

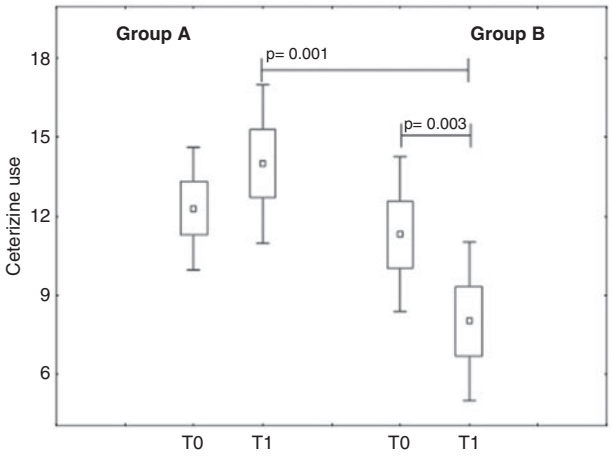

Figure 2. Mean (central box) ± standard error (box) and 95% CI (bars) of cetirizine use scored as days of on demand consumption in Groups A (placebo) and B (active treatment) assessed before (T0) and after (T1) treatment.

Discussion

Parietaria allergy is characterized by persistent symptoms as the pollination period is usually prolonged in the Mediterranean area. In addition, *Parietaria* pollen sustains intense mucosal inflammation that induces severe complaints, seldom refractory to common antihistaminic medications[23]. A hallmark of allergic inflammation is an abundant eosinophilic infiltrate in the nasal mucosal tissue. Several factors are involved in the inflammatory cascade, including ICAM-1 expression on nasal epithelial cells[24].

Recently, an intranasal medical device containing resveratrol plus β-glucan has become available for sale. The used concentrations of the two compounds were defined by a dose-ranging study evaluating solubility and stability[25]. This double-blinded, placebo-controlled and randomized study provided the first *in vivo* evidence that intranasally administered resveratrol combined with carboxymethyl-β-glucan was capable of significantly affecting nasal symptoms and antihistaminic consumption in children with AR due to *Parietaria* pollen.

These findings may be explained by the complex anti-inflammatory activity exerted by the two compounds. Particularly, this study confirms *in vivo* an experimental study conducted in a mouse model: in fact, resveratrol was capable of reducing eosinophil infiltration with potency similar to that of dexamethasone[10]. Another experimental study demonstrated that resveratrol was superior to some corticosteroids in diminishing IL-8 secretion[11] and preliminary experience reported that it reduced ICAM-1 expression on the epithelium[8]. In addition, it is well known that glucan may also be capable of exerting important anti-inflammatory and homeostatic activities[13].

It is noteworthy that the present study was the first conducted in humans using the combination of resveratrol plus carboxymethyl-β-glucan in the treatment of pollen-induced AR in allergic children.

However, there are some limitations of this study: (i) the relatively limited number of treated patients; (ii) the lack of objective parameters; (iii) the absence of inflammatory mediator assessment; (iv) the study was single center; and (v) there were only two measurements of symptoms (at baseline and at the end of treatment). For these reasons, the findings should be considered preliminary and further studies should be conducted addressing these issues.

Conclusions

This preliminary study shows that intranasal resveratrol plus carboxymethyl-β-glucan is capable of significantly improving nasal symptoms in children with AR due to *Parietaria* allergy.

Transparency

Declaration of funding

The study was partially funded by Noos, Rome, Italy.

The authors of this report contributed equally to the realization of the study.

Declaration of financial/other relationships

M.M.D.G., N.M., C.C., E.A., M.C., L.P., and G.C. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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