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Can the *Pelargonium sidoides* root extract EPs® 7630 prevent asthma attacks during viral infections of the upper respiratory tract in children?

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ABSTRACT

Introduction: Asthma is a chronic disease characterized by airway inflammation. Viral infection initiates an immune inflammatory response that may produce asthma attacks. There is no effective preventing therapy for asthma attack during upper respiratory tract viral infections.
Objective: To investigate the efficacy of 5 days of *Pelargonium sidoides* therapy for preventing asthma attack during upper respiratory tract viral infections.
Methods: Sixty one asthmatic children with upper respiratory tract viral infection were enrolled in the study. The patients were randomized to receive *Pelargonium sidoides* daily for 5 days ($n = 30$) or not ($n = 31$). Before and after treatment, they all were examined and symptom scores were determined. Following five days treatment, children were evaluated whether or not they had an asthma attack.
Results: Treatment with *Pelargonium sidoides* was not associated with a statistically significant differences in fever and muscle aches ($p > 0.05$, Chi-square test). There were significant differences in cough frequency and nasal congestion between the groups ($p < 0.05$, Chi-square test). There were statistically significant differences in having asthma attack between the groups ($p < 0.05$, Chi-square). *Pelargonium sidoides* group had less frequency of asthma attack.
Discussion: Our study shows that *Pelargonium sidoides* may prevent asthma attacks during upper respiratory tract viral infections.

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Introduction

Asthma is a chronic disease characterized by airway inflammation, episodic symptoms, and airflow obstruction (Busse and Lemanske 2001). The chronic inflammation observed in asthma leads to airway hyperresponsiveness, which is defined as an abnormal increase in airflow limitation after exposure to a nonallergic stimulus, such as exercise (Sterk et al. 1993; Lotvall et al. 1998). Asthma exacerbations are common, and the major morbidity, mortality, and health care costs. The majority of execerbations are related to viral infection, and although progress has been made in identifying the mechanisms of virus-induced asthma exacerbations, there is still much to be learned. A role for atypical bacterial infection in exacerbations is also increasingly recognized. Exacerbations are characterized by airway inflammation, which can differ in type depending on whether it is primarily infective or allergic in origin. An increased understanding of the inflammatory pathways might lead to identification of targets for the development of novel prevention or treatment strategies.

The proprietary *Pelargonium sidoides* (PS) root extract EPs® 7630, also known as Umckaloabo®, is a herbal remedy thought to be effective in the treatment of acute respiratory infections (ARIs). There are lots of studies about PS and respiratory tract infections (Timmer et al. 2008; Agbabiaka et al. 2008). These studies showed that PS may be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults, but doubt exists. It may be effective in relieving symptoms in acute bronchitis in adults and children, and sinusitis in adults (Timmer et al. 2008). EPs 7630 significantly reduced bronchitis symptom scores in patients with acute bronchitis by day 7 (Agbabiaka et al. 2008). No serious adverse events were reported. EPs 7630 has a positive effect on phagocytosis, oxidative burst, and intracellular killing of cells (Conrad et al. 2007a). PS extract modulates the production of secretory immunoglobulin A in saliva, both interleukin-15 and interleukin-6 in serum, and interleukin-15 in the nasal mucosa (Luna et al. 2011).

In one research, PS represents an effective treatment of the common cold. It significantly reduces the severity of symptoms and shortens the duration of the common cold compared with placebo. Because of these effects, we aimed whether or not PS could effect the asthma attack frequency after upper respiratory tract viral infection.

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Table 1
Patients characteristics.

	Pelargonium sidoides ($n=30$)	No drug ($n=31$)	p Value
Age*	5 (1–12)	7 (1–14)	>0.05[a]
Gender			
Boy, n (%)	15 (50)	19 (61.3)	>0.05[b]
Girl, n (%)	15 (50)	12 (38.7)	
Eosinophil (%)	3.3 (0.4–9.6)	2.3 (0.1–12.5)	>0.05[a]
Total IgE (ku/l)*	34.7 (5–681)	30.8 (5–3570)	>0.05[a]
Atopy, n (%)	6 (20)	4 (12.9)	>0.05[b]

[a] Mann Whitney U test.
[b] Chi-square test.
* Median (Interquartile range).

Table 2
Effect of *Pelargonium sidoides* on symptoms.

	Pelargonium sidoides ($n=30$)	No drug ($n=31$)	p Value
Nasal symptoms, n (%)	13 (43)	23 (74)	<0.05[a]
Cough, n (%)	17 (56)	28 (90)	<0.05[a]
Asthma attack, n (%)	6 (20)	15 (48)	<0.05[a]

[a] Chi square test.

Materials and methods

Children with asthma ($n=61$) aged 1–14 years were recruited from the Pediatric Allergy and Asthma Unit of Erciyes University School of Medicine, Kayseri, Turkey (Table 1). Asthma was diagnosed according to the published Global Initiative for Asthma guidelines (GINA 2010) by a history of intermittent wheezing and the presence of reversible airway obstruction, as defined by at least a 12% improvement in forced expiratory volume in one second (FEV1) after bronchodilator administration, therapeutic response to antiasthma treatment. In an attempt to prevent severity of disease from being a confounding factor, only children who strictly fulfilled the criteria for mild asthma (GINA 2010) were enrolled. Children who had moderate-to-severe asthma, lower airway infection, any other systemic disease or taking systemic steroid were excluded from the study.

Children who presented to the Department of Pediatric Allergy, Erciyes University School of Medicine, for upper respiratory tract viral infection were enrolled in the study ($n=61$). The study was approved by the Erciyes University Hospital Ethics Committee.

After written informed parental consent had been obtained, patients were randomly assigned to receive either daily PS administration and supportive treatment ($n=30$) or only supportive treatment ($n=31$) for 5 days. In PS group we used Umca solüsyon (Product name) and this dosage schedule: for 1–5 age 10 drops three times a day, for 6–12 age 20 drops three times a day, for 12 age and above 30 drops three times a day. For supportive treatment, we used antipiretics (paracetamol) when they need. The primary outcome was a change in symptom severity and duration, while secondary outcomes were whether or not PS could affect the asthma attack frequency.

At baseline (day one), demographic data (date of birth, sex, weight, height), vital signs, symptoms of common cold and physical examination were obtained. The study medication and the patient's diary were provided. At five days visit, the investigator assesed the clinical status of the patients, reviewed the patient's diaries, documented the consumption of investigational medication, and asked about occurrence of advers events. The investigational medication was supplied in bottles of 20 ml, containing PS. The patients were instructed to take drops (different according to their age) three times daily, at least 30 min before or after meals, from day one and continuing until day 5.

Blood samples were drawn into EDTA tubes. Spirometric measurements, total immunoglobulin E (IgE) and eosinophil counts were obtained and skin testing was done with a battery of 23 geographically relevant antigens with appropriate positive and negative controls on the upper back. Reactions with an induration more than 3 mm that of the negative control were considered positive.

Spirometry was performed using a dry rolling spirometer (2130 Spirometer, Sensor Medics Co., Yorba Linda, Calif., USA). IgE levels were measured with Uni-Cap technology in accordance with the specifications of the manufacturer (Pharmacia, Kalamazoo, Mich., USA). Eosinophil counts were determined from Coulter Counter leukocyte measurements.

Statistical analyses

Age, eosinophil percent, total IgE levels were compared by Mann Whitney U test. Symptom frequency was compared by Chi-square test. A p value of less than 0.05 was considered significant.

Results

Patient characteristics

A total of 61 children with asthma were included in the study. 30 patients received PS and 31 patients did not. There were no significant differences between the groups at randomization in terms of demographic variables. Likewise, there were no significant differences between the groups with respect to the number of eosinophils, plasma IgE levels and atopy status ($p>0.05$, Table 1).

Primary end points

Treatment with PS was associated with a significant reduction in nasal symptoms and cough frequency ($p<0.05$, Chi square test, Table 2). There were no significant differences in fever, sleep and muscle ache between the groups ($p>0.05$, Chi square test).

Secondary end points

Treatment with PS was associated with a significant reduction in asthma attack frequency ($p<0.05$, Chi square test, Table 2).

Discussion

To the best of our knowledge, this is the first study investigating the effect of PS treatment on preventing asthma attack during upper respiratory tract viral infections. The study was designed to determine whether PS treatment had any clinical effect on upper respiratory tract viral infections and had any effect on preventing asthma attack.

Respiratory infections are frequently primarily due to viruses. Viruses can provoke asthma attack. Increasing inflammation is the main reason of asthma attack. During viral infection, increasing in airway inflammation needs time. We think, if we can shorten the duration of viral infection, we may decrease developing airway inflammation, and we may prevent the asthma attack.

We showed that PS had significant improving effects on upper respiratory tract viral infections. The results of this study demonstrated that treatment with PS markedly improved symptoms of URTVI (Upper Respiratory Tract Viral Infections), which were more pronounced for the symptoms nasal congestion, nasal drainage, and cough. Our results were consistent with previous studies. In these studies, it significantly reduced the severity of symptoms

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and shortens the duration of the common cold (Ross 2012; Lizogub et al. 2007).

We found that PS decreased cough and asthma attack frequency. Viral infections have been implicated in most (>80%) asthma exacerbations in children (Busse et al. 2010; Jackson and Lemanske 2010). Although many viruses have been recovered from asthmatics, rhinovirus has been most commonly (65%) identified in proven viral-induced asthma exacerbations in children aged 2–17 years (Jackson and Lemanske 2010). RV induces epithelial cells to produce proinflammatory cytokines leading to airway hyperresponsiveness, neurogenic inflammatory responses, mucous secretion, inflammatory cell recruitment and activation, and plasma leakage (Yamaya and Sasaki 2003). RV infection resulted in an increase in mRNA expression and subsequent translation of IL-6, IL-8, and IL-16. This also occurred with RANTES, a C–C chemokine with chemoattractant activity for eosinophils, monocytes, and T lymphocytes. IL-6 and IL-8 are proinflammatory cytokines, and IL-8 is a specifically potent chemoattractant for neutrophils. IL-16 is a powerful lymphocyte chemoattractant and activator of macrophages and eosinophils and appears to be an important mediator in the pathogenesis of asthma and lower airway inflammation due to RV (Papadopoulos et al. 2000; Samuel et al. 2005). Airway hyperresponsiveness appears to be one manifestation of the airway inflammation induced by viruses. It has been shown that a correlation exists between numbers of mast cells, eosinophils and neutrophils and the degree of airway hyperresponsiveness (O'Byrne 1998).

PS had antiviral, antibacteriel, and immunomodulatory activities (Theisen and Muller 2012; Kolodziej and Kiderlen 2007; Conrad et al. 2007a,b; Carsten 2011). Theisen and Muller (2012) showed that PS had an anti-influenza activities (Theisen and Muller 2012). Conrad et al. (2007a,b) suggested that PS developed anti-infective properties; firstly PS reduces bacterial adhesion to intact epithelial cells and thus protects the organism from bacterial colonization (Conrad et al. 2007a). In one study, PS increased nitric oxid, IL-1alpha, TNF-alpha (tumor necrozis factor), IL-12 (Interleukin 12) (Carsten 2011). PS has some effects on phagocytosis, oxidative burst and intracellular killing of human periperal blood phagocytes (Conrad et al. 2007b). Gene expression experiments showed that PS could effect and increase, iNOS (nitric oxid), IFN-alpha (interferon alpha), IFN-gamma, TNF-alpha, Interleukin (IL)-1, IL-10, IL12, IL-18 levels (Kolodziej and Kiderlen 2007). And PS improves silier activities (Neugebauer et al. 2005).

Effect of PS in infectious conditions could also be explained by stimulation of the nonspecific immune system (Kayser et al. 2001). Induction of nonspesific host defence mechanism againist a number of pathogenesis including viruses is related to the IFN-system. IFNs can protect cells from viral infections, while IFN-gamma functions as the major macrophage activating factor (Carsten 2011). IFN-γ has potential to sensitize macrophages to react more effectively when needed (Schroder et al. 2006). The signal transduction is initiated via Toll-like receptors after pathogen recognition. LPS can stimulate innate immune responses (Schroder et al. 2006; Fujihara et al. 2003). It may be speculated that PS also mediates anti-infective activities by TLR signaling (Perera et al. 2001).

In conclusion, PS significantly reduced the severity of symptoms and shortens the duration of the URTVI. And PS significantly reduced asthma attack frequency. This result is encouraging for preventing asthma attack during URTVI. This area needs new multicenter, plasebo controlled trials.

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