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The efficacy of *Pelargonium sidoides* in the treatment of upper respiratory tract infections in children with transient hypogammaglobulinemia of infancy

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ABSTRACT

Transient hypogammaglobulinemia of infancy (THI), defined as prolongation of physiological hypogammaglobulinemia normally seen between the initial 3rd and 6th months of life, is one of the most common immune deficiencies of childhood. Recurrent upper respiratory tract infections (URTI) are rather common in this group of patients, and generally, antibiotic treatment is the usual choice, although viruses involved in most cases. *Pelargonium sidoides* extract a herbal drug with known immunmodulator, antiviral and antibacterial effects. In this randomized, placebo controlled, prospective, monocentric pilot study, 14 of 28 patients with a diagnosed THI, were given Pelargonium sidoides, while 14 were given placebo during the period of URTI. Before and after the treatment period of one week, complete blood count, prothrombin time, activated prothromboplastin time, serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, total and direct bilirubin levels were measured. Mothers were asked to fill in a questionnaire for the recovery of the clinical symptoms during the treatment. The results were evaluated and compared in both group to assess the effect of *Pelargonium sidoides*. As a conclusion, the *Pelargonium sidoides* group showed increased appetite. The *Pelargonium sidoides* were found to beneficial for the nasal congestion, recovery of daily and nocturnal cough but not found be significant. Further studies with large number of participants are necessary to highlight the effect of *Pelargonium sidoides* in children with transient hypogammaglobulinemia of infancy.

Introduction

The concept of Transient Hypogammaglobulinemia was firstly announced to the English medical literature by Gitlin and Janeway (1956). Transient hypogammaglobulinemia of infancy (THI) is defined as a prolongation of the physiological hypogammaglobulinemia period when maternal immunoglobulin (Ig) levels start to decline and the infant starts to synthesize his own Ig's between the initial 3rd and 6th months of the life, the criteria needed for diagnosis of this disorder have not yet been standardized. Its incidence is not fully and exactly known, and it is incidence does not differ by the sex (Keles et al. 2010). Though causes underlying THI are not exactly known either, a delay in maturation of B cells, and helper T-cell (CD4) maturation/development disorders, and disorders in interplay and relationship between cytokines, all as detected by pathological means, are suggested among the probable underlying reasons. Recurrent upper respiratory tract infections (URTI) are rather common in this disease. It is reported that normal Ig levels are reached between ages 2 and 5 years in most of the patients with THI, which is a self-limiting disease (Doğu et al. 2004; Karaca et al. 2010; Keles et al. 2010; Kiliç et al. 2000).

Historically, *Pelargonium sidoides* has been used by African indigenous tribes to treat various disorders such as gastrointestinal disorders and respiratory tract infections. The colonization of South Africa by the Dutch and British in 17th century, the effect of this herbal drug was also noticed by the Europeans, and the interest shown in this herbal drug increased after Colonel Charles Stevens personally used and benefitted from it (Brendler and van Wyk 2008; Kolodziej and Schulz 2003). Thereafter, a proprietary extract of the roots of *Pelargonium sidoides*, EPs® 7630, was emerged as a modern phyto-pharmaceutical drug after extensive research. EPs® 7630 has been proven to have antiviral, antibacterial and immunomodulatory and secretomotoric effects and is used in modern medicine in the treatment of respiratory tract infections such as acute bronchitis, sinusitis and the common cold (Brendler and van Wyk 2008; Haidvogl et al. 1996; Haidvogl and Heger 2007).

We aimed and planned to conduct a randomized, placebo-controlled, prospective pilot study with a view to investigating the efficiency of *Pelargonium sidoides* extract, known to have immunomodulator and antiviral effects, for treatment of upper respiratory tract infections in patients with THI, which is primarily an immune deficiency syndrome.

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Materials and methods

This double-blinded and monocentric pilot study was conducted with 28 patients suffering from URTI complicated with THI at Erciyes University, Faculty of Medicine, Department of Pediatric Immunology between September 2007 and April 2009. The study was approved by the 01/368 numbered, 07.11.2006 dated decision of Erciyes University Ethics Committee. In addition the study was carried out after obtaining a written informed consent from all parents of the subjects. The study followed the guidelines of the Declaration of Helsinki and Tokyo for the enrolled subjects.

Plant material

EPs® 7630 is a herbal drug preparation from the roots of *Pelargonium sidoides* (1:8–10); extraction solvent:ethanol 11% (w/w) (Schoetz et al. 2008) and was kindly provided by Dr. Willmar Schwabe GmbH & Co. KG., Karlsruhe, Germany.

Inclusion criteria of patients

(1) Diagnosis of THI
(2) Patients suffering from acute URTI symptoms
(3) Age between 1 and 5 years,
(4) Normal values of complete blood count, prothrombin time (PT), activated prothromboplastin time (aPTT), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), total and direct bilirubin
(5) Tuberculosis skin test (PPD skin test) result of 5–10 mm (+),
(6) Negative result in STREP test

Patients who did not conform to the above listed criteria, and patients with elevated average white blood cell count and/or high CRP values indicative of a bacterial infection were excluded from the study. Patients using any other medication were also excluded.

Study plan

All patients admitted with symptoms of URTI (cough, nasal draining, fever, etc.) first underwent a STREP test in order to exclude the probability of group-A streptococcus infection, and secondly a PPD skin test in order to assess cellular immunity. Then, the blood samples of the patients with a negative result in the screening visit (STREP test, and with a PPD of 5–10 mm (+), were monitored for complete blood count, serum AST, ALT, GGT, total bilirubin, direct bilirubin tests and PT, aPTT tests) before administration of *Pelargonium sidoides* or placebo. The patients on the two groups underwent the treatment within 1 week of the screening visit.

The randomization was made by the consecutive order of initial application and the subjects were randomized into two arms (*Pelargonium sidoides* extract or placebo), respectively. The drugs (*Pelargonium sidoides* and placebo) were delivered by another physician and the empty bottles were asked to return. The collected data were evaluated after the completion of the study.

Of the patients suitable according to the inclusion criteria, 14 patients were randomized to take *Pelargonium sidoides* extract and 14 to take placebo for a period of 7 days. The patients were recommended to use their drugs as 10 drops at each time 3 times a day for a period of 7 days. A questionnaire comprising of 9 questions aiming to assess and evaluate the symptoms of patients by means of a 2-point scale (0–1) was filled in by the mothers on a daily basis (Table 1). At the end of the seventh day, the baseline laboratory tests were repeated.

Table 1
Scale of the symptom score.

General state of health	Good	0
	Poor	1
Nasal congestion	Absent	0
	Present	1
Appetite	Absent	0
	Present	1
Daily cough frequency	Absent	0
	Present	1
Nocturnal cough frequency	Absent	0
	Present	1
Fever	<38 °C	0
	>38 °C	1
Pain	Absent	0
	Present	1
Sleep pattern	Normal	0
	Bad	1
Additional symptoms including dyspnea, vomiting, chest pain	Absent	0
	Present	1

Statistical method

Study results for categorical parameters are presented by means of absolute and relative frequencies, Fisher's exact test, chi-square test was employed to compare the two groups of patients, and the tests of McNemar and Bowker, respectively, were applied for the comparison between days 1 and 7 within both groups. Metrical data like the age are presented by median and range, the Mann–Whitney *U*-test was used to compare the treatment groups. All calculations were performed with a statistical software-package named "SPSS for Windows, Version 16.0, SPSS Inc., USA".

Results

Of the 28 patients enrolled to the study, 20 (71.4%) were boys, and 8 (28.6%) were girls. The age range of patients in both groups was between 12 and 60 months, and their average median age was 30.14 months. *Pelargonium sidoides* extract was administered to 11 (78.5%) boys and 3 (21.5%) girls, while placebo was given to 9 (64.2%) boys and 5 (35.8%) girls. We did not notice any incompliance by the measure of returned empty bottles.

The two groups were compared in terms of average white blood cell count, platelet count, hemoglobin level, and serum AST, ALT, GGT, total bilirubin, direct bilirubin, PT/PTT and INR levels, and no relevant differences were found.

A comparison of two groups in terms of appetite revealed an obvious increase in the number of subjects with increased appetite starting from the 5th day in the *Pelargonium sidoides* extract group ($p = 0.022$) (Table 2).

In terms of nasal congestion a highly relevant improvement could be observed in the Pelargonium sidoides extract group, compared to no improvement in the placebo group (Table 3), the ratio of patients without nasal congestion on day 7 is clearly higher in

Table 2
Appetite comparison in groups between 1st and 7th days.

Day	Appetite	Group		*p*
		Pelargonium sidoides n (%)	Placebo *n* (%)	
1	Absent	5 (35.8%)	7 (50%)	0.703
	Present	9 (64.2%)	7 (50%)	
5	Absent	3 (21.5%)	9 (64.2%)	
	Present	11 (78.5%)	5 (35.8%)	0.056
6	Absent	2 (14.3%)	10 (71.4%)	0.008
	Present	12 (85.7%)	4 (28.6%)	
7	Absent	3 (21.5%)	10 (71.4%)	
	Present	11 (78.5%)	4 (28.6%)	0.023

Table 3
Intergroup nasal congestion comparison between 1st and 7th day.

Group	Nasal congestion	Day		p
		1	7	
Pelargonium sidoides *n* (%)	Present	9(64.2%)	4(28.6%)	0.063
	Absent	5(35.8%)	10(71.4%)	
Placebo *n* (%)	Present	10(71.4%)	11(78.5%)	0.0213
	Absent	4(28.6%)	3(21.5%)	

the Pelargonium sidoides extract group (71.4%) than in the placebo group (21.5%) ($p = 0.0213$, Fisher's exact test).

The complaints of daily and nocturnal cough was found to be decreased but not significant on the 7th day in comparison to the 1st day in the *Pelargonium sidoides* extract group ($p > 0.05$). In addition no improvements were detected between the *Pelargonium sidoides* extract group and the placebo group for the complaints of daily and nocturnal cough ($p > 0.05$).

A comparison between of two groups according to symptom scoring, in terms of general status of health, fever and pain revealed no meaningful differences between the placebo group and the *Pelargonium sidoides* extract group ($p > 0.05$). Also the intergroup comparison between the 1st and 7th day separately in both groups revealed no significant difference in terms of improvement of general status of health, reduction of fever and pain between 1st and 7th day in the *Pelargonium sidoides* group.

Discussion

Pelargonium sidoides has a long healing tradition in South African folk medicine where it has been used to treat various infections. The modern extract EPs® 7630 derived from the roots of *Pelargonium sidoides*, has been shown to have immunomodulatory, antiviral, antibacterial and secretomotoric effects (Brendler and van Wyk 2008; Haidvogl and Heger 2007; Matthys and Heger 2006, 2007). This extract is currently used worldwide for the treatment of acute respiratory tract infections where antibiotic use is unnecessary (Timmer et al. 2008). In some studies, it is reported that rates of side effects associated with use of antibiotics are higher than the rates of side effects associated with the use of *Pelargonium sidoides* (Bent et al. 1999; Fahey et al. 1998). There are many adult and children studies proving the efficiency of *Pelargonium sidoides* extract in treatment of bronchitis. Among others these studies have clearly demonstrated that *Pelargonium sidoides* extract is more efficient than placebo in reduction of cough frequency (Chuchalin et al. 2005; Kamin et al. 2010a,b; Matthys et al. 2003, 2010; Matthys and Heger 2007). Consistent with the medical literature, our pilot study also indicated a reduction in daily and nocturnal cough frequency but the p values were under the level of significance.

Nasal congestion and draining are the most common seen initial symptoms of upper respiratory tract infections. A study conducted by Lizogub et al. (2007) on 103 common cold patients revealed that the extent of nasal congestion decreases faster in the *Pelargonium sidoides* group compared to the placebo group. In our pilot study, we also observed that nasal congestion symptoms diminished in most of the patients in the Pelargonium group but increased in the placebo group.

Behavioral changes may be observed in patients during infection periods. Particularly in children, lack of appetite (anorexia) and low spirits are common findings. A rat study revealed that *Pelargonium sidoides* helped in relieving anorexia in rats (Nöldner and Schötz 2007). In another study, it was shown that the anorexia (lack of appetite) symptom improved by approximately 80% in the initial 3 days in 259 patients under *Pelargonium sidoides* treatment (Dome and Schuster 1996). In our study, appetite, being one of the best representative factors in terms of indicating the general state of health of patients, improved significantly from the 5th day in the *Pelargonium sidoides* group in comparison to the placebo group.

Though the medical literature contains some study reports reporting beneficial effects of *Pelargonium sidoides* in terms of control of high fever, effects on anxiety, and effects on symptoms accompanying cough, such as dyspnea, vomiting and chest pain, and in terms of regular sleep pattern (Chuchalin et al. 2005; Heger and Bereznoy 2002). In our pilot study we detected improvement in all of these symptoms but the small number of the study showed no significant difference in these aspects between the *Pelargonium sidoides* group and the placebo group. Recent study conducted in adult population with acute bronchitis showed significant improvement at the bronchitis specific symptoms (Matthys et al. 2010).

Similarly, Kamin et al. (2010a,b) conducted two pediatric studies, and found that *Pelargonium sidoides* is effective and ensures a favorable course of acute bronchitis and a good tolerability as compared with placebo.

Although the major limitation of our study is the small number of the participants; to best of our knowledge we present the first study focusing on the assessment of *Pelargonium sidoides* in children with THI.

Variations in white blood cell, hemoglobin and platelet counts or elevation in liver enzymes may be observed in association with bone marrow suppression as a result of use of medical drugs. Loew and Koch (2008) demonstrated that coumarine derivatives contained in *Pelargonium sidoides* do not have any hepatotoxic effect. In our study, we did not find any significant difference in liver enzymes and CBC values between pre-treatment and post-treatment results either; neither in the *Pelargonium sidoides* group nor in placebo group.

The probability of increase in treatment-associated bleeding risk comes to mind due to presence of coumarines in basic ingredients of *Pelargonium sidoides*. Studies conducted by Chuchalin et al. and Koch et al. indicated no effect of *Pelargonium sidoides* on PT, PTT values. This is associated with the non-anticoagulant character of coumarine derivatives contained (Chuchalin et al. 2005; Koch and Biber 2007). In our study, consistent with the medical literature, we did not detect any significant difference between the pre-treatment and the post-treatment PT, PTT values in the *Pelargonium sidoides* group either.

Many studies have been conducted about adverse reactions or side effects of *Pelargonium sidoides* extract since it was introduced to market. As a part of the pharmacological monitoring program of WHO, de Boer et al. (2007) reported a total of 34 allergic reaction cases, a great many of which may be related to German-origin *Pelargonium sidoides* extracts. However, Matthys and Köhler (2010) recently had systematically reviewed the safety profile of Pelargonium sidoides extract EPs 7630 based upon 25 clinical trials and post-marketing surveillance studies with a total of more than 9000 patients – including pediatric safety with about 4000 children and adolescents – and reported a good tolerability and no serious adverse drug reactions. Our study did also not reveal any severe side effects in any of the patients.

As a conclusion, it is noted that all studies reported in the medical literature have been conducted during infection periods in normally healthy subjects with no underlying disease, and that *Pelargonium sidoides* is fairly effective in treatment of these infections. In our study, which was conducted during URTI, of patients suffering from THI, an increase in appetite and, close-significant reduction of nasal congestion were detected. In addition, the symptoms of cough frequency, fever, pain, sleep pattern, and general state of health in the *Pelargonium sidoides* group were improved; but the results of these symptoms were under the level of significance. The major limitation of our study design is the limited number of the patients which does not allow making confirmatory

results from our pilot-study. Moreover, these study data and findings must be supported by more comprehensive further studies due to the low number of subjects and due to the subjectivity caused by the questionnaire being completed by mothers in the presented pilot-study.

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