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EFIKASNOST PRIMENE PROPOLISA I N-ACETILCISTEINA U LEČENJU AKUTNIH RESPIRATORNIH INFEKCIJA KOD DECE

EFFICIENCY OF PROPOLIS AND N-ACETYLCISTEINE FOR THE TREATMENT OF ACUTE RESPIRATORY INFECTIONS IN CHILDREN

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Ključne reči
akutne respiratorne infekcije, deca, propolis, N-acetilcistein.

Key words
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Sažetak

Akutne respiratorne infekcije su vrlo čest problem sa kojima se susreću deca, naročito mlađeg uzrasta. Simptomatologija je u slučaju virusnog porekla infekcije nespecifična, pa se je i terapija simptomatska. Fitoterapija predstavlja upoređivanje farmakoloških svojstava hemijskih lekova u interakciji sa biljem i proizvodima iz prirode. Savremeno doba donelo je moderne smernice u ispitivanjima biljaka, što je potvrdilo iskustvo naših predaka u korišćenju bilja pri lečenju i ublažavanju tegoba. Cilj istraživanja bio je da se proceni efikasnost primene propolisa i N-acetilcisteina (*PropoMucil*® sirupa i *PropoMucil*® spreja za nos) kod dece sa respiratornim infekcijama. Istraživanje je sprovedeno od januara do aprila 2016. godine u Institutu za majku i dete „Dr Vukan Čupić" u Beogradu. Istraživanjem su obuhvaćene dve grupe dece: grupa A-deca sa simptomima sekretornog zapaljenja srednjeg uha i gupa B-deca sa simptomima zapaljenja nosne sluznice. U obe grupe dece beleženi su na prvom pregledu demografski podaci, dužina trajanja simptoma, dok su na prvom i kontrolnom pregledu beleženi tipovi simptoma, otoskopski i timpanometrijski nalaz - u grupi A i endoskopski nalaz, izgled sekreta i mikrobiološki nalaz u grupi B. U grupi A dece je pri kontrolnom pregledu statistički bila manje zastupljena simptomatologija infekcije, uz normalizaciju otoskopskog i timpanometrijskog nalaza. U grupi B dece je na ponovnom pregledu statistički bila manje zastupljena simptomatologija infekcije, došlo je do normalizacije endoskopskog nalaza, izgleda sekreta i mikrobiološkog nalaza.

INTRODUCTION

Acute respiratory infections are the leading cause of children mortality under 5 years of age worldwide (10.6 million deaths), and the most of them are due the bronchiolitis and pneumonia[1,2]. Acute respiratory infections are infective diseases manifested by mild infection of the respiratory mucosa and most frequently caused by viruses[3]. Most acute respiratory viruses' infections in early childhood are confined to the upper respiratory tract, leading the symptoms of the common cold, with coryza, cough, and hoarseness. Upon examination, rhinitis and pharyngitis are found and are frequently associated with tympanic vascular injec-

tions. In some cases, symptoms and signs of otitis media occur, such as earache, tenderness of the tragus upon pressure, and a red bulging tympanic membrane upon inspection. Upper respiratory tract infection in children is often accompanied by fever and may lead to lethargy and poor feeding. Specific treatment is usually neither available nor required. However, analgesics/antipyretics (e.g., paracetamol) and, in some cases, nasal decongestants may be helpful in reducing discomfort and symptoms, making feeding easier, and allowing an adequate supply of oral fluids[4]. About one-third of infants with respiratory viral infections develop lower respiratory tract symptoms such as tachypnea, wheeze, severe cough, breathlessness, and respiratory distress. These symptoms may be accompanied by clinical signs including nasal flaring; jugular, intercostal, and thoracic indrawings; rarely cyanosis; and, on auscultation of the chest wheeze, crackles, crepitations, and inspiratory rhonchi or generally reduced breath sounds due to air trapping and peripheral hyperinflation of the lung[4]. The treatment and care for viral lower respiratory tract infections depend on the assessment of the severity of respiratory compromise by using measurements of oxygen saturation and of blood gases and the clinical assessment of the severity of respiratory distress and of respiratory exhaustion with decreased respiratory effort, increasing carbon dioxide retention, and respiratory acidosis[4]. Therefore, the treatment should begin with relieving the symptoms, involving antitussives, decongestives, expectorants and antihistaminics[3].

Previous studies have shown that propolis have immunomodulatory, antibacterial, and antiviral properties[5-8]. Also, some studies have reported the antioxidant effect of propolis[9,10]. Clinically, propolis has shown antioxidative actions without altering blood parameters[11], or increasing respiratory parameters in asthmatic patients[12]. On the other hand, NAC acts as a cellular precursor of thiol antioxidant glutathione (GSH), and becomes deacetylated in the gut to cysteine following oral administration[13]. NAC may also reduced cystine to cysteine, which is important mechanism for intracellular GSH elevation in vivo in lungs. It reduces disulfide bonds (a property of a good reducing agent), and has the potential to interact directly with oxidants. NAC is also used as a mucolytic agent, to reduce mucus viscosity and to improve mucociliary clearance[14].

Based on the discussed problems and the tendency to clinically relieve the symptoms of acute respiratory infection to the youngest patients, the aim of this study was to assess the efficiency of propolis and N-acetylcisteine (PropoMucil® syrup and PropoMucil® nasal spray) in children with acute respiratory infections.

METHODS AND PATIENTS

The study was conducted as a prospective clinical study at the ORL Department of the Institute for mother and child „Dr.Vukan Čupić“in Belgrade from January to April 2016. The study included 173 children, who were based on symptoms of secretory otitis media and inflammation of the nasal mucosa divided into two groups: group A (n=100) and group B (n=73). The children of A group were given PropoMucil® sirup for children (combination of standardized propolis with 12% of polyphenol and N-acetylcystein; Abela Pharm, Belgrade, Serbia) and the children of B group were given PropoMucil® nasal spray for children (combination of standardized propolis with 12% of polyphenol and N-acetylcystein; Abela Pharm, Belgrade, Serbia) to use them for 2 weeks (14 days). The recommendation for syrup was to use it 2 to 3 times per day (for children up to years old), or 3 to 4 times per day (for children older than 6 yers), in a single dose of 12 ml (1 soup spoon), after meal. In the case of a nasal spray, the recommendation was to use it optionally, but maximum of 4 times 2 splash per nostril. Follow-up examinations were carried out after 14 days of using dietary supplements / first examination.

On the first examination, demographic data of children in both groups were recorded (age, gender and stay in a kindergarten) and duration of, while the type of symptoms, ORL examination findings, otoscopic findings, hearing data processing (tympanometry and audiometry), and the data obtained on a microbiological test of the nasal secretion were recorded on two time points (first and follow-up examinations). On the follow-up visit (after 2 weeks), the parents or caretakers were given the opportunity to comment on the products their child had got to use between two visits: efficiency, taste, undesirable effects, and the child's assessment.

The obtained data were statistically processed using the statistical program (SPSS 17.0 Inc., Chicago, IL, USA). The attributive observation marks of the tested groups were described using percentages, numerical values were assessed by central tendency and variable measures while the data from two time points (first and follow-up) were compared using the one-factor analysis with repeated measurement (ANOVA). The results were presented in a graph and a table.

RESULTS

Group A included 55,0% of boys, with a medium age of 5, 07 ± 2, 78 ages old (1 to 15 years), and most of them (53,0%) were older preschool age (Table 1). Similar finding was in group B of children; 56,2% of them were boys, with similar age group (5, 48 ± 3, 44; 1-6 years old) and age group (57,2% of older preschool age) - Table 1. The majority of children in both groups were regular attendees of collective groups (81,0% vs. 86,3%) - Table 1.

Table 1. *Socio-demographic characteristics of children in both groups*

Socio-demographic characteristics	Group A n (%)	Group B n (%)
Gender:		
boys	55 (55,0)	41 (56,2)
girls	45 (45,0)	32 (43,8)
Age (in years):		
X ± SD; min-max	5, 07 ± 2, 78; 1-15	5, 48 ± 3, 44; 1-6
Age group:		
younger preschool age	22 (22,0)	14 (19,2)
older preschool age	53 (53,0)	42 (57,5)
school age	25 (25,0)	17 (23,3)
Stay in collective group:		
yes	81 (81,0)	63(86,3)
no	19 (19,0)	10 (13,7)

n-number of subjects; % percent of subjects; X-mean value; SD-standard deviation; min-minimum; max-maximum

In aspect of duration of symptoms, half of children in both groups had symptoms that last 1 to 3 days (Figure 1).

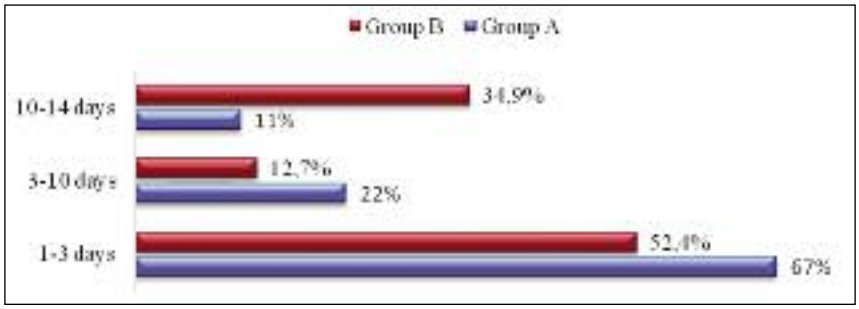

Figure 1. *Duration of symptoms in both groups*

Speaking of types of symptoms, in children of A group, most of them had intermittent or permanent nasal obstruction (86,0%), intermittent or permanent cough (83,0%) and impaired hearing (91%) - Table 2. After one moth of using syrup, a statistical significance was registered in all observed symptoms: 64,0% of children had intermittent or permanent nasal obstruction, 30,0% had intermittent cough and 57,0% had impaired hearing - Table 2. Also, in aspect of clinical findings in group A of children, on first visit, most of them (95,0%) had cloudy eardrum and finding B of tympanometry (Table 2). After 2 weeks (on follow-up examination), a statistical significance was registered in all clinical findings; 57,0% of children had cloudy eardrum and 59,0% of them had finding B of tympanometry - Table 2.

Table 2*. Symptoms and clinical findings of children in A group on the first and on follow-up visit*

Symptoms and clinical findings	First examinationn n(%)	Follow-up examination n (%)	Significance [a](p)
Nasal obstruction:			
no	24 (24,0)	36 (36,0)	
intermittent	56 (56,0)	57 (57,0)	<0,001*
permanent	20 (20,0)	7 (7,0)	
Cough:			
no	28 (20,0)	70 (70,0)	
intermittent	59 (50,0)	30 (30,0)	<0,001*
permanent	13 (13,0)	0 (0)	
Impaired hearing:			
no	5 (5,0)	37 (37,0)	
yes	91 (91,0)	57 (57,0)	<0,001*
doesn't know/not sure	4 (4,0)	6 (6,0)	
Otoscopic finding:			
normal	3 (3,0)	40 (40,0)	
cloudy eardrum	95 (95,0)	59 (59,0)	<0,001*
cloudy and hyperemic eardrum	2 (2,0)	1 (1,0)	
Tympanometry:			
finding A	2 (2,0)	30 (30,0)	
finding B	95 (95,0)	57 (57,0)	<0,001*
finding C	3 (3,0)	13 (13,0)	

n – number of subjects; % percent of subjects; aANOVA;
*statistical significance

On first examination, 95,9% of children in B group had nasal secretion and 87,7% of them had intermittent or permanent nasal obstruction (Table 2). After two weeks of using nasal spray, a statistical significance was registered in all observed symptoms: 39,7% had nasal secretion and 47,9% had intermittent or permanent nasal obstruction (Table 2). Also, in aspect of clinical findings in group B of children, on first visit, most of children had abnormal endoscopic finding (91,4%), mucous appearance of secretion (42,5%) and negative microbiological finding (56,2%) - Table 3. After two weeks (on follow-up examination), a statistical significance was registered in all clinical findings; 58,9% of children had normal endoscopic finding, 84,9% had clear appearance of secretion and 93,2% of them had negative microbiological finding (Table 3).

Table 3. *Symptoms and clinical findings of children in B group on the first and on follow-up visit*

Symptoms and clinical findings	First examination n (%)	Follow-up examination n (%)	Significance [a](p)
Nasal secretion:			
yes	70 (95,9)	29 (39,7)	
no	0 (0)	40 (54,8)	<0,001*
doesn't know/ not sure	3 (4,1)	4 (5,5)	
Nasal obstruction:			
no	9 (12,3)	38 (52,1)	
intermittent	47 (64,4)	33 (45,2)	<0,001*
permanent	17 (23,3)	2 (2,7)	
Endoscopic finding:			
normal finding	7 (9,6)	43 (58,9)	
hyperemic mucosa	30 (41,1)	9 (12,3)	
edematous mucosa	24 (32,9)	21 (28,8)	<0,001*
hyperemic and edematous mucosa	12 (16,4)	0 (0)	
Appearance of secretion:			
clear	27 (37,0)	62 (84,9)	
mucous	31 (42,5)	11 (15,1)	<0,001*
purulent	15 (20,5)	0 (0)	
Microbiological finding:			
negative	41 (56,2)	68 (93,2)	
positive	32 (43,8)	5 (6,8)	<0,001*

n – number of subjects; % percent of subjects; aANOVA;
*statistical significance

On follow-up examination, when the parents of group A of children were asked for their comments on the syrup recommended to their children (in terms of efficiency, taste and quality), they most frequently said that, based on their assessment, they had observed improvement of the health condition of their children (56,0%), that the syrup had a good taste (71,0%) and that they had not observed any undesirable effects in their children (96,0%) - Table 4. Similarly, the parents of group B of children reported the improvement of the health condition of their children who used spray (69,9%) - Table 4. Also, many of them (50,7%) said the spray was good, that children loved to use it and that it produced no undesirable effects (100,0%) - Table 4.

Table 4. *Comments of parents of children in both groups*

Parents' comment	n (%)
GROUP A	
Syrup efficiency:	
improvement	56 (56,0)
no change	44 (44,0)
worse	0 (0)
Syrup taste:	
good	71 (71,0)
neutral	28 (28,0)
bad	1 (1,0)
Undesirable effects:	
yes	4 (4,0)
no	96 (96,0)
GROUP B	
Spray efficiency:	
improvement	51 (69,9)
no change	22 (30,1)
worse	0 (0)
Child's evaluation:	
good, loves to use it	37 (50,7)
indifferent	27 (36,9)
bad, hates to use it	9 (12,4)
Undesirable effects:	
yes	0 (0)
no	73 (100,0)

n - number of subjects; % percent of subjects

DISCUSSION

In our study, children were divided into two groups based on their symptoms. Demographic data were approximately similar for both groups: somewhat more male children (55,0% in group A, or 56,2% in group B), similar average age (5,07 ± 2,78;1-15 and 5,48 ± 3,44; 1-16, respectively) and age (older preschool children: 53,0% in group A and 57,5% in group B), with similar data on stay in collective groups (81,0% and 86,3%, respectively). Many studies show the connection between an early enrollment in a kindergarten and incidence of airway inflammation[15,16]. Moreover, the risk for the occurrence of the infection of lower airways is three times greater in kindergarten groups aged 2 to 5 than in the children of the same age who were at home [17,18]. Preschool children are in a specific risk of increased incidence of infective airways infections due to the reduced ability to produce some antibodies (IgG type 2 and IgG type 3), more so in preschool groups where children are in contact with their peers, where the exposure to potential sources of infection is greater to which children are generally less resistant. In addition, older children had already adopted hygiene habits, so that the possibility for spreading infections with dirty hands, or nasal and oral excretion was diminished [19].

Both groups showed a statistically significant difference in the severity of symptoms between the first and follow-up visits. Group A children experienced much less nasal obstructions, cough and impaired hearing. The situation was similar in group B – the percentage of children without the symptoms of nasal obstruction and secretion was significantly higher. Also, group B showed statistically significant normalization of the otoscopic and tympanometric findings, while group B showed statistically significant shift in terms of the normalization of the endoscopic finding, secretion appearance and microbiological result. The children in group A used PropoMucil® pediatric syrup during two weeks (Abela Pharm, Belgrade, Serbia), while the children in group B used PropoMucil® pediatric spray during two weeks (Abela Pharm, Belgrade, Serbia), each of which contained a combination of purified standardized propolis with 12% of polyphenol and N-acetylcystein, and the PropoMucil® pediatric syrup also contained honey, marshmallow and rose hips. Propolis found in commercial products showed to be very efficient for inflammatory processes of the airways owing to which its application is recommended for acute respiratory infections [20], which can be explained by the fact that it is a complex mixture of different compounds with synergistic action contributing to its anti-inflammatory effect [21,22]. When it comes to polyphenols, they show numerous benefits, such as: anti-inflammatory, antimicrobial and spasmolytic [23,24]. The advantages of marshmallow are induced by its beneficial effects on the dry, unproductive cough, and on the inflamed mucosa of the upper respiratory airway. Owing to its copious content of polysaccharides, marshmallow exerts an immunomodulatory effect through the increased activity of phagocytes [25,26]. Rose hip is the fruit with exceptional anti-inflammatory, antimicrobial and antioxidative properties [27].

When the parents of group A children were asked for their comments on the syrup recommended to their children (in terms of efficiency, taste and quality), they most frequently said that, based on their assessment, they had observed improvement of the health condition of their children, that the syrup had a good taste and that they had not observed any undesirable effects in their children. Similarly, the parents of group B children reported the improvement of the health condition of their children who used spray. Also, many of them said the spray was good, that children loved to use it and that it produced no undesirable effects.

The main limitation of our study is the lack of control groups treated with standard non-specific therapy, as well as the absence of more detailed laboratory findings.

CONCLUSION

More clinical studies need to be conducted related to the efficiency of propolis and N-acetylcisteine in terms of specific action on some microbial agents – causes of acute respiratory infections.

Abstract

Acute respiratory infections are a very frequent problem in children, especially young ones. In case of the infections of viral origin, the symptomatology is unspecific; therefore, the therapy is symptomatic. Phytotherapy is the comparison of the pharmacological properties of chemical medicines in interaction with herbs and natural products. The modern era brought modern guidelines for herbs testing, which was confirmed by our predecessors' experience in using herbs for healing and relieving complaints. The aim of this study was to assess the efficiency of propolis and N-acetylcisteine (PropoMucil® syrup and PropoMucil® nasal spray) in children with respiratory infections. The study was conducted during the period January-April 2016 at the Institute for Mother and Child „Dr. Vukan Čupić" in Belgrade. The study included two groups of children: group A - children with the symptoms of the secretory inflammation of the middle ear and group B - children with the symptoms of the inflamed nasal mucosa. Demographic data and duration of symptoms were recorded for both groups at first examination, while group A was assessed for type of symptoms, otoscopic and tympanometric findings and group B was assessed for endoscopic finding, appearance and microbiological finding of the excretion both at visit one and at the follow-up visit. At follow-up, the children in group A had statistically less infection symptoms, with the normalization of the otoscopic and tympanometric findings. At the repeated examination, the children in group B had statically less infection symptoms, with the normalization of the endoscopic finding, appearance of excretion and microbiological finding.

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