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Research Article

Evaluation of Efficacy and Tolerability of a Fixed Combination of N-Acetyl Cysteine (NAC) with Propolis as a Supplement in Treatment of Adults with Acute Respiratory Infections a Real Life Observational Single Centre Clinical Trial

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Abstract

Introduction and Aim: The aim of this study was to assess the efficacy of N-acetyl cysteine (NAC) in formulation with propolis as a supplement in treatment of patients with acute respiratory infections.

Patients and Method: The prospective study was conducted in Clinic for Pulmonology (Clinical Centre of Serbia, Belgrade) in period February 2017-July 2017 enrolling patients with symptoms of acute respiratory infections. After a detailed analysis of the symptoms, adequate standard therapy was applied together with the preparation of 600 mg N-acetylcysteine and 80 mg propolis, sachet (PropoMucil® AbelaPharm, Serbia), once daily for 10 days.

Results: Number of 71 patients with average age 60.7 ± 14.9 years was included in the study. Cough as a symptom was present in 85.9% of patients, with clear sputum in 63.4%. Among the patients included 41% were diagnosed with acute bronchitis, 28% with bronchial asthma, 20% with chronic obstructive pulmonary disease (COPD) and 11% with pneumonia. Ten days after initiation of therapy, regression of inflammatory parameters such as C-reactive protein (CRP), sedimentation rate, fibrinogen, white blood cells count and neutrophils count was observed, while simultaneously observing and increase in quantity of mucus.

Conclusion: Use of preparation containing N-acetyl cysteine and propolis alongside the standard therapy in the treatment of the acute respiratory infection, during the course of 10 days, have shown a positive effect via stabilizing the overall condition, inducing coughing of the viscous secretions.

Keywords: *Acute Respiratory Infections; Dietary Preparation; N-acetylcysteine; Propolis*

Abbreviations

COPD: Chronic Obstructive Pulmonary Disorder; NAC: N-acetyl Cysteine; ESR: Erythrocytes Sedimentation Rate; WHO: World Health Organization

Introduction

Inflammation, as a string of related processes, is one of the main pathophysiological mechanisms present in many diseases [1]. In respiratory medicine, inflammation is, among others, present in acute and chronic infections. With their high frequency, infectious inflammatory diseases of the respiratory system contribute significantly to overall mortality all over the world [2], as well as in Serbia [3]. Direct contact of the large surface of the respiratory tract with unsuitable substances from the environment may, in part, explain the high frequency of the respiratory infections. Environmental factors, especially in industrialized and well-populated areas, such as industrial smoke, cigarette smoke and free radicals, influence immune response of the organism, making it more prone to the infections. Function of the immune system can be additionally affected by presence of chronic diseases accompanied by corresponding therapies. The degree to which the infection will progress depends on the interaction between the organism itself and the agent, as well as the organism's ability to active full immune response against it.

The most common manifestations of acute respiratory infections include acute bronchitis, pneumonia, worsening of the chronic obstructive pulmonary disorder (COPD), and bronchial asthma. Course of these conditions may be prolonged leading to a need for additional therapies, such as standardized antibiotic therapy, antipyretic or bronchodilation agents. Pathogenesis of these conditions is associated with several pathophysiological mechanisms, with oxidative stress being one of the. It has been reported that COPD is characterized with the imbalance inside the redox-antioxidant system [4]. The inhalation of the cigarette smoke, that is a huge oxidative stress in COPD, stimulates activity of elastase, and starts apoptosis [5]. Oxidizing agents activate redox-sensitive transcription, signal transduction, pro-inflammatory gene expression, that after a line of chemical reactions leads to pulmonary or systemic inflammation process [6]. Therefore, interfering and reducing the effects of the oxidative stress may have a role in suppressing the inflammation and improving the clinical course of the disease in patients with inflammatory diseases of the respiratory system [7]. N-acetyl cysteine (NAC) has been reported to have a mucolytic effect with a direct/indirect anti-oxidizing and anti-inflammatory potential [3], leading to reduction of infections and reduction the recurrence of the COPD. It acts directly as a reactive substance of oxygen as well as a precursor of reduced glutathione (GSH), bringing rearrangement inside the cellular redox status and affecting inflammatory pathway in patients with COPD via reduction of inhibiting redox- sensitive cell signals through transduction and pro-inflammatory gene expression [3]. NAC may reduce exacerbations in COPD patients via disrupting cellular conductivity between ciliary and epithelial cells and bacteria [3]. Furthermore, it reduces adhesion of *H. influence, S. pneumonia* to the oropharyngeal epithelial tissue and inhibits their colonization and growth [4]. It also inhibits replication process of the viruses via reducing H_2O_2 and cell's sulfhydryl levels and by stopping expression of adhesive molecules [5]. Therefore, N-acetylcysteine (NAC) may play a significant role in treatment of inflammatory conditions of respiratory system. The aim of this study was to assess the efficacy of NAC in formulation with propolis as a supplement in treatment of patients with acute respiratory infections.

Materials and Methods

A real life observational single-centre study was conducted in the Clinic for Lung diseases Clinical Centre of Serbia in the period February 2017 - July 2017. The protocol was approved by the Ethical Committee of the hospital. Informed consent was obtained from of the participants. The study group consisted of patients suffering from symptoms of acute respiratory infection treated in the named period. Inclusion criteria implied age over 18, presence of acute respiratory inflammation or exacerbation of acute respiratory infection symptoms. Exclusion criteria implied presence of asthma exacerbation and hypersensitivity on NAC or propolis. The study was supported by a questionnaire that included: the type of cough, look of the sputum, duration of symptoms. Spirometry testing was also performed at the beginning of the follow up period as well as radiographic imaging (chest X ray). We performed also whole blood count with erythrocytes sedimentation rate (ESR), CRP and fibrinogen at the beginning and at the end of follow up period. In additional patients were asked about life style including smoking habits and physical activity. Data on comorbidities were taken from medical records of included patients. Additional to standardized antibiotic treatment, patients were treated with supplement formulation containing 600mg of NAC and 80mg of propolis in sachets, once daily (PropoMucil® 600, sachets, manufacturer AbelaPharm, Serbia). Therapy was administered for 10 day followed by reassessment of the presence of clinical symptoms and signs and biochemical analyses.

Statistical analysis

The sample size was calculated with the software package G power. Descriptive and analytical statistical methods were used. The following descriptive variables were described: measures of central tendency (mean, median), measure of dispersion (standard deviation, interval of variation). Analytical statistical methods were used to test differences, parametric and nonparametric variables. Student's t test and analysis of variance of repeated measurements were used. Chi square test, McNemar test, Mann-Whitney test, Wilcoxon test, Friedman test were also included. All data were analyzed in SPSS 15.0 software package. (SPSS Inc., Chicago, Illinois, USA).

Results

71 patients were included in the study. Table 1 reports demographics of the patients included. Median age of the patients included was 60.7 ± 14.9, ranging from 29 to 87 (Table 1). Study included 35 (49.3%) males and 36 (50.7%) females. Table 2 reports the lifestyle habits of the patients included. Among the included, 73.2% were smokers while 57.7% did not practice more than 30 minutes of physical activity daily (Table 2). Table 3 reports clinical presentation of the patients included. Cough as a symptom was present in 85.9% of patients, with clear sputum in 63.4% (Table 3). Spirometry disclosed normal findings in 59.2% of the included while chest x-ray showed no pathological findings in 88.7% (Table 3). In 97.2% patients symptoms lasted more than 10 days (Table 3). Among the co-morbidities arterial hypertension was observed most frequently (Table 3). Among the patients included 41% were diagnosed with acute bronchitis, 28% with bronchial asthma, 20% with COPD and 11% with pneumonia (Figure 1). 73.3% of patients were treated in ambulatory settings while 26.7% were hospitalized (Figure 2). Figure 3 reports the effects of treatment represented by biochemical parameters as well as quantity of sputum. We observed regression of inflammatory parameters such as C-reactive protein (CRP), sedimentation rate, fibrinogen, white blood cells count and neutrophils count, while simultaneously observing and increase in quantity of mucus, 10 days after initiation of therapy (Figure 4). During the whole follow up period we didn't observe any adverse events and the treatment was very well tolerated among selected patients.

Demographic characteristics of respondents	n (%)
Gender	
Male	35 (49.3)
Female	36 (50.7)
Age	
X ± SD; Med (min-max)	60.7 ± 14.7 (29 - 87)

Table 1: *Demographics of 71 patients included in the study.*

n: Number of Respondents; %: Percentage of Respondents; X: Mean; SD: Standard Deviation; min: Minimum; max: Maximum.

Habits for own health	n (%)
Smoking	
Yes	52 (73.2)
No	19 (26.8)
Daily physical activity *more than half an hour*	
Yes	30 (42.2)
No	41 (57.7)

Table 2: *Lifestyle habits of 71 patients included in the study.*

Symptoms and signs of disease	n (%)
Cough with an expectoration	
No	1 (1.4)
Poor	9 (12.7)
Expressive	61 (85.9)
Look of sputum	
Clear	45 (63,4)
Mucous	22 (31.0)
Purulent	4 (5.6)
Signs of obstruction	
Orderly	42 (59.2%)
Signs of obstruction	26 (36.6%)
Signs of restriction	3 (4.2 %)
Radiological finding of the lungs	
Without pathology	63 (88.7%)
Duration of symptoms	
7 to 10 days	2 (2.8 %)
More than 10 days	69 (97.2%)
Associated diseases	
Arterial hypertension	29 (33.7)
Diabetes mellitus	16 (18.6)
Cardiovascular diseases	16 (18.6)
Rheumatoid disorders	1 (1.2)
Other	2 (2.4)
No comorbidity	22 (25.5)

Table 3: *Clinical presentation of 71 patients included in the study.*

n: Number of Respondents; %: Percentage of Respondents.

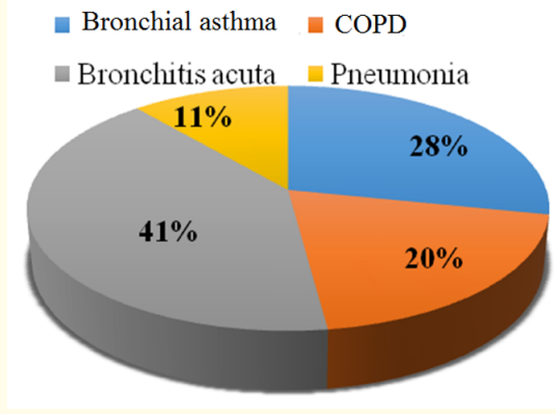

Figure 1: *Distribution of clinical entities among 71 patients included in study.*

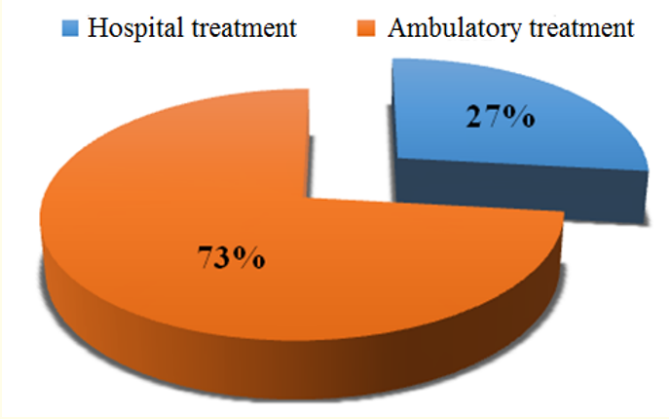

Figure 2: *Distribution of treatment settings among 71 patients included in the study.*

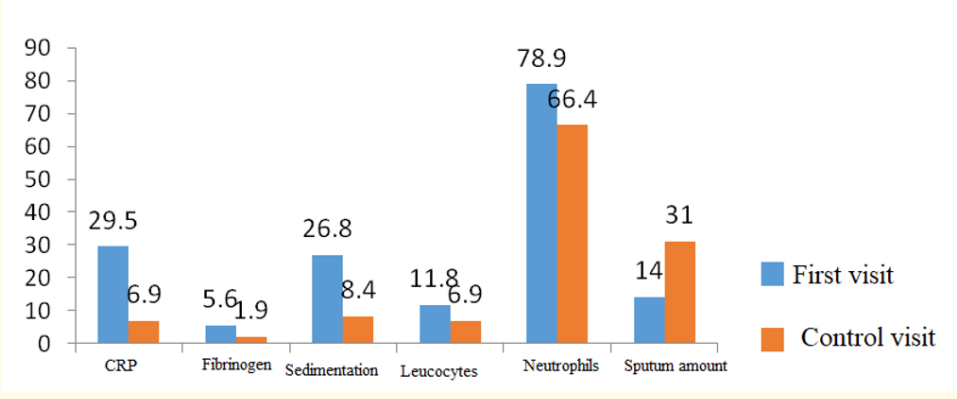

Figure 3: *Effects of therapy in 71 patients included in the study.*

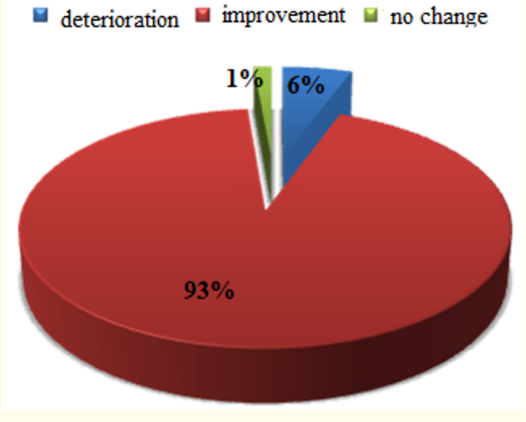

Figure 4: *Improvement in the overall health condition after 10 days of treatment in 71 patients included in the study*

Discussion and Conclusion

We report therapy with NAC concomitant with standardized antibiotics to be efficient in treatment of acute respiratory infections represented by biochemical and clinical parameters. The unfavourable epidemiological data of the World Health Organization (WHO) regarding acute respiratory problems [2] pointed out a need for additional non-standardized medicaments. The incidence of acute bronchitis in adults is reported to be high, being 30 to 50 in 1000 people a year [2]. In European countries, more than 16 000 adults each year refer to the primary care physician with the symptoms of acute respiratory infections, or acute bronchitis [2]. The symptoms can last for more than 2 weeks, with a significant negative effect on the patient's quality of life [2]. The incidence of acute respiratory infections has reported to be high also in Serbia, especially in elderly population as well as in youngest age groups [7]. Institute for Public Health of the Batut Institute, Belgrade, Serbia has reported the incidence of acute respiratory infections of 1536,25 per 100,000 for the 41st week of 2017/2018 only [7], depicting not only healthcare but also socioeconomic burden of this clinical entity. Among the patients included majority was treated for acute bronchitis while the smaller portions were treated for pneumonia and deterioration of bronchial asthma and COLD. Gender distribution of patients was equal among the different clinical entities. However, most of the patients included were 50 years and more with a large percentage associated with smoking habits. We reported productive caught to be the main symptom among our patients with acute respiratory infection. The cough represents a physiological aspect of the function of the respiratory tract and the first line of defence against harmful agent. It is the first sign of warning of unusual respiratory conditions. The frequency and presence of other symptoms and signs depicts the presence of inflammation. Results of the bacterial swab of the expectorate most frequently disclosed *Haemophilus influenza* followed by *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and *Streptococcus pneumoniae*. These results are in line with the results of studies conducted in other European and North America [4]. Antibiotic therapy in all the patients was conducted without complications. Deterioration of COPD and bronchial asthma are often caused by infectious agents. Determining the agent type together with antibiotic sensitivity leads to more effective treatment and shortens the recuperation period. The therapy used was based on patients' clinical and microbiological profile. Standard therapy for patients with acute respiratory infections implies use of antibiotics and broncho dilating therapy. However, the substances with potential to affect the redox system can lead to faster recovery. Furthermore, the majority of patients in our study had co-morbidities reported to be associated with changes in redox-antioxidant ratio giving further rationale for using such a supplement as addition to the standard therapy. One such a supplement is NAC. Antimicrobial properties of NAC have been observed and well determined. NAC was reported to improve the flow through the small airways. Furthermore, NAC leads to rise in cough frequency and eases the excretion of the mucus. In this way the aggregated sputum can be easily expelled outside the respiratory system. Respiratory epithelial tissue is consequentially relieved and can resume its physiological function. NAC in this study was used with the addition of propolis. Using this formulation as an addition to standard therapy in our study led to improvement observed on the control check consisting of improvement in the overall state, improvement in biochemical parameters of inflammation, the reduction of the radiographically verified pneumonia, and the reduction of the cough frequency. Finally, the observed positive effect determined the improvement in overall wellbeing. In conclusion, use of preparation containing 600 mg of N-acetyl cysteine and 80 mg of propolis, in sachets, once daily alongside the standard therapy in the treatment of the acute respiratory infection, during the course of 10 days, have shown a positive effect via stabilizing the overall condition, inducing coughing of the viscous secretions.

Authors' Contributions

Jelica Videnović-Ivanov, Violeta Mhailović-Vučinić and Suzana Filipović -Stepić conceived and designed the study and coordinated the data collection. Zorica Zivkovic, Anita Agic revised the study results and drafted the manuscript. Ivana Filipovic and Marco Camintai contributed to data interpretation and manuscript preparation. All authors read and approved the final manuscript.

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Not applicable.

Competing Interests

The authors declare no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript, except Anita Agic who is employed in Abela Phram, a pharmaceutical company that supported the study in terms of products supply.

Availability of Data and Materials

Data requests can be sent to Dr. Ivana Durjc-Filipovic.

Ethics Approval and Consent to Participate

The study was approved by the Ethical Committee of Clinic for Pulmonology, Clinical Centre of Serbia, Belgrade. Informed consent was obtained for all participants.

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