Original Article

The Comparative Analysis of the Impact of N-Acetyl-L-Cysteine and its Combination with Propolis on Quality-of-Life in Patients with Acute Bronchitis

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ABSTRACT

Objectives: Evidence suggests that both N-Acetyl-L-cysteine (NAC) and NAC in combination with propolis (NAC-P) reduce symptoms of acute bronchitis and improve Health-Related Quality of Life (HRQoL). This study aimed to compare the impact of NAC and NAC-P therapy on acute bronchitis patients' quality of life. Design, setting, and subjects: A randomized, single-blind parallel-group study was achieved at Municipal Institute for Lung Diseases and Tuberculosis Medical Centre, Belgrade, Serbia. Patients with acute bronchitis were randomly assigned into two groups to receive NAC (200mg three times a day) or NAC-P (200mg+80mg three times a day) orally for a minimum of ten days. HRQoL of patients was measured twice (at two appointments) using the Leicester Cough Questionnaire (LCQ) and EQ-5D questionnaires. **Results:** The study included 42 patients in the NAC-P group and 43 in the NAC group. The correlation between the LCQ total score and Health State Values (HSV) was positive and statistically significant in the NAC-P and the NAC groups at the second appointment. The differences between values of EQ-5D scores were slightly higher (but not statistically significant) in the NAC-P group compared to the NAC group, indicating a more remarkable improvement of HRQoL using NAC-P. **Conclusion:** NAC-P and NAC may improve HRQoL in patients with acute bronchitis. EQ-5D scale values indicated that NAC-P might improve quality of life more than NAC. Our results may provide the basis for better decision-making by healthcare professionals when choosing the right therapy.

Keywords: Respiratory disease, Bronchitis, Health-Related Quality of Life, N-Acetyl-L-cysteine, Propolis, Treatment.

INTRODUCTION

Living longer and better is what every human being wants. A long life, by itself, is not always satisfying. Satisfaction goes hand-in-hand with the quality of life, primarily health-related. Health-Related Quality-of-Life (HRQoL) is a broad term as individuals perceive the term "being healthy" from different viewpoints; therefore, different factors can influence it. HRQoL is multifactorial and integrates how health conditions and treatments affect the patient's life and daily well-being.[1,2]

Upper respiratory tract conditions have a considerable influence on the quality of life of patients. Such conditions, including acute bronchitis and acute cough, may affect several aspects of HRQoL. These include physical functions, physical status, body pain, vitality, social functions, emotional status, and mental health.[3] Therefore, such conditions require measuring humanistic outcomes alongside those of a clinical nature to monitor the improvement of patient health status.

Approximately 5% of the older population worldwide will suffer from acute bronchitis each year, caused by viruses in 95% of cases. Considering these rates, the treatment presents a global economic burden with more than 10 million GP visits yearly.[4]

In 2018 in Serbia, the rate of diagnosed patients with acute bronchitis was 33.31 per 1000 inhabitants. This condition was one of the most common respiratory diseases.[5] In most

cases, patients alone cannot resolve symptoms related to acute bronchitis (such as productive cough, high body temperature, headache, dyspnoea, and nasal congestion). Therefore, patients require frequent visits to General Practitioners (GPs).[6] Symptoms related to acute bronchitis led to increased numbers of GP visits, additional costs for patient treatment, and increased direct and indirect health care costs.[7]

N-Acetyl-L-cysteine (NAC) has beneficial effects, for example, against impaired mucous secretion clearance, and is used as a treatment option in different conditions.[8] Although the NAC is primarily indicated for therapy of acetaminophen toxicity, the NAC is also used for viscous and mucus hypersecretions during some respiratory diseases (pneumonia, bronchitis, tracheobronchitis, coughing, and flu infections). The maximum daily dose for respiratory diseases is 600mg once daily. The most common adverse drug reactions when the maximum dose is applied were Gastrointestinal (GIT), but in some studies, their frequency was similar to placebo.[9] Accordingly, paying attention to patients with a gastric or duodenal ulcer is necessary. Also, precautions should be taken in patients with bronchospasm and histamine intolerance or those who already take antitussive, antibiotics, carbamazepine, nitroglycerin, and activated charcoal medicines.[10] In the Republic of Serbia, products that consist NAC are registered as medicines (over-the-counter medicines in oral dosage forms and as i.v. infusion) and as dietary supplements.

One published study aimed to analyze the effects of an antimicrobial agent Thiamphenicol Glycinate (TG) compared to TG-acetylcysteine administered as an aerosol in treating acute bronchitis (among other acute diseases of the upper respiratory tract). The results indicated that the antimicrobial agent, in combination with acetylcysteine, was more effective in eliminating coughs over six days of treatment.[11] Two studies indicated the importance of NAC with Propolis (NAC-P) in antioxidant protection and respiratory symptom reduction in pediatric patients with adenoid hypertrophy.[12,13] Propolis possesses antibacterial, antiviral, and antifungal effects. Unsurprisingly it is widely used as a treatment for upper respiratory tract infections.[14] A further study examined the combination of NAC with propolis (600mg + 80mg, NAC with propolis daily, for ten days) for acute respiratory infection treatment. Improved patient health, cough reduction, and mucus secretions were observed.[15]

There are several published reports which have measured HRQoL in patients with acute bronchitis and/or acute cough conditions using generic questionnaires (SF-36[3] and EuroQol[16]) and specific questionnaires (Infant/Toddler Quality of Life Questionnaire (ITQOL-97),[2] Cough-specific quality-of-life questionnaire (CQLQ),[17] Leicester Cough Questionnaire (LCQ-acute)[18,19] and Parent-proxy Children's Acute Cough-specific QoL Questionnaire (PAC-QoL).[20-22]) Questionnaires have been used in both adult[3,17-19] and paediatric populations.[2,20,21]

The LCQ was originally developed for chronic cough conditions.[23] This questionnaire was recently validated to assess HRQoL in acute cough conditions (LCQ-acute). The LCQ-acute questionnaire offered good psychometric characteristics for all sub-domains and total scores.[18,24-26]

This study aimed to compare the impact of NAC and NAC-P therapy on acute bronchitis patients' quality of life.

MATERIALS AND METHODS

Patients

A randomized, parallel-group study was conducted at the Municipal Institute for Lung Diseases and Tuberculosis Medical Centre, Belgrade, the Republic of Serbia. Patients were randomly assigned into two groups to receive NAC (200mg three times a day) or NAC-P (200mg+80mg three times a day) orally for a minimum of ten days. The producer of the dietary supplements used in the study was Abela Pharm. The patients were informed about the products they would use in the study, how to use them and their effectiveness. Patients were also instructed within the informed consent to comply with the product use regimen. The compliance with the treatment was checked after the treatment was over.

The inclusion criteria were: Patients older than 18 years with a confirmed diagnosis of acute bronchitis (J20 according to International Classification of Diseases (ICD) ver. 10).[27] The exclusion criteria were: Pregnant or lactating female patients, patients allergic to propolis or NAC, patients with pre-existing respiratory disease (such as asthma or chronic bronchitis, evidence of fixed airflow obstruction), patients with gastric or duodenal ulcers, and patients that use nitroglycerin in their therapy.

The study was conducted from April 2018 to May 2020. Patients were recruited after medical examination by an experienced pulmonologist (Ž.D.). Diagnosis of acute bronchitis was established if patients met the following criteria: Positive abnormal chest auscultation, current predominant cough, C-Reactive Protein (CRP) < 30mg/L, negative chest X-ray, and positive results from inflammatory cytology of sputum samples. Every patient's chest X-ray excluded pneumonia. Positive results of inflammatory cytology of sputum included the observation of a foul smell and thick white or purulent appearance. A microbiological test of the sputum indicated microbial infection.

During the initial visit, all patients were informed about the study procedure, the potential risks, and the possibility of discontinuing participation at any time. All patients needed to sign an informed consent form.

The sample size was calculated as the number of patients needed for a paired *t*-test (to test the difference in results between NAC

and NAC-P groups). For α = 0.05 and 80% detection power 33 patients in each group were needed.[28]

The study was approved by the Ethics Committees of the Municipal Institute for Lung Diseases and Tuberculosis and was conducted following the requirements of ICH/GCP and regulations and principles for conducting clinical trials in the Republic of Serbia.

Measurements

Two medical appointments were scheduled for all patients (NAC and NAC-P groups). The time interval between the two appointments was set for 10±5 days. During the first visit, all medical data were recorded. Blood samples were collected from both groups of patients. Each patient completed two questionnaires (LCQ and the 3-level EQ-5D version (EQ-5D-3L)) during the first and second appointments.

Biochemical, oxidative, and inflammatory parameters were examined in all blood samples (results presented in another study). Data collected at the first and second appointments included smoking status (smoker/non-smoker), alcohol consumption status (alcohol consumer/non-consumer), cough status (occasional/persistent), expectoration (present/not-present), sputum appearance (thick white/purulent), sputum volume, the microbiological test of sputum (positive/negative) and the average value of CRP.

The LCQ consists of 19 questions assigned to three domains; physical, psychological, and social. Question numbers 1, 2, 3, 9, 10, 11, 14, and 15 belong to the physical domain. The psychological domain refers to questions 4, 5, 6, 12, 13, 16, and 17, and the social domain refers to questions 7, 8, 18, and 19. All questions have positive scoring on a 7-point Likert scale. Each domain score was calculated as an average value of scores of questions that are only part of the domain and may be in the range from 1 to 7. The total score was also calculated as the sum of all three domain scores (ranging from 3 to 21). A higher score reflected a higher HRQoL.[23]

The EQ-5D questionnaire is a general HRQoL questionnaire. The EQ-5D questionnaire consists of five statements with three possible answers and a Visual-Analog Scale (VAS). Each answer indicates the function level: level 1, "no problem" (scored as 1); level 2, "there are certain problems" (scored as 2); and level 3, "extreme problems" (scored as 3). The combination of levels assigned to each statement forms a code of 5 numbers. In this way, there are 245 possible codes. Code 11111 reflects the condition of perfect health as opposed to code 33333, which hypothetically represents the worst health condition. The code of five numbers was converted into a unique number, "Health State Value" (HSV), using the HSV formula.[29,30] The HSV value ranged from 0 (the worst possible health condition) to 1 (the best possible health condition). Another part of the EQ-5D is a VAS scale, where a value of 0 represents the worst and 100 represents the best health

condition. The VAS value was obtained by crossing the scale at the degree that best describes the respondent's current health condition.

Permission for using questionnaires was obtained by copyright holders (EQ-5D from EuroQol group and for the LCQ from Professor Surinder Birring).

Statistical analysis

Demographic and clinical patient data were analyzed and presented using descriptive analysis, including calculation of mean value and standard deviation. Types of variable distribution were confirmed using the Shapiro-Wilk normality test.

For interval variables with normal distribution, the Student *t*-test was used to test the mean difference within the same group of patients (between data collected during two different appointments) and between two patient groups. Otherwise, the non-parametric Wilcoxon–Mann–Whitney U test was applied for differences between two groups of patients. The Wilcoxon signed-rank test was used to test differences in repeated measurements within the same group of patients. The Chi-square test was used to test the association between categorical variables.

Psychometric properties were tested using analysis of internal consistency, test-retest reliability, and concurrent validity. Internal consistency of the LCQ domain and total scores, as well as EQ-5D HSV values, were assessed by calculating Cronbach's α coefficient and determining the range of Cronbach's α if the item was deleted. A scale with a value of Cronbach's α coefficient greater than 0.7 was considered to exhibit good consistency.[31]

The level of significance was determined by a value of $p<0.05$. Microsoft Office Excel 10 and Predictive Analytics SoftWare, version 28 (SPSS Inc. Chicago, Illinois, SAD) were used for data analysis.

RESULTS

Forty-nine patients received NAC-P (the NAC-P group) and 45 patients received NAC (the NAC group) at the initial medical appointment.

Seven patients from the NAC-P group exited the study because of the smell of NAC-P (one patient), nausea (one patient), and other unspecified reasons (five patients). Two patients left the NAC group without specified reasons. Therefore, the analysis was performed on a sample of 42 patients in the NAC-P group (drop-out rate 14.28%) and 43 in the NAC patients group (drop-out rate 4.44%).

The average period between the first and second medical appointments was 13.23 days (SD=5.05).

All patients were 54.60 years old on average (SD=16.50, range: 18-85 years). Most of the patients were female (74.12%).

Table 1: Socio-demographic and clinical characteristics of patients.

	NAC-P group, (n=42)	NAC Group, (n=43)	Difference between NAC-P and NAC groups (*p*-value)
Age, mean in years (SD)	54.38 (16.39)	54.81 (16.79)	t= -0.12 (0.90)
Gender (N, (%))			χ2= 0.31 (0.57)
Female	30 (71.43)	33 (76.74)	
Male	12 (28.57)	10 (23.25)	
Smoking status (N, (%))			χ2= 0.22 (0.64)
Current smokers	17 (40.48)	20 (46.51)	
Non-smokers	25 (59.52)	13 (53.49)	
Alcohol consumption, (N, (%))			χ2= 0.00 (0.97)
Consumers	4 (9.52)	4 (9.30)	
Non-consumers	38 (90.48)	39 (90.70)	
Cough status (N, (%))			χ2= 2.75 (0.09)
Occasional	30 (73.17)	24 (55.81)	
Persistent	11 (26.83)	19 (44.19)	
Expectoration (N, (%))			χ2= 0.90 (0.34)
Present	34 (80.95)	38 (88.37)	
Not present	12 (19.05)	5 (11.63)	
Sputum appearance (N, (%))			χ2= 0.47 (0.49)
Thick white	24 (68.57)	31 (75.61)	
Purulent	11 (31.43)	10 (24.39)	
Sputum volume, mL (mean (SD))	1.92 (1.07)	1.58 (0.60)	t = 0.99 (0.32)
The microbiological test result of sputum (N, (%))			χ2= 0.21 (0.94)
positive	2 (4.88)	3 (7.32)	
Negative	39 (95.12)	38 (92.68)	
Average CRP value (mean (SD))			
1st appointment	4.75 (1.49)	4.19 (7.36)	Z = -0.38 (0.70)
2nd appointment	3.99 (10.89)	1.97 (2.83)	Z = -1.22 (0.22)

t- Student *t*-test, χ2- Chi-square test, Z - Wilcoxon Sign-Rank Test, NAC - N-Acetyl-L-cysteine, NAC-P - NAC combination with propolis, CRP - C-reactive protein, SD - standard deviation, p-value - level of significance.

There were no significant differences between the two groups concerning socio-demographic and clinical data (Table 1).

There was no statistically significant difference in the CRP at both appointments in the NAC-P patients (Z=-0.067, *p*=0.94) and NAC patients (Z=-1.89, *p*=0.058).

The LCQ questionnaire provided good internal consistency. The Cronb ach's α coefficient of the total LCQ scales was greater than 0.7 in both groups of patients at both appointments and was different from that of the HCV scale (Table 2).

Correlation between the LCQ total score and EQ-5D HSV was positive and statistically significant both for the NAC-P and the NAC groups of patients at the second appointment (r_s = 0.43,

p<0.05 and r_s = 0.38, *p*<0.05, respectively), as oppose to the first appointment (r_s = 0.18, *p*=0.24 and r_s = 0.28, *p*=0.63, respectively).

Nevertheless, statistically significant differences were noted in the quality-of-life (in all domains and total scores) of patients at the beginning and the end of the study (improvement in HRQoL after completing therapy with both NAC-P and NAC) (Table 3). The differences between the HSV and VAS score values were slightly higher in the NAC-P compared to the NAC group but not statistically significant (HSV mean difference between two appointments in the NAC-P group was 0.13 *vs.* 0.09 in the NAC group; VAS mean difference between two appointments in the NAC-P group was 9.43 *vs.* 8.56 in the NAC group). These values indicated that a greater improvement in HRQoL had been achieved with NAC-P.

Table 2: Internal consistency of the LCQ and EQ5D questionnaires.

Questionnaire/ Domain	Cronbach's α (range of Cronbach's α if item deleted)			
	NAC-P group		NAC group	
	1st appointment	2nd appointment	1st appointment	2nd appointment
LCQ				
Physical domain	0.75 (0.64-0.77)	0.75 (0.69-.079)	0.70 (0.61-0.74)	0.85 (0.80-0.86)
Psychological domain	0.73 (0.65-0.77	0.81 (0.75-0.85)	0.77 (0.68-0.82)	0.92 (0.89-.093)
Social Domain	0.63 (0.44-0.68)	0.78 (0.69-0.79)	0.83 (0.77-0.82)	0.82 (0.73-0.81)
Total Score	0.88 (0.88-0.89)	0.91 (0.91-.092)	0.89 (0.87-0.90)	0.95 (0.95-0.95)
EQ5D				
HSV	0.45 (0.14-0.54)	0.63 (0.48-0.59)	0.66 (0.55-0.63)	0.70 (0.60-0.72)
VAS	/	/	/	/

NAC-P - NAC combination with propolis, SD – standard deviation, HSV – health state value, VAS – visual analog scale.

Table 3: LCQ and EQ-5D scores in the NAC-P and the NAC groups.

	NAC-P group			NAC group			Difference between NAC-P and NAC groups at 1st appointment, U (p)	Difference between NAC-P and NAC groups at 2nd appointment, U (p)
	1st appointment Mean (SD), (W, p)	2nd appointment Mean (SD), (W, p)	Difference between appointments, Z (p)	1st appointment Mean (SD), (W, p)	2nd appointment Mean (SD), (W, p)	Difference between appointments, Z (p) (20) (20)		
LCQ								
Physical domain	4.73 (1.00) (W=0.97, p=0.38)	6.11 (0.75) (W=0.89, p=0.001)	-5.42 (p<0.001)	4.52 (0.98) (W=0.97, p=0.37)	6.17 (0.91) (W=0.85, p<0.001)	-5.19 (p<0.001)	771.00 (p=0.24)	853.50 (0.66)
Psychological domain	4.53 (1.04) (W=0.98, p=0.61)	5.99 (1.02) (W=0.86, p<0.001)	-5.25 (p<0.001)	4.47 (0.98) (W=0.89, p=0.001)	6.12 (1.08) (W=0.78, p<0.001)	-5.02 (p<0.001)	873.50 (p=0.79)	842.50 (p=0.59)
Social Domain	4.94 (1.23) (W=0.96, p=0.20)	6.20 (0.98) (W=0.80, p<0.001)	-4.94 (p<0.001)	4.65 (1.30) (W=0.97, p=0.46)	6.30 (1.01) (W=0.73, p<0.001)	-5.08 (p<0.001)	785.00 (p=0.29)	834.00 (p=0.52)
Total Score	14.20 (3.00) (W=0.98, p=0.92)	18.31 (2.57) (W=0.87, p<0.001)	-5.53 (p<0.001)	13.65 (2.91) (W=0.96, p=0.13)	18.44 (2.87) (W=0.79, p<0.001)	-5.29 (p<0.001)	782.00 (p=0.28)	874.50 (p=0.80)
EQ5D								
HSV	0.69 (0.07) (W=0.82, p<0.001)	0.82 (0.15) (W=0.82, p<0.001)	-4.49 (p<0.001)	0.68 (0.15) (W=0.89, p=0.001)	0.77 (0.21) (W=0.85, p<0.001)	-3.94 (p<0.001)	843.00 (p=0.59)	789.50 (p=0.30)
VAS	74.47 (4.67) (W=0.94, p=0.02)	83.90 (6.23) (W=0.92, p<0.05)	-5.52 (p<0.001)	70.16 (7.60) (W=0.96, p=0.20)	78.72 (8.34) (W=0.98, p=0.53)	-5.48 (p<0.001)	575.00 (p<0.05)	564.50 (p<0.05)

DISCUSSION

Our study is the first in Serbia that investigated the impact of NAC and NAC-P treatment of acute bronchitis on patients' HRQoL.

Both NAC and NAC-P contributed to HRQoL improvement. Although acute bronchitis includes less severe symptoms such as the acute onset of cough, with or without sputum production, and is self-limited, there is evidence that NAC could disrupt biofilms,

inhibit biofilm formation and thus contribute to faster patient recovery[8] and faster HRQoL improvement. Total LCQ scores, as well as scores in all LCQ questionnaire domains (physical, psychological and social) in both patient groups (NAC and NAC-P), were significantly higher after the second appointment (after a minimum period of 10 days). Each EQ5D score value (HSV and VAS) was also significantly higher.

Similar to the study by Yousaf *et al.*, the LCQ questionnaire exhibited good internal reliability (Cronbach's α > 0.9) on a sample of patients with acute bronchitis.[18] Our study included additional reliability analysis of "Cronbach's α if the item was deleted," which also assured good questionnaire reliability. The LCQ-acute is a valid tool to assess specific HRQoL in patients with acute bronchitis. On the other hand, the general scale EQ-5D did not achieve Cronbach's α minimum value for good consistency. As acute bronchitis is a short-term condition, the possible reason for such a result may be that the general scale, such as that for EQ-5D, is not specific enough to detect slight differences in a short period.

Yousaf *et al.*, also found a significant negative correlation between LCQ total score and cough VAS scale.[18] Our study did not include the cough VAS scale but the general VAS scale as part of the EQ-5D tool.

The correlation between LCQ total score and VAS was significant at the second appointment for the NAC and NAC-P groups, but not at the first appointment. As both tools (LCQ and EQ5D) were positively correlated, higher LCQ scores led to higher VAS scores.

It is well known that propolis possesses antibacterial, antiviral, antifungal, and anti-inflammatory properties.[32] Propolis-based products could be beneficial for treating otitis media, tracheitis, rhinosinusitis, and bronchitis.[33] Our results failed to show greater LCQ scores in NAC-P patients over NAC patients, unlike the EQ5D scores of HSV and VAS. Obradovic *et al.*, demonstrated significant antioxidant protection from NAC-P when compared with NAC.[12]

In our study, potential confounding factors were limited as the two groups of patients (NAC and NAC-P) were not significantly different for variables: age, smoking status, cough status, expectoration, sputum appearance, sputum volume, microbiological sputum test, and CRP values. However, our study possessed several limitations. The study was conducted over 2 years due to the complex selection of patients to be matched, the complex inclusion criteria, and the workload of doctors who performed the patient selection. The EQ-5D scale was used as a comparative tool to the LCQ questionnaire missed to prove satisfactory reliability.

CONCLUSION

The results of our study indicated that both NAC-P and NAC could significantly influence HRQoL improvement in patients with acute bronchitis. EQ-5D scale values indicated that NAC-P might contribute to a greater improvement in HRQoL than NAC. Further analysis with more participants could contribute to more precise data. Our findings could lead to better decision-making by healthcare professionals about patient therapy leading to more successful patient recovery.

ACKNOWLEDGEMENT

FUNDING DETAILS

DISCLOSURE STATEMENT

The authors report that there are no competing interests to declare. Abela Pharm provided the supplement but did not have any impact on its testing and the results, and have no benefit or be at a disadvantage/advantage financially or reputationally from the published findings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NAC: N-Acetyl-L-cysteine; **NAC-P:** N-Acetyl-L-cysteine in combination with propolis; **HRQoL:** Health-Related Quality of Life; **LCQ:** Leicester Cough Questionnaire; **EQ-5D:** Health State Value Questionnaire EuroQol group; **HSV:** Health State Value; **GP:** General Practitioner; **SF-36:** Short Form Health Survey; **ITQOL-97:** Infant/Toddler Quality of Life Questionnaire; **CQLQ:** Cough-specific Quality-of-life Questionnaire; **PAC-QoL:** Parent-proxy Children's Acute Cough-specific QoL Questionnaire; **ICD:** International Classification of Diseases; **ICH/GCP:** The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use/Good clinical practice; **CRP:** C-reactive protein.

SUMMARY

Our study confirmed that the correlation between the questionnaire scores, which specifically measure the quality of life in patients with acute cough conditions (LCQ total score), and the generic health value questionnaire subscale (HSV), was positive and statistically significant in the NAC-P and the NAC groups after ten days of treatment. The differences between

values of EQ-5D scores were slightly higher (but not statistically significant) in the NAC-P group compared to the NAC group, indicating a more remarkable improvement of HRQoL using NAC-P. The general conclusion of this paper is that NAC-P and NAC may improve HRQoL in patients with acute bronchitis, and NAC-P might improve quality of life more than NAC. This conclusion could help healthcare practitioners better decide the appropriate patient treatment.

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