

UDK: 616.24–008.41–08

**I.V. Baranova¹, I.A. Ilyuk¹, S.I. Leshchenko², O.V. Soleyko¹,
K.P. Postovitenko¹, O.V. Dolynna¹**

¹ National Pyrohov Memorial medical University, Vinnytsia

² Public Institution «National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky NAMS of Ukraine»

Dry cough: a modern approach to treatment

Key words: *postinfectious cough hypersensitivity syndrome, treatment, nebulizer therapy, hyaluronic acid.*

Problem statement

According to the European Respiratory Society (2014), coughing is one of the most common symptoms that makes patients seek medical assistance [8]. The interest of practicing physicians in this problem is to study pathophysiology, methods of evaluation and therapies for various types of cough [21, 29].

Dry non-productive cough is observed less frequently than productive, but the definition of its causes and treatment is a rather complicated problem [6, 15]. According to the recommendation of the American College of Chest Physicians (ACCP), a dry cough for convalescents after acute infectious diseases of respiratory ways (3–8 weeks after the disease) is defined as the postinfectious cough hypersensitivity syndrome [1, 9].

The main role in shaping the natural viscosity of the mucous layer, which covers the endothelium of the bronchial tree and the intercellular matrix, belongs to hyaluronic acid (HC) [19, 30]. It ensures the intake of biologically active substances, molecules and micro elements in the bronchial tissue, accelerates regeneration and repair processes. The HC itself is synthesized by a special class of built-in membrane proteins that are contained on the surface of glass-shaped cells. Partial destruction of the latter, or malfunction as a result of viral or bacterial infection leads to acquired inverse mucociliary clearance. As a result, the state of «dryness» of the mucous membrane of the respiratory tract is formed, which is one of the main causes of cough hypersensitivity [16]. Significant decrease in the thickness of the epithelial layer and protective mucus leads to the appearance of nerve endings. Consequently there is the development of constant irritation of irritative receptors, which are polymodal, and therefore they respond to a variety of mechanical and chemical stimulating agents [22].

Dry cough becomes sustainable, and the prescription of antitussive drugs does not always eliminate quickly a pathological process [16, 26, 27]. The above mentioned

remedies can affect only the cough reflex mechanism, however, the state of epithelium of respiratory ways remains out of their action. Therefore, the search for new methods of treatment for post-infectious dry non-productive cough is a very topical problem of practical medicine [28].

Clinical studies that highlight the efficacy of nebulizer therapy with drugs of reparative action, namely the solution of hyaluronic acid in the treatment of PCHS on the review of the literature were not found, so this area of immunosuppressive therapy requires further study.

Study objective: To determine treatment efficacy of cough hypersensitivity syndrome in convalescents after acute infectious diseases of the respiratory ways by application of nebulizer therapy with 0.1% solution of sodium hyaluronate.

Methods and Materials: the criteria for inclusion into the study were patients after acute infectious diseases of the respiratory tract with dry cough lasting from 3 to 8 weeks.

The exclusion criteria were: tuberculosis, chronic obstructive pulmonary disease, bronchial asthma, cardiovascular disease with the signs of circulatory failure higher I stage, neurosis-like and psychotic conditions, oncological diseases, propensity to polyvalent allergy.

Since PCHS is a diagnosis of inclusion, in each clinical case, a diagnostic search for possible causes of dry unproductive cough was performed: general laboratory tests, repeated chest x-ray examination, spirometry, electrocardiography, allergologist, neuropathologist, pulmonologist, and cardiologist consultation. The absence of pathological changes in laboratory and instrumental diagnostic methods indicated PCHS in all patients who were included in the study [4, 7, 12, 13, 14, 18].

The study was prospective and controlled. By the method of free choice, the patients were divided into two groups: the main (group 1) and the comparison group (group 2). The study design was approved by the Bioethics Commission of National Pyrohov Memorial Medical University, Vinnytsia (Minutes Nr 10 as of November 23, 2017). The

research plan provides the prescription of antitussive drugs for all patients in the recommended daily dosage. Besides, the persons in the main group underwent nebulizer therapy with 0.1% solution of hyaluronic acid with an average molecular weight (30–100 kDa). The procedures were carried out twice a day (a break between them 5–6 hours), the course of treatment made 12–16 sessions. For inhalation, OmronNE–C900 (Japan) nebulizer was used, in the mode of natural respiration, the average particle size was 3.0 μm , spraying speed – 0.5 ml / min. The nebulizer chamber was filled with 4 ml (1 nebula) of readymade 0.1% solution of sodium hyaluronate («Lord Eso», «Yuriya–Farm», Ukraine), which was being sprayed for 8–9 minutes.

The final points of the study were: improvement of quality of life indicators, achievement of the state of subjective health by the patients, reduction of terms of temporary disability of patients with PCHS.

The substantiation of the suggested method of treatment lies in the fact that the solution of hyaluronic acid falling into the respiratory tract by the method of nebulizer therapy can directly reduce the histological and pathophysiological effects of bacterial and viral infections. Due to physiological solvent (0.9% NaCl), the preparation has a high bioavailability. The advantage of nebulizer therapy is painlessness, direct intake of medication in the pathological center, practical absence of limitations and possibilities of overdose, and economic availability [2, 6, 10, 25].

We have examined 66 patients aged 19 to 52 years old who had a dry cough after acute infectious diseases of the respiratory system who were treated in the inpatient and outpatient departments of the Clinical facility of Vinnytsia City Clinical Hospital Nr 2. The main group (n = 33) and the comparison group (n = 33) were of the same and gender.

Objective assessment of treatment efficacy has some difficulties, as far as to determine the condition of the mucous membrane of the tracheo–bronchial tree and mucociliary clearance, to which pathogenetic therapy using a solution of GA is applied, is a rather complex issue. Quality of life (QL) is a key indicator for patients, which allows to evaluate the effect of treatment and correlates with instrumental methods of examination. Therefore, treatment outcomes were measured using an adapted questionnaire SF-36. Statistical data processing was carried out in accordance with the instructions of Evidence Company «Clinical and Pharmacological Research» [17]. Scales form two indicators: physical and mental health levels. The questionnaire was filled independently by the patient twice – before the treatment and two weeks after the treatment. For comparison, we used study outcomes received by domestic authors who used SF-36 in 52 apparently healthy adult respondents [3, 5, 11]. To summarize the outcomes, the following was taken into account: physical health (PH) (physical functioning (PF), physical role function (RP), pain intensity (BP), general state of health (GH)). Other 4 indicators namely mental health (MH), psychological role function (RE), social functioning (SF) and vital activity (VT) form mental health (MH).

Besides, for rapid assessment of therapy efficacy patients were asked to determine independently their health status on 5, 10 and 15 days of treatment according to the following scale: «health deterioration», «no change», «improvement», «significant improvement», «consider myself apparently healthy». At the beginning of the treatment and two weeks later, the patients determined the functional status according to the differential self–assessment of cough by force and frequency [24]. The period of temporary disability was taken into consideration as well. The reliability of obtained outcomes was determined using Student's criterion (package Stat Soft Statistica v.6.0.). The outcomes with an error $p < 0,05$ were considered as reliable.

At the beginning of treatment, patients complained of a dry cough that troubled them during the day, occasionally at night. Unproductive cough was associated with fatigue, sleep disturbances, dryness and «tickling» in the throat, periodic or constant hoarseness, muscle and skeletal pain, urinary incontinence and emotional instability. Cough attacks were provoked by a sharp smell, physical activity, prolonged emotional conversation, changes in the air temperature, its moisture, and less often the attack of dry cough was developed without a specific reason. The state of health caused discomfort for the patients in the course of communication and prevented them from fulfilling their professional duties.

Pathological objective changes on the part of the respiratory system have not been found in any case, with the exception of imperceptible hyperemia of the posterior wall of the oropharynx in 15 patients. Indicators of external respiration, assessed by spirometry, were consistent with normative parameters, which was confirmed by the absence of obstructive and restrictive causes of non–productive cough

At the beginning of the study, data of QL scales in the patients of both groups were similar ($p > 0.05$). Prior to treatment, the data of the questionnaire in patients with PCHS were significantly ($p < 0.01$) different in patients with PCHS from the physical and mental health of apparently healthy cohort of age–appropriate persons, except for the assessment of pain intensity, vital activity and mental health (Figure 1).

It should be noted that the lines reflecting QL indicators in the patients of the main group and in the comparison group on the diagram (Figure 1) coincide because they do not have a significant difference. The presence of prolonged dry cough, hoarseness, dissatisfaction with the duration of treatment or a slight positive dynamics and other symptoms explain the decline in social activity, physical and role limitations due to physical health.

Study outcomes and their discussion

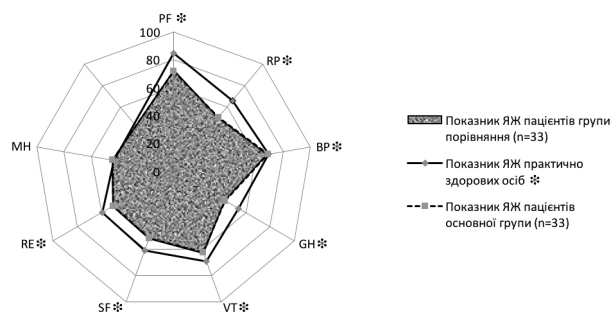
Patients perceived the treatment well, side effects of medication have not been recorded in any case. On the fifth day of therapy, the vast majority of patients in the first group (75.8%) noticed «improvement» and «significant improvement» in contrast with the persons in the second group (24.2%, $p < 0.01$). On the fifteenth day of treatment, all patients felt «apparently healthy» after a combination

treatment with nebulizer therapy with a 0.1% solution of GA. In the comparison group, treatment outcomes were significantly lower ($p < 0.01$) (Table 1).

The comparison of the indicators of differential cough score scale measured on the first day of treatment and on the fifteenth day showed an average indicator regression in the first group from (5.3 ± 1.4) points to (1.8 ± 0.4) points (by 33.9%). The data of appropriate scale in the persons of the second group were significantly ($p < 0.01$) lower – (3.9 ± 0.7) points (by 25%) under the condition of practically identical ($p > 0.05$) outcomes.

It should be noted that antitussive drugs were canceled in 39.4% of patients in the first group, and they proceeded to work since 10th day of treatment. However, 45.5% of patients in the second group still continued taking antitussive drugs on the fifteenth day of treatment and could not perform fully their professional duties (if required prolonged linguistic communication). Thus, the average duration of temporary disability in the persons that underwent a combination treatment with the use of nebulizer therapy with a solution of hyaluronic acid was $(12 \pm 1,7)$ days, and in the patients who took just antitussive drugs was $(18 \pm 2,9)$ days. The significant advantage ($p < 0.05$) of combination treatment plan in the main group emphasizes the expediency of pathogenetic area of dry cough therapy in case of PCHS.

Repeated survey of patients in the Ukrainian version of SF-36 allowed to objectivize the state of health of individuals after undergoing a different treatment plan (Figure 2).

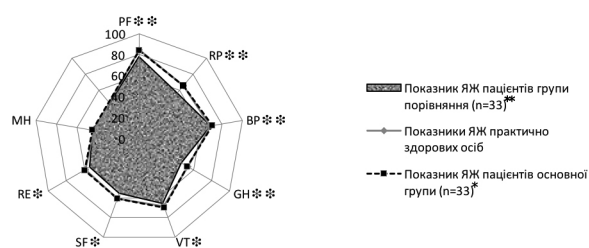


* difference in indicators of QL of healthy persons, patients 1 and 2 groups before the treatment is reliable ($p > 0,01$), except MH.

Fig. 1 Indicators of quality of life of patients before treatment

On the fifteenth day of treatment, obtained indicators of QL of persons after a combination treatment using nebulizer therapy with a 0.1% solution of sodium hyaluronate became normal in compliance with all scales ($p < 0.01$) and did not differ ($p > 0.05$) from the indicators of healthy cohort of respondents (on the diagram quality of life indicators of healthy adult cohort of respondents and persons in the first group after the treatment coincide and are determined by one line). However, after the treatment patients of the second group showed a positive dynamics, which proved to be significant ($p < 0.05$) only when calculating physical health. The indicator of mental health was 14% lower than that of healthy individuals (Table 2).

In literary sources many domestic and foreign authors have identified the pathogenetic feature of the origin of various variants of dry cough. The commonly used methods of treatment consist in the use of antitussive, bronchodilatory agents of chemical and plant origin, but references in the medical literature to the use of GA in patients with PCHS have not been found. A well-known fact is the use of a mixture of hypertonic (3% and 7%) solutions of sodium chloride and GA in nebulizer therapy for chronic pulmonary diseases [19, 20]. The data obtained from 14 controlled international studies certify that the recovery of mucociliary clearance in a short time contributed to a significant improvement in the respiratory function (FEV1); the use of saline solution had no age limitations and side effects [20, 30, 31]. Allegra L., Della Patrona S., Petrigni G. (2012) have proved (in vivo and in vitro) the



* difference in the quality of life indicators of patients in the first group and apparently healthy persons is unreliable ($p > 0,05$); ** difference in the quality of life indicators (PF, RP, BP, GH) of patients in the first and second comparison group is reliable ($p < 0,01$).

Fig. 2. Quality of life indicators of patients after various methods of treatment

Table 1

Indicators of the efficacy of different treatment methods in people having postinfectious cough hypersensitivity syndrome

Subjective state of patients	5th day of treatment		10th day of treatment		15th day of treatment	
	1 group* (n = 33)	2 group (n = 33)	1 group* (n = 33)	2 group (n = 33)	1 group* (n = 33)	2 group (n = 33)
Deterioration	–	–	–	–	–	–
No changes	8 (24,2%)	25 (75,7%)	–	14 (42,4%)	–	–
Improvement	15 (45,5%)	5 (15,1%)	5 (15,1%)	11 (33,3%)	–	15 (45,5%)
Significant improvement	10 (30,3%)	3 (9,1%)	15 (45,5%)	8 (24,2%)	–	8 (24,2%)
Consider myself healthy	–	–	13 (39,4%)	–	33 (100%)	10 (30,3%)

* – difference in treatment efficacy between the patients in the main group and the comparison group is reliable, $p < 0,01$.

Table 2

Indicators of physical and mental health of patients after various treatment methods.

Показники	Before treatment		After treatment		Healthy cohort of respondents
	1 group (n = 33)	2 group (n = 33)	1 group (n = 33)	2 group (n = 33)	
Physical health (PF, RP, BP, GH)	60,4 ± 4,2	61,0 ± 5,1	74,5 ± 4,3*	68,3 ± 4,7	73,3 ± 6,1
Mental health (MH, RE, SF, VT)	51,9 ± 3,3	51,3 ± 5,2	63,9 ± 4,1**	55,5 ± 5,8	63,1 ± 6,7

* – difference in indicators of patients in groups 1 and 2 after the treatment is reliable ($p < 0,01$)
 ** – difference in indicators of patients in groups 1 and 2 after the treatment is unreliable ($p > 0,05$)

effectiveness of using GA as the main component of the mucociliary matrix in the prevention and treatment of exacerbations of chronic pulmonary diseases [19].

Thus, as a result of the conducted study, design endpoints were achieved with a significant predominance of the outcome ($p > 0,01$) according to all parameters of the treatment efficacy of individuals in group 1. Apparently self regeneration of the mucous membrane of the respiratory tract and restoration of the mucociliary matrix take some more time, as evidenced by the clinical course of the disease, data of quality of life indicators and indicators of differential cough score scale obtained after various treatment options. The absence of side effects of the drug, the effect of treatment after the first procedures, pathogenetic reasonableness and economic availability certify the appropriateness of a combination treatment of PCHS with the use of 0.1% solution of sodium hyaluronate

The above mentioned data arouses a greater interest in the study of pharmacodynamic peculiarities of the

action of hyaluronic acid solution on the state of the mucous membrane of the bronchial tree and its application in rehabilitation programs for patients with respiratory system disease.

Conclusions. The pathogenic cause of postinfectious dry cough is the functional failure of the mucociliary matrix, which leads to irritation of the irritative receptors and is presented as the postinfectious cough hypersensitivity syndrome.

Combination treatment using 0.1% solution of sodium hyaluronate has a pathogenetic importance. A rational combination of medicines and a nebulizer method of administering hyaluronic acid can eliminate the symptoms of the disease within the shortest time period and restore the quality of life of patients.

The suggested scheme of treatment has a significant economic advantage: financial availability of drugs of domestic production and a significant reduction of the terms of temporary disability.

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I. V. Baranova, PhD, Associate Professor

Department of Medical Rehabilitation, National Pyrogov Memorial Medical University, Vinnytsia,

78/169, Kotsyubynsky st., Vinnytsia, Ukraine, 21009

Tel.: +38 (096) 442-02-43; e-mail: ibaranova566@ukr.net