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EFFECTIVENESS OF INHALED ACETYLCYSTEINE AND HYPERTONIC SALINE IN PATIENTS WITH COPD

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A – concept and design of the study; B – data collection; C – data analysis and interpretation; D – writing the article; E – editing the article; F – final approval of the article

Abstract. Part of the patients with chronic obstructive pulmonary disease (COPD) despite receiving the recommended inhalation treatment continues to complain of cough with difficulty expectorating sputum. For this group of patients, the additional prescription of mucolytic drugs, namely acetylcysteine and 3% hypertonic saline is indicated.

Materials and methods. To compare the effectiveness of additional inhalation of acetylcysteine and 3% hypertonic saline in patients with stable COPD, 67 patients with a confirmed diagnosis of COPD and disease duration from 1 to 18 years were examined. Simple randomization was used to form two groups of patients. The first group (n = 34) inhaled 3 ml of 10% acetylcysteine solution twice daily via a nebulizer, which amounted to 600 mg of the active substance daily, while the second group (n = 33) received 4 ml of 3% hypertonic saline solution also twice daily. All 67 patients completed the 10-day course of inhalation treatment and underwent a control examination. The treatment effectiveness was evaluated with validated questionnaires, including the CAT, CCQ, SGRQ, mMRC, and a questionnaire for the severity of daytime and nighttime cough, as well as laboratory and instrumental studies: spirometry and sputum analysis before and immediately after the treatment.

Results. In both groups of patients after a course of inhalation of acetylcysteine and hypertonic saline a significant improvement in the patient's condition was observed according to the results of the CAT, CCQ questionnaires and the decrease in the severity of both daytime and nighttime cough. In addition, the use of acetylcysteine also had a positive effect on the dynamics of the value of forced expiratory volume in 1 second (FEV_1). Significant changes in the results of the 6-minute walk test, mMRC, SGRQ questionnaires, the number of leukocytes in sputum in both groups, as well as FEV_1 values in the group where the hypertonic solution was used were not detected.

Conclusions. Additional inhalation of mucoactive drugs in patients with COPD in a stable condition who continued to complain of cough with sputum production had a positive effect on the clinical manifestation of the disease, and also improved lung function parameters in patients who took acetylcysteine.

Key words: COPD, mucoactive drugs, acetylcysteine, 3% hypertonic saline, nebulized therapy.

Introduction. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide [7], making the question of improving the effectiveness of treatment for this disease one of the most pressing issues today. In Ukraine, at least 4%, and according to various data 6–12%, of the population have COPD, while approximately 2% of deaths among Ukrainians are caused by this condition [22].

COPD is known to be a heterogeneous lung disease accompanied by persistent respiratory symptoms and characterized by inflammatory changes in the airways and alveoli, leading to a permanent, often progressive bronchial obstruction. This disease can be prevented and treated, but some patients who receive modern international guideline-based therapy in the form of inhaled bronchodilators and glucocorticoids, or their various combinations, continue to complain of a prolonged cough with production of viscous sputum. For this group of patients particularly, the prescription of mucoactive agents among which acetylcysteine and 3% hypertonic saline with the aim of improving airway patency and reducing the risk of sputum infection and the development of infectious exacerbations of COPD is appropriate [14, 20]. Previous studies have demonstrated that the use of mucoactive agents, primarily acetylcysteine, reduces the number of COPD exacerbations during the year at long-term use, and during exacerbations reduces the level of inflammatory markers, enhances bacterial eradication, and provides better subjective outcomes compared with placebo. These findings can be explained by the effects on mucus viscosity and mucociliary clearance [6, 9]. Several clinical

trials of acetylcysteine and carbocysteine indicate that these drugs influence not only on mucociliary properties of the airways, but also act as antioxidant agents [21], as growing evidences suggests that oxidative stress plays a key role in the pathogenesis of COPD. Oxidative stress triggers several secondary effects, such as inactivation of antiproteases, activation of proteases, and the expression of interleukin-8 and tumor necrosis factor-α, which are directly involved in inflammatory mechanisms. The mechanism of action of hypertonic saline, in turn, can be explained by its effects on the regulation of fluid transport through the respiratory epithelium and on improvement of mucociliary clearance [2].

Objective. To compare the effectiveness of additional inhalation of acetylcysteine and 3% hypertonic saline in patients with stable COPD and hyperproduction of sputum that is difficult to expectorate.

Materials and Methods. By simple randomization, 55 men (82.8%) and 12 women (17.2%) aged 47 to 80 years (mean age 64.1 ± 7.2 years) were included in the groups receiving inhaled acetylcysteine and a 3% hypertonic saline. All patients had a diagnosis of COPD established at least 12 months prior to study inclusion according to international guidelines (spirometric criterion FEV_1 / FVC < 0.7), with disease duration ranging from 1 to 18 years (7.7 ± 5.2 years). According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) clinical classification, which takes into account the frequency of exacerbations and the presence of symptoms in patients with COPD, the patients belonged to clinical groups B (n = 38) and E (n = 29), which is corresponding to group D in earlier versions of the guidelines. All patients had spirometric parameters consistent with GOLD stages 2–4 of airflow obstruction [7].

As shown in the table, the group receiving inhaled acetylcysteine included a higher number of female participants compared to the group receiving 3% hypertonic saline ($p < 0.05$), although no statistically significant difference between groups for the number of male participants was found. In the same group nighttime cough also was more pronounced. All other characteristics assessed during the study were comparable.

Patients in both groups received inhalation therapy administered via a compressor nebulizer for 10 days. Participants in the first group (n = 34) used 3 ml of 10% acetylcysteine solution (Ingamist, YURiA PHARM), while the patients in the second group (n = 33) inhaled 4 ml of 3% hypertonic saline solution (LORDE Hyper 3%, YURiA PHARM). All 67 patients completed the 10-day treatment course and underwent follow-up evaluation.

The treatment effectiveness was assessed using validated questionnaires CAT (COPD Assessment Test), CCQ (Clinical COPD Questionnaire), SGRQ

Table 1. Clinical-demographic and spirometric characteristics of the patients with COPD before a course of inhalation treatment with mucoactive drugs

Indicators		Acetylcysteine (n = 34)	3% hypertonic saline (n = 33)
Women, %		26.4%	10%*
Men, %		73.6	90%
Age, years (±σ)		65.2 ± 7.18	63.9 ± 8.21
Disease duration, years		8.5 ± 7.11	8.0 ± 7.83
Clinical group B, %		70.4	24.2
Clinical group E, %		29.6	75.8
Smoking, %	Smokers	73.5%	60.6%
	ex-smokers	26.5%	39.4%
6-minute walk test, m (±σ)		266.7 ± 48.5	289 ± 59.3
CAT, points		22.97 ± 3.6	23.08 ± 4.00
mMRC, points Me (QI-QIII)		2 (2-3)	2 (2-3)
CCQ, points		32.48 ± 8.64	30.54 ± 7.06
SGRQ total, points		51.40 ± 8.05	48.87 ± 7.90
Daytime cough, points Me (QI-QIII)		2 (2-3)	2 (2-3)
Nighttime cough, points Me (QI-QIII)		1 (1-2)	1 (0-1)*
FEV_1	L	1.23 ± 0.49	1.48 ± 0.66
	%	43.98 ± 18.30	45.67 ± 15.21
Leukocyte count in sputum, quartiles Me (QI-QIII)		2 (2-3)	2 (2-3)

* — difference between the groups, $p \leq 0.05$.

(St. George's Respiratory Questionnaire), mMRC (modified Medical Research Council), a questionnaire evaluating daytime and nighttime cough severity, as well as laboratory and instrumental studies such as spirometry and sputum analysis, where leukocyte count was expressed numerically as 1, 2, 3, or 4 according to the quartile distribution of the obtained dataset before and immediately after treatment.

Statistical analysis included descriptive statistics. Data distribution was assessed using the Shapiro-Wilk test. Mean values are presented as mean ± standard error (±σ), qualitative data as percentages. For normally distributed data, parametric tests were applied: t-test for independent samples when comparing two groups, and paired t-test for comparing pre- and post-treatment results. For non-normal data distributions nonparametric tests were used: Mann-Whitney test and Wilcoxon test. Differences were considered significant at $p < 0.05$. Statistical analysis was performed using Microsoft Office Excel 2016 (Microsoft Corp., USA).

Results. In both patient groups, after the course of inhalations with either acetylcysteine or hypertonic saline, a significant improvement in clinical condition was observed. This was evidenced by a statistically significant reduction in COPD severity scores and respiratory symptom dynamics according to the CAT and CCQ questionnaires, as well as a decrease in the severity of both daytime and nighttime cough. In the group receiving inhaled acetylcysteine, a statistically significant positive improvement in FEV_1 was also detected. No significant changes were observed in the 6-minute walk test results, mMRC and SGRQ questionnaire scores, sputum leukocyte count in both groups, nor in FEV_1 values in the group treated with hypertonic saline. The between-group difference in the dynamics of the assessed parameters was significant only for the spirometric indicator, favoring the patients treated with acetylcysteine, as shown in Table 2.

The tolerability of the 10-day course of nebulized hypertonic saline and acetylcysteine was generally satisfactory. Adverse events were observed in 6 patients in the hypertonic saline group (18.8 %): in 3 patients, an increase in cough was noted during inhalations, though this did not interrupt completion of the treatment according to the study protocol. Two patients reported dryness of the oropharyngeal mucosa, and one patient complained of headache after the first two inhalations of the 3% hypertonic saline. Most patients also reported a salty taste in the mouth. In the group using inhaled acetylcysteine, three patients (8.8%) noted a significant increase in coughing immediately after starting the inhalation of the medication, but the symptoms disappeared on their own within a few minutes of rest after the inhalation, which allowed treatment to continue. The occurrence of adverse events during treatment in either group did not lead to interruption of the treatment course or discontinuation in any case.

Discussion. The impact of mucoactive agents on the course of COPD has been previously demonstrated in numerous studies that varied in patient population (stable duration or exacerbation), drug dosages, routes of administration, and duration of therapy. Overall, the

Table 2. Changes in clinical, spirometric, and laboratory parameters in the patients with COPD following a 10-day inhalation treatment

Indicators		Acetylcysteine (n = 34)			3% hypertonic saline (n = 33)			
		before treatment	after treatmentt	p_1	before treatment	after treatment	p_1	P_2
6-minute walk test, m (±σ)		266.7 ± 48,5	270.32 ± 48,4	0.309	289 ± 59.3	250.12 ± 55.91	0.775	0.224
CAT, points		22.97 ± 3.60	20.15 ± 5.17	0. 003	23.08 ± 4.00	21.13 ± 4.53	0.003	0.502
mMRC, points Me (QI-QIII)		2 (2-3)	2 (2-3)	0.061	2 (2-3)	2 (2-3)	0.129	0.201
CCQ, points		32.48 ± 8.64	29.91 ± 8.81	0.022	30.54 ± 7.06	27.88 ± 7.07	0.001	0.430
SGRQ total, points		51.40 ± 8.05	48.91 ± 12.06	0.509	48.87 ± 7.90	47.55 ± 9.14	0.156	0.298
Daytime cough, points Me (QI-QIII)		2 (2-3)	2 (2-3)	0.012	2 (2-3)	2 (1-2)	0.008	0.192
Nighttime cough, points Me (QI-QIII)		1 (1-2)	1 (0-2)	0.004	1 (0-1)	0 (0-1)	0.012	0.087
FEV_1	L	1.23 ± 0.49	1.36 ± 0.5	0.05	1.48 ± 0.66	1.50 ± 0.66	0.431	0.023
	%	43.98 ± 18.3	48.85 ± 16.07	0.048	45.67 ± 15.21	50.23 ± 20.04	0.521	0.432
Leukocyte count in sputum, quartiles Me (QI-QIII)		2 (2-3)	2 (2-3)	0.180	2 (2-3)	2(2-3)	0.433	0.945

Note. p_1 – significance of differences between baseline and post-treatment values within the group; p_2 – significance of differences in treatment-induced changes between the groups.

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results have been inconsistent and do not allow definitive conclusions regarding their use [3, 10, 17].

In a meta-analysis, Cazzola et al. [3] analyzed data from 13 studies of acetylcysteine treatment of COPD, in which the effects of high (above 600 mg / day up to 1200 mg / day) doses were compared with low (≤ 600 mg / day). The authors concluded that high doses should be used to prevent COPD exacerbations. Another meta-analysis [12] reported a positive effect of oral acetylcysteine on the manifestations of COPD exacerbation symptoms, improvement in lung function (FEV_1 and FEV_1 / FVC), and increased antioxidant capacity. However, in a later study assessing the effectiveness of long-term (24-month) oral high-dose acetylcysteine neither a reduction in exacerbation risk nor significant effects on spirometric parameters were confirmed [19]. In contrast, when patients were stratified by genetic markers in a study by Zhou et al. [17], a reduction in exacerbation frequency, improvement in spirometric values, and better quality of life were demonstrated in the patients with COPD without the L-allele of the HO-1 gene who received oral acetylcysteine 600 mg / day.

A 2023 meta-analysis demonstrated the effectiveness of long-term (from 2 months to 3 years) oral acetylcysteine in the patients with COPD, as well as improved quality of life in patients with chronic bronchitis [13]. Another meta-analysis published in the same year did not confirm these positive findings [10], which may be explained by the heterogeneity of the population of studied patients.

At the same time the use of inhaled acetylcysteine in COPD exacerbations has shown improvement in symptoms and increased partial pressure of arterial oxygen (PaO_2) [4], significant reductions in inflammatory markers in serum and sputum, and improvement in lung ventilation parameters [11]. According to Chin Kook Rhee et al. [15], a 12-week course of inhaled acetylcysteine reduced sputum volume in patients with stable COPD.

Our findings partially confirm results from previous studies, particularly regarding the positive effects of acetylcysteine on spirometric parameters and symptom severity, primarily nighttime and daytime cough. However, the most studies demonstrated these effects for oral rather than inhaled administration of drug.

Data on the use of hypertonic saline as inhalation therapy in patients with COPD also vary substantially in terms of concentrations, patient populations, and reported outcomes. In a study assessing 5.8% hypertonic saline in patients with bronchial hypersecretion, including patients with COPD, the treatment was found to be safe and showed significant clinical benefits: reductions in bronchorrhea, recurrent infections, frequency of antibiotic prescriptions, increases in FEV_1, and reductions in primary care visits, emergency department visits, and hospitalizations [8]. Good treatment tolerability was reported in 72.3% of participants. However, another study showed that adverse spirometric responses to hypertonic saline are common in patients with moderate to severe COPD, including bronchospasm and lung hyperinflation, potentially mediated partly by mast cell activation [16]. Another study found greater improvement in the 6-minute walk test with isotonic saline compared to hypertonic saline because hypertonic saline was associated with more adverse effects [21].

At the same time other authors using 7% hypertonic saline demonstrated good compliance and treatment safety in patients with COPD with moderate and severe lung function impairment [5]. In patients with chronic bronchitis, inhaled 7% hypertonic saline solution was also safe [1].

In our study, the positive effect of a 10-day course of inhaled 3% hypertonic saline on clinical manifestations of stable COPD consisted of reduction in severity symptoms according to CAT and CCQ questionnaires, as well as decreased daytime and nighttime cough, partially confirming previous findings. The tolerability of 3% hypertonic saline inhalations in our patient population was clinically acceptable and did not interfere with or worsen treatment outcomes.

Conclusion

1. In some patients with COPD who have persistent hyperproduction of viscous sputum even in a stable condition, the prescription of mucoactive agents is pathogenetically justified.

2. The use of inhaled mucoactive drugs via nebulizer in patients with COPD can improve sputum elimination, facilitate breathing, and improve the course of the disease.

3. A significant improvement in patients' condition after a course of inhalations with either acetylcysteine or hypertonic saline was observed. This was evidenced by a statistically significant reduction in COPD severity score and improvement in respiratory symptoms according to the CAT and CCQ questionnaires, as well as a decrease in the severity of both daytime and nighttime cough. In the group receiving inhaled acetylcyste-

ine, a statistically significant positive change in FEV_1 was also observed.

4. The tolerability of inhaled acetylcysteine and 3% hypertonic saline in patients with COPD was satisfactory. Adverse effects are observed only in a limited number of cases and do not significantly affect patients' condition or lead to discontinuation of treatment.

ЕФЕКТИВНІСТЬ ІНГАЛЯЦІЙНОГО ЗАСТОСУВАННЯ АЦЕТИЛЦИСТЕЇНУ ТА ГІПЕРТОНІЧНОГО РОЗЧИНУ НАТРІЮ ХЛОРИДУ У ПАЦІЄНТІВ З ХОЗЛ

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Резюме. Частина хворих на хронічне обструктивне захворювання легень (ХОЗЛ), незважаючи на отримання рекомендованого базисного інгаляційного лікування, продовжують скаржитися на кашель з мокротинням, яке важко відділяється. Саме для такого контингенту пацієнтів доцільне додаткове призначення мукоактивних препаратів, а саме ацетилцистеїну та 3% розчину натрію хлориду.

Матеріали і методи. З метою порівняльної оцінки ефективності додаткового до стандартного лікування інгаляційного застосування ацетилцистеїну та 3% розчину натрію хлориду у пацієнтів зі стабільним перебігом захворювання було обстежено 67 хворих з підтвердженим діагнозом ХОЗЛ та тривалістю хвороби від 1 до 18 років. Методом простої рандомізації було сформовано 2 групи хворих. Перша група (n = 34) застосовувала інгаляційно за допомогою небулайзера 3 мл 10% розчину ацетилцистеїну два рази на добу, що складало 600 мг діючої речовини щоденно, тоді як друга група (n = 33) отримувала 4 мл 3% розчину натрію хлориду також двічі на добу. Всі 67 хворих завершили 10-денний курс інгаляційного лікування та пройшли контрольне обстеження. Оцінка ефективності препаратів проводилася за допомогою заповнення верифікованих опитувальників CAT, CCQ, SGRQ, mMRC, опитувальника вираженості симптомів денного та нічного кашлю, а також лабораторно-інструментальних досліджень: спірометрії та аналізу харкотиння до та відразу після завершення лікування.

Результати. В обох групах хворих після курсу інгаляцій як ацетилцистеїну, так і гіпертонічного розчину натрію хлориду, спостерігалось суттєве покращення стану пацієнтів за результатами опитувальників CAT, CCQ та зменшення вираженості як денного, так і нічного кашлю. Крім того, застосування ацетилцистеїну також позитивно вплинуло на динаміку показника об'єму форсованого видиху за 1-шу секунду ($ОФВ_1$). Суттєвих змін результатів тесту із 6-хвилинною ходьбою, опитувальників mMRC, SGRQ, кількості лейкоцитів у мокротинні в обох групах, а також величин $ОФВ_1$ в групі, де застосовувався гіпертонічний розчин, не виявлено.

Висновки. Додаткове інгаляційне застосування мукоактивних препаратів у пацієнтів з ХОЗЛ в стабільному стані, у яких зберігались скарги на кашель з виділенням мокротиння, позитивно вплинуло на клінічні прояви захворювання, а також покращило показники тестування легеневої функції у хворих, які приймали ацетилцистеїн.

Ключові слова: ХОЗЛ, мукоактивні препарати, ацетилцистеїн, 3% розчин натрію хлориду, небулайзерна терапія.

Ethics Declaration. During the collection, analysis, and publication of data, the confidentiality of patients who provided voluntary consent to the use of their data in a scientific publication was ensured.

Conflict of interests. The authors declare no conflict of interests.

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