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Nebulizer therapy in patients with chronic obstructive pulmonary disease

Key words: *COPD, nebulizer therapy, mucoactive drugs, hypertonic saline, hyaluronic acid.*

Chronic Obstructive Pulmonary Disease (COPD) is a disease that can be prevented and treated, characterized by persistent airway congestion, which usually progresses and it is associated with an increased chronic inflammatory response of the respiratory tract and lungs to harmful particles and gases. Exacerbations and concomitant diseases further aggravate the general severity of health in some patients [8].

COPD is an important social problem and one of the main causes of chronic morbidity and mortality worldwide. Currently, COPD is ranked 4th in world mortality, but according to the latest forecasts by 2020, the disease will rank 3rd. More than 3 million people died from COPD in 2012, accounting for 6% of all deaths on the planet. Also, a further increase in the incidence of COPD in the coming decades in connection with the preservation of the impact of risk factors and aging of population is expected [41].

According to modern guidelines and protocols for the provision of medical care to patients with COPD, the main principles of therapy include gradual increase in the intensity of treatment, regularity, continuity of basic therapy depending on the severity of the course of the disease, as well as careful and regular monitoring of the clinical and functional signs of the disease due to the variability of the individual response to treatment [41].

The inhalation route of administration of drugs (bronchodilators, inhaled glucocorticoids, combined medications) has the advantage in the treatment of COPD, doses of aerosol drugs are usually less than those for systemic use, medications in the inhalation form begin to act more quickly. The drug is delivered directly to the target organ, thus minimizing the systemic exposure of the active substance; therefore the side effects are less severe and less common in comparison with the parenteral and enteral routes of administration [49].

The effectiveness of this route of administration is determined predominantly by the degree of proficiency of inhalation technique by patient, which depends on the technical characteristics of the inhaler. The following variants of devices for inhalation rote of administration of drugs are known today [19]:

- metered dose inhalers (pMDIs)
- dry powder inhalers (DPIs)
- spacers
- compressor nebulizers
- ultrasonic nebulizers
- mesh nebulizers.

Because there is a large option of different devices for delivering drugs to the respiratory tract in inhalation form, it raises the question of the effectiveness and appropriateness of using one or another inhaler for the treatment of patients with COPD and other nosologies that require this kind of therapy.

The development of technologies of inhalation therapy began in the middle of the nineteenth century with creation of glass inhalers – the first devices capable to form artificial aerosols. One of the first devices for spraying fluids for inhalation was proposed by Schneider and Waltz in 1826, the portable version of the device was created by the French scientist Salles-Giron in 1859. In 1872, the Oxford Dictionary first introduced the term «nebulizer» (from the Latin *nebula* – a fog, «fogmaker»), the device which converts liquid drugs into an aerosol state with an optimal size of particles [9, 40]. The development of technology of inhalation therapy received a new powerful impulse associated with the creation of individual dose inhalers and ultrasound inhalers in the 60s and 70s of the 20th century.

There are two main types of nebulizers:

1. Ultrasonic, in which spraying is achieved due to high-frequency vibration of piezoelectric crystals. The dispersion of aerosols formed by such inhalers is quite high, the size of the particles is from 2 to 50 microns;

2. Jet, in which the aerosol generation is carried out by compressed air or oxygen. Compressor nebulizer system

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consist of a compressor, which is a source of gas flow, and a nebulizer chamber where the liquid is sprayed directly. The camera differs from the usual inhaler with the presence of a special valve, which selectively removes large particles of aerosol. This important part of the nebulizer determines its main characteristics – the size of «working» aerosol particles [7].

Recently a new third type of nebulizer has been introduced, which uses a fundamentally different mechanism of spraying the drug: a vibrating membrane or a plate with multiple microscopic apertures (sieve) through which a liquid drug is passed, it leads to the generation of aerosol [36]. This generation of nebulizers has several names: membrane nebulizers, electronic nebulizers, Vibrating MESH Technology (VMT) [4].

Nebulizer therapy takes an important place in the treatment and rehabilitation of patients with bronchopulmonary diseases at all stages of medical care. It can be used both with a stable course of respiratory diseases, and with their exacerbation. Nebulizers were proposed about 150 years ago, but only today they have received widespread use in the treatment of patients with obstructive syndrome [2]. Modern guidelines recommend inhalation therapy as the best way to administer a drug for the treatment of COPD [41]. Previous systematic reviews obtained similar clinical results for drugs that were used with pocket inhalers (pMDIs, DPIs) and nebulisers, considering that the device was used correctly [18]. However, in routine clinical practice critical mistakes are encountered when patients use pocket inhalers (patients do not shake the cartridge before use, do not exhale before inhaling the drug, inhale too early or too late until they are pushing to the cartridge, can inhale too fast, do not hold their breath after inhalation [38]), which often leads to insufficient relief of the symptoms of the disease. Effective delivery of the drug through traditional compressor (jet) nebulizers requires less effort and time to train the patient compared to pMDIs and DPIs. In addition, new compressor nebulizers are more comfortable in design and more effective than their first generation.

Recent studies of the role of nebulizer therapy in patients with moderate or severe COPD for maintenance treatment and exacerbations suggest that long-term treatment is similar and in some cases higher than pMDIs / DPIs [18]. However, the effect of supportive nebulizer therapy on other significant clinical effects in patients with COPD, especially progressive reduction of lung function and frequency of exacerbations, requires further investigation [12, 18].

In 1996, the O'Donohue and the National Association for Medical Immune Respiratory Care (NAMDRC) Consensus Group formulated criteria for the administration of nebulizer therapy [3, 6], which have not yet been reviewed:

1) a decrease of the inspiratory vital capacity less than 10.5 ml/kg (eg, < 735 ml in a patient with weight 70 kg);

2) inspiratory flow less than 30 l/min;

3) the inability to hold the breath for more than 4 seconds;

4) motor disorders, violations of consciousness.

It was also recommended for application in the elderly, patients with severe respiratory diseases and frequent exacerbations.

Certain economic benefits contribute to the expansion of nebulizer therapy: nebulizers are reusable devices and they can be purchased separately from drugs for nebulizer therapy; the dosage of medications delivered with a nebulizer in the lungs may be ≥ 10 times greater than with the less effective inhalers (pMDIs, DPIs). Together with simplicity and ease of use, it results in better compliance.

The main advantages of nebulizer therapy are [1, 2, 16]:

1. drugs are delivered directly to the respiratory tract and higher concentration of the drug can reach a bronchial tree with fewer side effects than with systemic use;

2. the possibility of application at any age due to the lack of need for synchronization of breathing and inhalation;

3. a small fraction of drugs is deposited in the oral cavity;

4. absence of propellants – inert chemicals that provide excess pressure in the aerosol can and can irritate the airways;

5. possibility inclusion of oxygen in the supply contour;

6. simplicity of technique and comfort for the patient;

7. the cost-effectiveness of drugs usage.

It is believed that the side effects are mainly caused by drugs, and not by the nebulizer itself. The disadvantages include the need in accordance with the requirements of the European Respiratory Society [12] to conduct an annual inspection of the quality of the nebulizer. If the nebulizer does not undergo hygienic processing regularly, the chances of developing of bacterial infection in the user rise. Some patients have an allergy to plastic parts, such as masks, mouthpieces.

Inhalation therapy is carried out with bronchodilators, glucocorticoids, antibiotics, and antiseptics in the treatment of diseases of the upper respiratory tract and lungs with the help of nebulizer [46]. In the case of COPD therapy, besides the standard treatment regimen with bronchodilators, glucocorticoids and methylxanthines, depending on the severity of the disease, mucoactive drugs with an additive anti-inflammatory effect are used.

Classification of mucoactive agents involves the allocation of several classes of drugs that differ in the mechanism of action [33]:

- mucolytics
- expectorants
- mucokinetics
- mucoregulators (Table 1).

Mucolytics break the structure of mucus gel, thereby reduce its viscosity and elasticity. The main representatives of this group are N-acetylcysteine, N-acistelin, ergostein, dornase alfa, heparin.

The goal of mucolytic therapy is to improve the viscoelastic properties of sputum to facilitate the cleaning of respiratory tract. Treatment with oral mucolytics (N-acetylcysteine) reduces the frequency of exacerbations and the total number of days of disability in patients with COPD or chronic bronchitis [17, 53]. The positive effect may be bigger in people with frequent or prolonged

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exacerbations, or in those who have been repeatedly hospitalized with exacerbation of COPD [34]. The Cochrane Review states that it is advisable to use mucolytics for at least in the winter months in patients with moderate to severe COPD when inhaled glucocorticoidsare not used [34]. In some countries, mucolytic drugs are prescribed not only per os, but also with the use of nebulizer, but there is a limited number of clinical studies that confirm the effectiveness of such therapy [12].

Drugs that regulate mucus secretion or affect DNA / F-actin binding are classified as mucoregulators. They are include carbocysteine, anticholinergic drugs, glucocorticoids and antibiotics from the group of macrolides.

Most mucokinetics raise mucociliary clearance, increase the frequency of fluctuations of the cilia of the flashing epithelium of the bronchi. Although a wide range of mucokinetics is available today, their effectiveness is ambiguous, and expediency remains questionable [27]. It is believed that bronchodilators, tricyclic nucleotides and ambroxol have mucokinetic properties. Surfactant also facilitates the expectoration of sputum during coughing by reducing the adhesion surface between the mucus and the epithelium of the respiratory tract [11].

Expectorants enhance the physiological activity of the ciliated epithelium and peristaltic movements of the bronchioles, promoting the sputum from the lower respiratory tract in the upper part and its expectoration. The effect is usually combined with increased secretion of the bronchial glands and some decrease in the viscosity of the sputum. This class of drugs include guaifenesin, as well as hypertonic solution of sodium chloride. Nevertheless, hypertonic solution is difficult to classify only within this category because it has other mechanisms of action. Hypertonic saline can lead to a disruption of ion bonds inside the mucous gel, reduce cross-stitching. This mucolytic effect may cause a marked decrease in the viscosity of the sputum [5, 11, 20, 22]. However, it does not belong to mucolytics, since mucosis is not its main activity.

In many studies of the efficacy of drugs for nebulizer therapy, an isotonic solution was used as a placebo. There is evidence that the isotonic saline for nebulizer therapy is used to relieve shortness of breath in patients with COPD [31]. Indicators of the lung function test do not change, therefore such therapy can be used as placebo in studies of action of bronchodilators, but not in studies, which assesses the relief of symptoms of the disease.

Table 1.

Mucoactive drugs and their potential mechanisms of action.

Mucoactive drugs	Potential mechanism of action
Mucolytics	
N-Acetylcysteine	Breaks disulphide bonds linking mucin polymers Antioxidant and anti-inflammatory effects
N-Acystelyn	Increases chloride secretion and breaks disulphide bonds
Erdosteine	Modulates mucus production and increases mucociliary transport
Dornase alfa	Hydrolyses the DNA in mucus and reduces viscosity in the lungs
Gelsolin	Severs actin filament cross-links
Thymosin β4	Severs actin filament cross-links
Dextran	Breaks hydrogen bonds and increases secretion hydration
Heparin	Breaks both hydrogen and ionic bonds
Expectorants	
Hypertonic saline	Increases secretion volume and / or hydration
Guaifenesin	Stimulates secretion and reduces mucus viscosity
Mucokinetics	
Bronchodilators	Improves cough clearance by increasing expiratory flow
Surfactants	Decreases sputum / mucus adhesiveness
Ambroxol	Stimulates surfactant production and inhibits neuronal sodium channels
Mucoregulators	
Carbocysteine	Metabolism of mucus producing cells, antioxidant and anti-inflammatory effects, modulates mucus production
Anticholinergic agents	Decreases secretion volume
Glucocorticoids	Reduces airway inflammation and mucin secretion

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As for hypertonic saline, long-term treatment of patients with cystic fibrosis by 7% hypertonic solution was investigated in a controlled study by Mark R. Elkins et al. [21]. Changes in the parameters of the lung function tests – forced vital capacity (FVC), of forced expiratory volume in 1 second (FEV_1), forced expiratory flow 25–75% (FEF25–75) were statistically different from those of the control group (0,9% solution of sodium chloride). An increase in FVC, FEV1 was significantly higher, although the FEF25–75 was comparable in the study group. The group of hypertonic solution also had significantly less respiratory exacerbations (relative risk of decrease – 56%, p = 0.02) and significantly higher percentages of patients without exacerbations (76% vs. 62%, p = 0.003).

The mucous membrane of the respiratory tract of the patient with cystic fibrosis, a healthy person and the effect of the use of hypertonic solution in patients with cystic fibrosis are depicted schematically in fig. 1 [43]. In the epithelium of the healthy respiratory tract, the cystic fibrosis transmembrane conductance regulator (CFTR) is unchanged and plays an important role in the regulation of airway surface liquid (ASL) hydration, which consists of a pericillary layer (PCL) and a mucous layer (A). Due to defective CFTR, secretion of Cl– is disturbed, and absorption of Na+ through the epithelial sodium channel (ENaC) is activated. It is resulting in dehydration of the ASL with accumulation of dense mucus causing the destruction of the PCL (B). Hypertonic solution is used to reduce the viscosity of mucus and contributes to its clearance in various ways. High concentration of salt contributes of osmosis of water in the ASL, thereby rehydrating the mucus and partially restoring the PCL, facilitating the clearance of the mucous layer. In addition, the high ionic strength of sodium chloride weakens ionic bonds between negatively charged ions of glycosaminoglycans (GAG) and reduces mucus viscosity (C).

Studies of the anti–inflammatory properties of the drug were conducted. Thus, GAGs that are synthesized by the epithelial cells of the respiratory tract have the ability to influence on the chemokine's profile by binding and stabilizing IL-8. It is a potent chemoactive agent and the activator of neutrophil function. Nebulizer therapy with hypertonic saline in patients with cystic fibrosis interfered the interaction between GAG and IL-8, it made IL-8 sensitive to proteolytic degradation with subsequent reduction of neutrophil chemotaxis and decreased inflammation activity [44] (figure 2. A). According to E.P. Reeves et al. [43] hypertonic saline in cystic fibrosis has not only immunomodulatory, mucoactive but also antimicrobial properties, they are depicted schematically in fig. 2. B, C. Hypertonic solution draws water into dehydrated PCL, improves the rheological properties of mucus and enhances mucociliary clearance (B). An antimicrobial protein cathelicidin, LL-37, which is inhibited in cystic fibrosis by binding to GAG, is released by hypertonic solution that brakes the electrostatic interaction between LL-37 and GAG and provides antimicrobial activity (C).

In addition to cystic fibrosis, the efficacy and safety of inhaled hypertonic and physiological solutions in combination with physical exercises in a randomized trial in COPD patients were also evaluated. In both groups of patients (inhalation of physiological or hypertonic solution), there was a significant improvement in the 6–minute walk test, dyspnea and quality of life, more (p < 0.001) with inhalation of isotonic solution. It is noted that in 4 patients (12%) hypertonic saline caused cough and bronchospasm [51]. In another study, a small sample of patients (n = 20) did not receive any positive changes in the parameters that characterized the lung ventilation function after inhalation of 3% of hypertonic and physiological solutions [47].

The long–term effect of nebulizer therapy with 6% hypertonic solution in patients with bronchiectasis was also studied. Forty patients were randomized in 2 groups for 20 patients, they inhaled daily 0,9%, or 6% solution of sodium chloride for 12 months. The quality of life, spirometric indices and bacteriological changes in sputum were evaluated, patients recorded the symptoms of the disease in a daily questionnaire. The results showed that in both groups the frequency of exacerbations during the 12 months was the same, comparable clinically significant improvement in quality of life was recorded. The values of FEV1 increased in both groups after 6 months, (on the

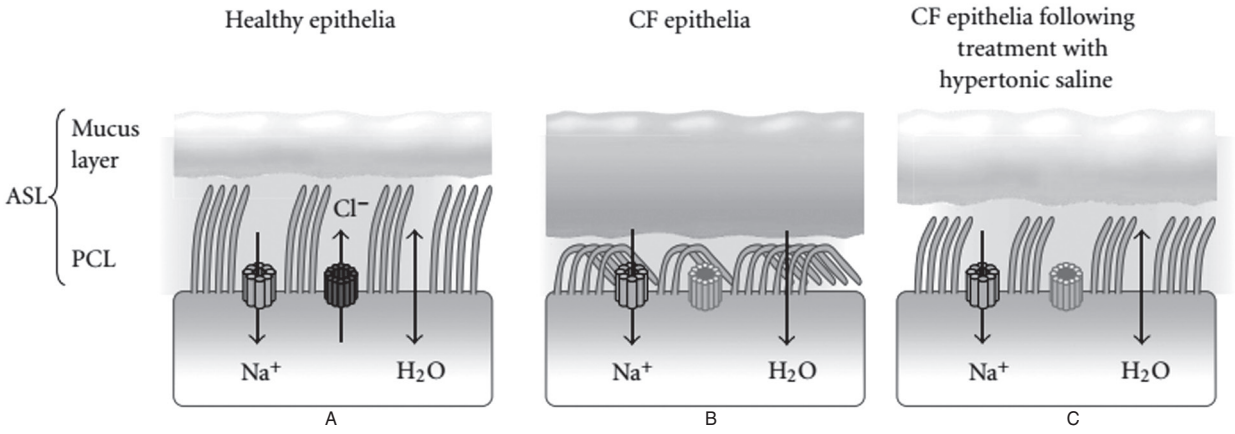

Fig. 1. Mucous membrane of the respiratory tract of a healthy person (A), a patient with cystic fibrosis (B) and CF epithelia following treatment with hypertonic saline (C).

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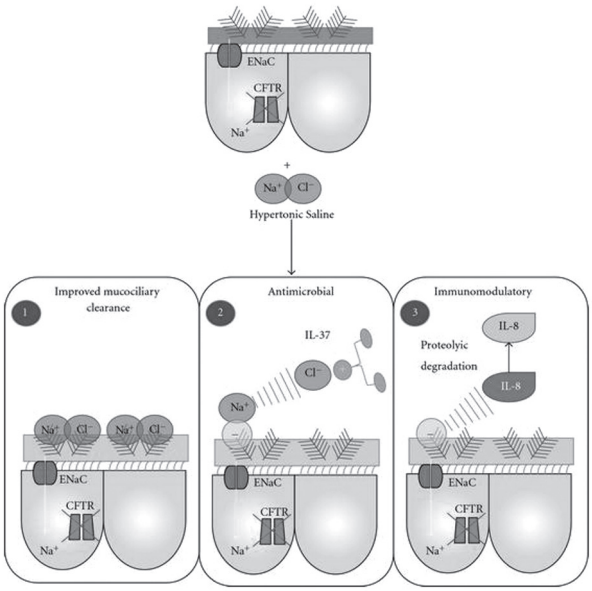

Fig. 2. Mechanisms of actions of hypertonic saline in patients with cystic fibrosis.
ENaC – epithelial sodium channel
CFTR – cystic fibrosis transmembrane conductance regulator

average 90 ml), and the rates of colonization of sputum decreased [39].

Results about presence of anti-inflammatory action in hypertonic saline, the ability to increase tolerance to physical activity, and improve quality of life, were obtained in patients with different diseases (cystic fibrosis, COPD, bronchiectasis). But some patients may have undesirable effects in form of increased cough and bronchospasm. Possible explanations for such negative reactions to inhalation of hypertonic solution in some patients with COPD can be the results of the study C. Taube et al. [47], which revealed that after inhalation of hypertonic solution in 10 patients, the concentration of histamine in the sputum (38,9 ± 1,28 ng/ml) was increased in comparison with the isotonic solution (29,8 ± 1,23 ng/ml, $p < 0,01$). Bronchoconstriction and hyperinflation of the lungs may be mediated, at least in part, by the activation of mast cells.

One possible way to improve the tolerability of hypertonic solution for nebulizer therapy is the combination with hyaluronic acid, which is a simple linear chain of polysaccharide belonging to the GAG family. Its function is the balance of aqueous homeostasis in the extracellular matrix [51]. This approach is based on experimental data of the potential therapeutic properties of hyaluronic acid, which are presented in table 2 [50].

As can be seen from the data in the table, hyaluronic acid has anti-inflammatory potential due to its effects on various pathogenesis of inflammation, it affects pro-inflammatory mediators, can change the «behavior» of cells of the immune response: reduces the mobility of lymphocytes, inhibits their stimulation and proliferation, blocks phagocytosis, and degranulation of neutrophils [29]. Hyaluronic acid is used not only in pulmonary practice, but also in otorhinolaryngology, dermatology, cosmetology, rheumatology [10, 28, 30, 32]. The additional usage of hyaluronic acid has a positive effect in patients with poor tolerability of hypertonic solution, which may be explained by its additive anti-inflammatory effect [15, 48, 52] and it can decrease hyperreactivity of the bronchi.

Consequently, an important component of COPD patients' treatment is the inhalation route of administration, in which a special place is occupied by nebulizer therapy, which allows to use of inhaled drugs at any age, minimizes the amount of drug that can settle into the oral cavity, eliminates the effect of propellants, and allows to provide oxygen supplying as needed. Mucoactive drugs take a special place among the drugs wich are used for nebulizer therapy in patients with COPD, one of them is hypertonic saline. It demonstrates ability to perform anti-inflammatory, antimicrobial and mucolytic activity. From the point of view of improving the efficiency and the tolerability of treatment, the combination of hypertonic solution with hyaluronic acid looks promising. However, to confirm the efficacy of this combination in patients with COPD and to develop rational treatment regimens further studies are needed.

Table 2

Potential therapeutic effects of hyaluronic acid in diseases of the respiratory system.

Categories of Lung Disease	Therapeutic mechanisms
COPD and pulmonary emphysema	Prevention of elastolysis by barrier function Decreased chemotaxis through decreased elastin fragmentation Blocking elastase secretion by neutrophils and macrophages Blocking airway obstruction by Kallikrein Hyaluronan content reduced in human emphysematous lung Cigarette smoke degrades HA in vitro and in vivo
Cystic fibrosis	Prevention of elastolysis in airways Decreased chemotaxis through decreased elastin fragmentation Blocking elastase secretion by neutrophils and macrophages
Asthma	HA reduces airway hyperreactivity to provocations of exercise and distilled water HA blocks airway obstruction by Kallikrein
Pharyngeal streptococcal infection	HA blocks epithelial cell CD-44 receptor of HA to prevent streptococcal colonization

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