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Hypertonic saline solutions for nebulization

Hypertonic saline solution in the nebulization

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Synopsis:
The aim of this study was to present the current place of concentrated sea salt solutions (HRS, hypertonic salt solutions) used in nebulization in the treatment of respiratory tract diseases in humans. The focus was on lower respiratory tract disorders. Evidence for the efficacy of hypertonic saline solutions used in nebulization in lower respiratory tract disorders in children and adults is presented. Special attention was paid to bronchiolitis, cystic fibrosis, bronchodilation and chronic obstructive pulmonary disease.

Abstract:
The aim of the study was to present the current place concentrated sea salt solutions (HRS, hypertonic salt solutions) used in nebulization in the treatment of respiratory diseases in humans. The focus was on ailments of the lower respiratory tract. Evidence of the efficacy of nebulized hypertonic saline solutions in upper and lower respiratory diseases in children and adults were presented. Particular attention was paid on bronchiolitis, cystic fibrosis, bronchiectasis and chronic obstructive pulmonary disease.

Key words: hypertonic saline solution, nebulization, rhinosinusitis, bronchiolitis, cystic fibrosis, bronchial dilatation, chronic obstructive pulmonary disease, asthma
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Introduction

Sodium chloride (NaCl) solutions or solutions of various salts found in sea water (NaCl, magnesium chloride, magnesium sulfate, calcium sulfate, potassium sulfate, calcium carbonate, magnesium bromide and others) have been used in medicine for many years [1, 2]. From a practical point of view we divide them into solutions:

- isotonic (IRS, isotonic water salt solution) - 0.9% sodium chloride solution, commonly known as saline
- hypertonic (HRS).

The latter are used in medicine in various concentrations: 1-10%, most commonly 2.0-4.5% [3]. They are available as intranasal solutions (various techniques of ap-

The solutions for nebulization (various nebuliza-tors) [4].

HRS are widely used in acute and chronic inflammatory and infectious diseases of the upper and some lower airways [3, 5]. HRS solutions administered in any formulation intra-nasally dilute the retained secretion, facilitating the clearing of nasal cavities, but also reduce edema and moisturize the nasal mucosa [6]. A detailed description of the action and indications for the use of HRS in colds, allergic rhinitis and rhinosinusitis has been recently presented in "Alergoprofil" [4]. [4].

HRS administered intratracheally (in nebulization) act as mucoactive drugs, belonging to the group of expectorants [7]. Their mechanism of action is based on the stimulation of glandular secretion, increasing the water content in bronchial secretion and decreasing the viscosity of secretion retained in the airways [8]. This is because after intrathoracic administration HRS create the intrathoracic osmotic gradient leading to increased passive secretion of water to the airways through the apical aquaporin channels [9]. In animal studies, it has been shown that they also stimulate airway neurons to trigger epithelial fluid secretion [10]. Finally - HRS trigger coughing, providing further mechanical removal of bronchial secretions [11]. Nebulization of HRS may reduce the spread of pathogens in the airways [12]. More recent studies indicate that HRS enhance the bactericidal, virucidal and anti-inflammatory effects of other drugs [13, 14].

Clinical trials are also underway for the use of HRS spray on face masks in COVID-19 patients [15].

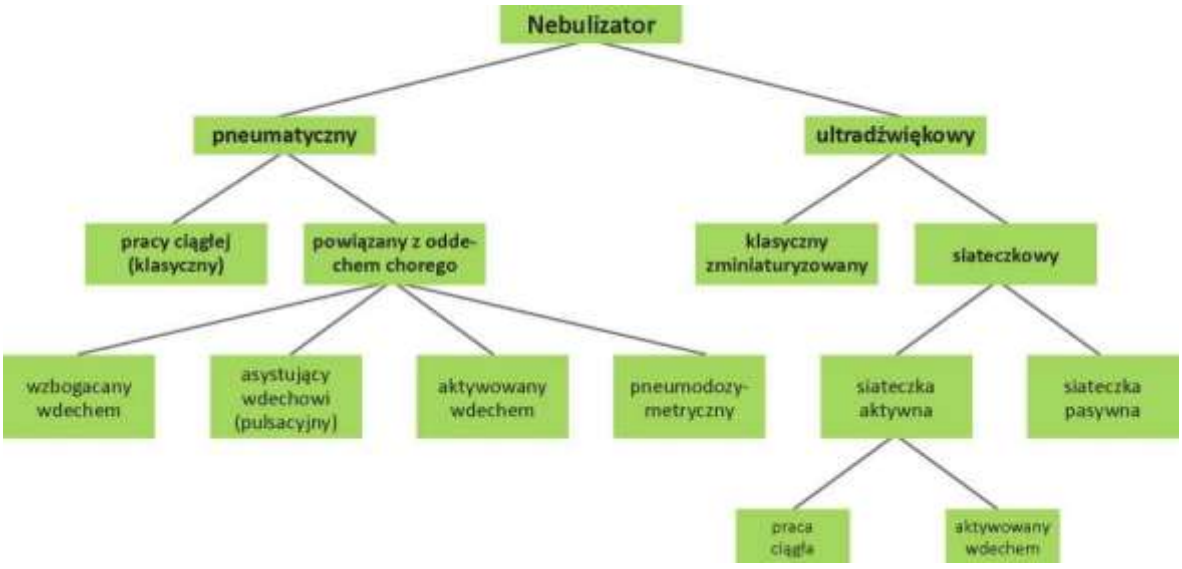
HRS Nebulization

HRS in the form of nebulization solutions, due to their physicochemical properties, are suitable for pneumatic, classic and ultrasound retinal nebulizers [16, 17]. The selection of an appropriate nebulizer is the key element of proper pulmonary deposition of a drug and desirable clinical effect. Fig. 1 presents the types of nebulizers currently available in practice [17, 18].

It should be remembered that each type of nebulizer has advantages and disadvantages and a specific place in aerosol therapy. Nebulizers from each group are not interchangeable in a simple way [17]. For HRS nebulization in upper respiratory tract disorders, all types of nebu-lizers can be used: classic ultrasonic, pneumatic (all types), and reticular ultrasonic [19]. However, for the treatment of lower respiratory tract diseases, mainly pneumatic or retinal ultrasonic nebulizers are recommended [20]. Moreover, some basic rules of effective nebulization should be remembered [17, 20-23]:

- Nebulisation should be carried out using equipment with which the drug or medical product has been tested *in vitro* or *in vivo.*
- Choose a nebulizer with adjustable particle size for the aerosol produced,

Figure 1: *Division of nebulization devices (based on [17, 18]).*



which will allow more efficient deposition in the desired airway areas (larynx, trachea, bronchi, bronchioles).
- Nebulisation through a mouthpiece is preferred and a mask should only be used in non-cooperative patients and in children < 4-5 years of age.
- The use of a mesh inhaler significantly reduces the nebulisation time and leads to significantly less drug loss, as these devices have a very small reservoir volume in the nebulisation chamber (usually < 0.5 ml).
- In the era of the COVID-19 pandemic, it is imperative that outlet filters (additionally fitted) be used in both pneumatic and mesh nebulizers used in the hospital.
- Inhalation technique is important as it affects the clinical efficacy of the drug and possible side effects. For example, to increase de-positioning in the laryngotracheal region, the patient should take short, forceful inhalations (which is possible in children over 5 years of age and adults).
- Nebulization administered in the hospital should be supervised by trained medical personnel, and in the home setting by a trained patient or caregiver (so-called supervised therapy).

HRS in lower respiratory tract disorders

Cystic fibrosis

The beneficial effects of HRS in this group of patients are clearly confirmed by a recent systematic review with meta-analysis, although the authors point to the existence of evidence of mainly low quality [5]. Indeed, it was shown that:
- HRS nebulised (3-7%, 10 ml twice daily) used for 4 weeks in children over 12 years of age.
  1 adults results in a 3.44% increase in FEV_t (enhanced first-second expiratory volume) from baseline (very low quality evidence from three studies, n = 225)
- After 48 weeks of treatment, the effect was slightly worse, with an increase in FEVj of only 2.31% (low quality evidence from one study, n = 134)
- one study (162 adults) found a significant reduction in disease exacerbations requiring antibiotic therapy in the HRS group (low quality evidence)
- In one study in children (243 children, mean age:
  2 years) no therapeutic effect has been demonstrated or
  was significantly less than rhDNase nebulization (low quality evidence)
- HRS appears to be an effective adjunct to physiotherapy during pulmonary exacerbations of this disease in adults (very low quality evidence).

Bronchial dilations unrelated to cystic fibrosis

For these conditions, nebulization with both HRS and IRS has been shown to have fairly similar effects in terms of impact on disease exacerbations, patient quality of life, sputum colonization, and spirometric parameters over a period of at least 12 months of therapy, although the effects of 3-month treatment are better after HRS [24, 25]. Nebulization with HRS is considered standard management in this group of patients [26]. The safety of HRS therapy in patients with bronchiectasis is emphasized in the 2010 British *Thoracic Society* (BTS) study [27]. [27]. The authors of this guide indicate that:
- When nebulizing HRS for the first time in a patient, measure FEV_t or PEF before and 5 min after treatment to assess the risk of bronchospasm
- In patients with bronchial hyperresponsiveness undergoing nebulization with HRS, a bronchodilator (salbutamol) should always be used initially.

Bronchiolitis in children

HRS solutions alter the properties of bronchial retained secretions, which in turn improves mucociliary clearance and thus lower airway patency in children with bronchiolitis [28, 29]. In a 2018 meta-analysis of clinical trials. Zhang et al. point out that the reduction in the risk of hospitalization applies only to children in whom nebulized HRS was administered together with inhaled bronchodilators [30]. However, a publication by Harrison et al. (which used the *trial* sequential analysis method) showed that meta-analyses of studies in this area may provide false-positive results [31]. The latest available systematic review with meta-analysis in 2020 suggests that HRS nebu- lation may be an effective treatment for viral bronchiolitis vs IRS solutions [32]. Nevertheless, the authors of this publication conclude that further studies should be conducted on the efficacy of both short-term and long-term HRS nebulization. A recent network meta-analysis, published in May 2021, indicates that the combination of HRS (always with salbutamol) and adrenali¬

ny in nebulization is the most effective treatment in the ED (reduces the risk of hospitalization) and in the hospital ward (reduces the duration of hospitalization) vs. other therapies [33]. Furthermore, HRS therapy by nebulization has been shown to be cost-effective in infants hospitalized for bronchiolitis [34]. This indication for HRS is still the most controversial.

COPD

For COPD, there is no recommendation for the use of HRS with nebulization in the current GOLD 2021 document [35]. However, incoming publications indicate a possible beneficial effect of nebulization with HRS in some COPD phenotypes, with good treatment tolerance in the general patient population [36].

Asthma

The use of HRS in asthma therapy has been controversial and is currently not recommended by experts in the latest GINA 2021 Report [37]. However, there are studies whose results suggest that this intervention may be effective in asthma exacerbations in patients treated with (3 $_2$-mimetics. The administration of HRS by nebulization improves mucociliary clearance and reduces bronchial mucus retention in the course of viral infection or contact with a sensitizing allergen [38]. However, further experimental and clinical studies are needed.

Summary

Intra-bronchial nebulization of HRS is an established treatment for some acute and chronic disorders of the lower respiratory tract characterized by a high retention of secretions in the trachea, bronchi or bronchioles. However, the quality of evidence for the clinical efficacy of HRS in these conditions is generally low, due to very large methodological differences between studies. These include, for example, the variety of HRS concentrations, volumes (doses) used, dosing regimens, types of nebulization and duration of treatment. HRS formulations are generally well tolerated by patients, especially at lower concentrations of 1.5-2.2%. The primary indications for the use of HRS in nebulization are bronchiolitis, cystic fibrosis, and bronchial dilatation. This type of therapy may also be helpful in other conditions with retention of secretions in the lower airways (some forms of bronchitis, COPD). It is important to be very careful.

General caution during HRS nebulization in children and adults with features of bronchial hyperreactivity by preceding it with salbutamol inhalation.

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