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COMPARISON OF THE EFFICACY AND TOLERABILITY OF INHALED HYPERTONIC SALINES OF SODIUM CHLORIDE IN PEDIATRIC PRACTICE

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Ключевые слова: *гипертонические растворы хлорида натрия, эффективность, переносимость, муковисцидоз, дети*

Abstract. Comparison of the efficacy and tolerability of inhaled hypertonic salines of sodium chloride in pediatric practice. Ilchenko S.I., Fialkovska A.O., Cherhinets V.I., Skriabina K. V. *In modern pediatric practice, inhalated hypertonic saline (IHS) is often used for therapeutic and diagnostic purposes. However, the potential development of serious side effects in children is not predicted. The aim of the study was to determine the efficacy and tolerability of IHS of various concentrations in children with cystic fibrosis (CF). The study involved 34 children with CF aged 6 to 18 years (middle age is 13.0±4.4 years). The comparison group consisted of 27 children (middle age is 7.8±2.3 years) without chronic respiratory diseases. The study included three consecutive inhalations. Sterile 0.9% NaCl solution was used for the first inhalation, 3 % NaCl solution – for the second one and 7% NaCl solution – for the third inhalation. For children under 7 years of age, a patented method of obtaining sputum without forced coughing was used. Spirometry was performed before and after each inhalation, and clinical changes were analyzed. It was noted that after inhalation of IHS, the cough in patients became more productive, moist rales were more often heard over the entire surface of the lungs. The activity of induced sputum secretion after inhalation of 3% and 7% NaCl solution did not differ significantly. However, after inhalation of 7% NaCl solution, side effects, such as sore throat, shortness of breath, spastic cough, auscultatory symptoms of bronchospasm were recorded significantly more often compared with lower concentrations of the solution. The decrease in FEV_1 was observed in 5.8% of patients after inhalation of 3% NaCl solution and in 11.8% of patients after inhalation of 7% NaCl solution, which was significantly associated with the clinical symptoms of bronchospasm. Inhalation of IHS has an effective mucolytic effect in patients with CF, however, it is necessary to determine the individual sensitivity of the patient to predict a positive therapeutic effect.*

Реферат. Сравнение эффективности и переносимости ингаляционных гипертонических растворов хлорида натрия в педиатрической практике. Ильченко С.И., Фиалковская А.А., Чергинец В.И., Скрябина Е.В. *В современной педиатрической практике часто используются ингаляции гипертонических растворов хлорида натрия (ГРХН) разных концентраций в лечебных и диагностических целях. Однако при этом не прогнозируется потенциальное развитие серьезных побочных эффектов у детей. Целью исследования явилось определение эффективности и переносимости ингаляций ГРХН различных концентраций у детей с муковисцидозом (МВ). Обследовано 34 ребенка с МВ в возрасте от 6 до 18 лет (средний возраст – 13,0±4,4 года). Группу сравнения составили 27 детей (середний возраст – 7,8±2,3 года) без хронических заболеваний органов дыхания. Исследование включало три последовательные ингаляции. Стерильный 0,9% раствор NaCl использовали для первой ингаляции, 3% раствор NaCl для второй и 7% раствор NaCl для третьей ингаляции. Для детей младше 7 лет использовали запатентованную методику получения мокроты без принудительного откашливания. Спирометрия проводилась до и после каждой ингаляции, а также были проанализированы клинические изменения. Отмечено, что после ингаляций ГРХН кашель у пациентов становился более продуктивным, над всей поверхностью легких чаще выслушивались влажные хрипы. Активность индуцированной*

секреции мокроты после ингаляции 3% и 7% раствора NaCl достоверно не отличалась. Однако после ингаляций 7% раствора NaCl побочные эффекты, такие как боль в горле, одышка, спастический кашель, аускультативные симптомы бронхоспазма, были зарегистрированы достоверно чаще по сравнению с меньшими концентрациями раствора. Снижение $ОФВ_1$ наблюдалось у 5,8% пациентов после ингаляции 3% раствора NaCl и у 11,8% пациентов после ингаляции 7% раствора NaCl, что имело достоверную связь с клиническими симптомами бронхоспазма. Ингаляции ГРХН имеют эффективное муколитическое действие у пациентов с МВ, однако необходимым является определение индивидуальной чувствительности пациента для прогнозирования положительного терапевтического эффекта.

Respiratory diseases occupy a leading position in the structure of children's morbidity, so each pediatrician almost daily decides on the choice of tactics for the treatment of cough in children [3]. It is known that the cough reflex in a child is innate, but the ability to effectively cough up sputum is formed up to 4-6 years, which should be kept in mind when choosing a drug and rehabilitation measures. The ability to secrete sputum with normal rheological properties is also formed only up to 5-6 years, so at first the child's secretion is more viscous, adhesion is impaired, muscle work is reduced. All this leads to the so-called "unproductive cough" [7]. The result of acute or chronic inflammation of the mucous membrane of the respiratory tract in children is the development of stagnation of secretion, which leads to significant impairment of bronchial patency, causes impairment of gas exchange and pulmonary ventilation, promotes atelectasis and microbial inflammation in the focus of mucus accumulation, prolongs bronchopulmonary process [8]. The most pronounced symptoms of mucostasis are manifested in patients with cystic fibrosis (CF) [10].

The question of choosing a drug that effectively eliminates mucostasis is traditionally decided in favor of mucolytic or expectorant drugs. Today, doctors or patients themselves prefer dosage forms in the form of solutions for nebulizer therapy with the hope of their high efficiency in children, the absence of systemic effects and side effects [3, 8]. However, frequent self-administration by a child's parents of mucolytic therapy through a nebulizer, even in common acute upper respiratory tract diseases, can lead to complications such as bronchial “flooding” and the development of bronchoobstructive syndrome in children with low bronchopulmonary drainage. Today there are clearly regulated pathological conditions in which the appointment of certain drugs by inhalation is shown, namely: acute stenotic laryngitis, bronchial asthma, bronchiectasis and cystic fibrosis [3].

Recently, doctors pay special attention to the use in nebulizer therapy of inhalated hypertonic saline (IHS) of different concentrations (3, 4, 5, 6 or 7% NaCl solution). This natural solution can have a dose-dependent therapeutic effect – both mucolytic and bactericidal [4]. According to the current unified clinical protocol, inhalated hypertonic saline (IHS) is included in the list of mandatory appointments in the treatment of patients with CF [9]. The main mechanism of its action in CF patients is the osmotic activity of the solution, which removes fluid to the apical surface of the airway epithelium and thus compensates for the increased absorption of sodium, chloride and water, which occurs in the absence of normal CF CFTR gene function [10]. It has been shown that inhalation of inhalated hypertonic saline (IHS) in adult patients with CF for 3 months significantly improves FEV_1. The best improvement is observed after the use of 7% NaCl solution than 3% solution [12, 13]. It was also found that 7% NaCl solution reduces the number of exacerbations in patients with CF, as it exhibits an antimicrobial mechanism of action. This effect is mediated by the electrostatic interaction of inhalated hypertonic saline (IHS) with the cationic proinflammatory cytokine interleukin-8, as well as with the cationic multifunctional immunomodulator cathelicidin LL37 [4, 11].

In pediatric practice, there is another situation where the necessary inhalation of IHS is to obtain induced sputum. The main purpose of sputum induction is to collect a sufficient amount of biomaterial from the lower respiratory tract for further biochemical and cytological examination in cases where there is no spontaneous sputum secretion. Inhalations from isotonic to hypertonic solutions by nebulization stimulate the production of bronchial secretions by increasing the activity of mucous glands against the background of increased intrabronchial osmolarity and vascular permeability of the mucous membrane. However, obtaining both spontaneous and induced sputum in children has many obstacles. This is especially true for young children, as the sputum collection procedure requires the active participation of patients. Monitoring of spirometric parameters, which is mandatory for the introduction of hypertonic solutions into the bronchi, for the same reason is impossible in this age group of patients. In addition, the use of IHS in children can cause such side effects as a burning sensation in the throat and an unpleasant salty taste, increased

cough and bronchospasm [4, 5]. These symptoms appear as a manifestation of bronchial hyperreactivity, which can occur in 16-40% of children without manifestations of bronchial asthma [6]. Bronchial hyperreactivity can cause poor compliance with treatment requirements and discontinuation of inhalation therapy [12, 13].

Thus, despite the large number of studies to evaluate the effectiveness of inhalated hypertonic saline in children, much remains unexplored: for example, optimal treatment regimens, doses, concentration, delivery rate and order of administration. The study of the response of the bronchopulmonary system to inhalation of IHS in children is very important for the effectiveness of compliance with the requirements of inhalation therapy and timely adjustment of the concentration of inhalated hypertonic saline.

The aim is to study the effectiveness and tolerability of inhaled therapy of inhalated hypertonic saline of different concentrations in children with CF.

MATERIALS AND METHODS OF RESEARCH

To achieve this goal, 34 children with CF aged 6 to 18 years (mean age – 13.0±4.4 years), who were treated at the city children's pulmonology center in Dnipro, were examined. Among the examined children there were 18 boys (mean age – 13.8±4.0 years) and 16 girls (mean age – 12.0±4.8 years). In addition, a clinical and instrumental examination of 27 children (mean age – 7.8±2.3 years) without chronic respiratory diseases, who underwent inhalation of inhalated hypertonic saline (IHS) to obtain induced sputum for diagnostic purposes.

Criteria for inclusion in the study were: children with a confirmed diagnosis of CF, consent of the patient and his parents to participate in the study, the patient's ability to perform research procedures, clinically stable condition, lack of data on exacerbation of bronchopulmonary process, FEV1 more than 50%.

Exclusion criteria from the study were: exacerbation of bronchopulmonary process, history of episodes of hemoptysis/pulmonary hemorrhage, FEV1 <50% of the appropriate and previously detected intolerance to hypertonic NaCl solution.

Verification of the diagnosis of CF was performed on the basis of its diagnostic criteria in accordance with the Unified Clinical Protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care. Cystic fibrosis "(order of the Ministry of Health of Ukraine No. 723 of 15.07.2016). The severity of the patients' condition was determined according to the evaluation scale of Shvakhman Kulchytsky. At the same time points on 4 basic parameters were summed up: the general activity of the patient, clinical manifestations of CF, indicators of physical development of the child, radiological changes in lungs. Each trait was evaluated on a scale of 5 to 25 points. The condition was assessed as excellent in the presence of the sum of 86-100 points, good – 71-85, satisfactory – 56-70, moderate – 41-55 and severe – 40 points or less.

To determine the individual tolerability of inhalations, official solutions of sodium chloride of various concentrations were used: sterile 0.9% NaCl solution, sterile 3% NaCl solution and sterile 7% NaCl solution.

Patients used Pari personal ultrasonic nebulizers for inhalation. Prior to inhalation, initial spirometry was performed using a modern MicroLab spirograph. The study included three consecutive inhalations. For the first inhalation, 2.0 ml of sterile 0.9% NaCl solution was used, for the second and third, 2.0 ml of 3% NaCl solution and 7% NaCl solution, respectively. The interval between inhalations averaged 15-20 minutes. After each inhalation, clinical changes (cough nature, induced sputum, auscultatory changes in the lungs) and changes in external respiration function were analyzed. The test was stopped if against the background of inhalation there was shortness of breath and spastic cough, a decrease in FEV_1 by 12% or more. Inhalations of short-acting β2-agonists in age doses were used to eliminate the provoked bronchospasm.

To implement the process of induction and collection of sputum in children aged 3-7 years a unified multifunctional inhaler was additionally involved, a feature of which is the additional ability to collect sputum during its production without the need for coughing [1].

The license program "Statistica 6.1" (serial number – AGAR909E415822FA) was used for statistical processing of the obtained results. Quantitative and qualitative indicators were evaluated. In the normal distribution of parameter values, the arithmetic mean value (M) and its standard error (m) were determined. Significance of differences in quantitative traits was determined using a paired Student's t-test for dependent populations. The results were considered statistically significant at $p<0.05$ [2].

RESULTS AND DISCUSSION

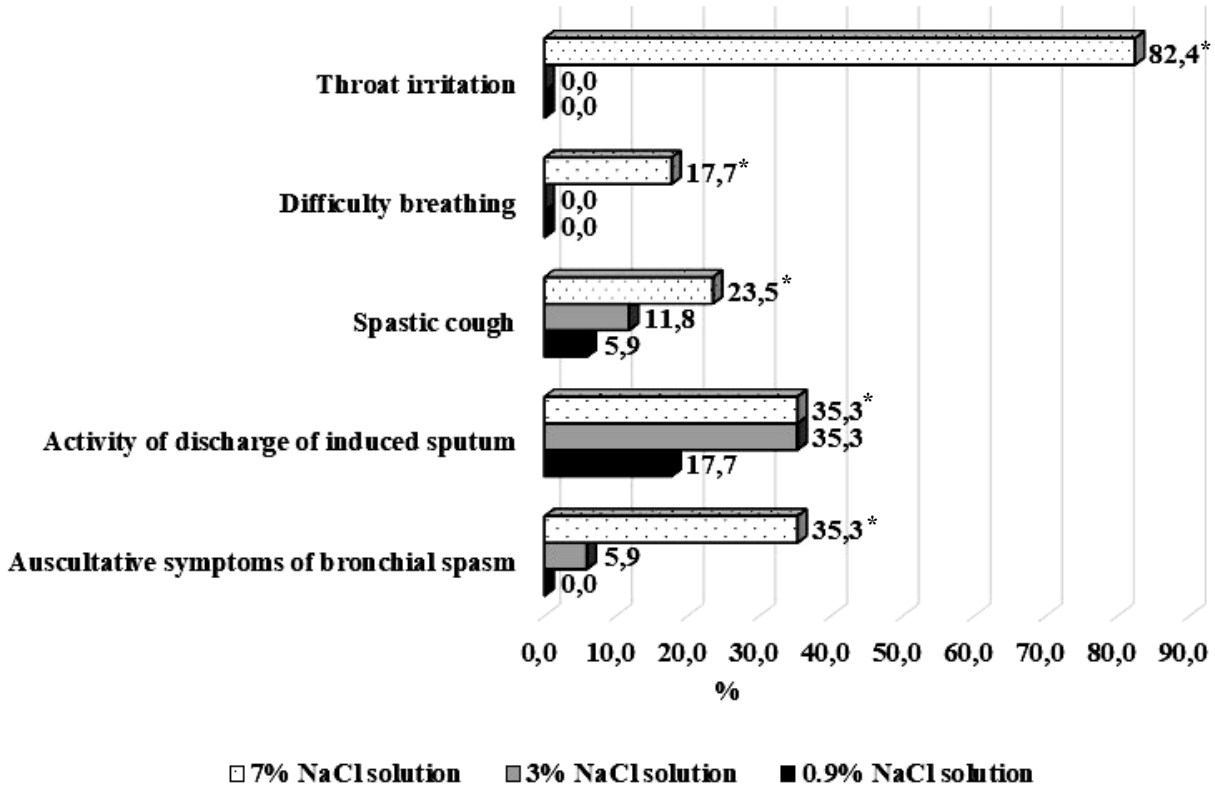
The analysis of clinical data showed that 76.5% of CF patients had a severe course of the disease and 23.5% of patients had a moderate course. Lesions of the bronchopulmonary system in the form of chronic bronchitis were diagnosed in 70.6% of examined patients.

At the time of examination before inhalation, the vast majority of patients (75.0%) complained of wet

unproductive cough, 16.7% – productive cough and 8.3% of patients – dry. In 90.9% of patients with lesions of the bronchopulmonary system, cough was accompanied by discharge of mucopurulent and in 9.1% – mucous sputum. According to auscultation data, in every third child (32.4%) wet rales of various calibers were recorded over the entire lung surface.

After inhalation of 0.9% NaCl solution, no significant clinical differences were found compared with the initial data ($p>0.05$). However, after inhalation of IHS cough became productive in 50% of patients ($p<0.05$), wet rales of various calibers over the entire lung surface were heard in 58.3% of patients ($p<0.05$). At the same time, no significant clinical differences were detected when using 3% NaCl solution and 7% NaCl solution ($p>0.05$).

Side effects such as sore throat, difficulty breathing and spastic cough have been reported in patients studying the tolerability of inhaled inhalated hypertonic saline. In the analysis of side effects of IHS therapy, statistically significant differences were found (Fig.). Thus, complaints of sore throat and difficulty breathing occurred only after inhalation of 7% NaCl solution in 82.4% and 17.7% of patients, respectively. Spastic cough was observed in 5.9% of patients after inhalation of 0.9% NaCl solution, in 11.8% of patients ($p<0.05$) after inhalation of 3% NaCl solution and in 23.5% of patients after inhalation of 7% NaCl solution ($p<0.05$). Auscultatory symptoms of bronchospasm occurred only after inhalation of IHS and were significantly more often recorded after inhalation of 7% NaCl solution than after 3% NaCl solution (35.3% vs. 5.9%; $p<0.001$).



Note. * – $p<0.05$ compared to the original data.

Frequency of side effects when using solutions of sodium chloride of different concentrations,%

The results of the spirometric study showed that the average volumetric and velocity indicators of the function of external respiration in patients before inhalation were within normal limits (Table). However, in 23.5% of the examined patients were found mixed ventilation disorders of moderate degree with a predominance of obstructive component.

Indicators of external respiratory function before and after inhalation of sodium chloride solutions in patients with CF (P±m, n=34)

Indicators	Before inhalation	After inhalation		
		0.9% NaCl solution	3% NaCl solution	7% NaCl solution
FEV1,%	86,1±4,7	84,5±4,8	83,2±5,1	82,1±4,9*
EFR,,%	93,8±4,1	92,6±4,5	92,0±4,7	91,4±4,8
FEV1 / EFR,,%	84,6±6,2	84,3±6,2	83,3±6,4	83,0±6,4
PEF,%	80,2±6,8	77,9±7,1	73,7±7,5	75,5±7,4

Note. * - p <0.1 compared to the initial data.

After inhalation with 0.9% NaCl solution and 3% NaCl solution, no significant differences in the mean values of the function of external respiration compared to the initial average data were detected (p>0.05). However, in 17.7% of patients after inhalation with 0.9% NaCl solution, a decrease in FEV1 in the range from 10 to 20% was recorded. These changes coincided with an increase in productive cough in children and were probably associated with sputum diffluence, reaffirming the need for kinesitherapy in patients with impaired bronchial drainage.

After inhalation of 3% NaCl solution, a decrease in FEV1 in the range from 10 to 20% was observed in 11.8% of patients. Clinically significant reduction (more than 20%) of FEV1 was observed in only 5.8% of patients, which is a diagnostic sign of bronchospasm. The development of bronchospasm in patients with CF dramatically complicates the course of the bronchopulmonary process – leads to the intensification of the infectious process and the formation of a vicious circle: obstruction-infection-inflammation with damage to lung tissue. The clinical manifestation of the vicious circle is a progressive decrease in the functional indicators of respiration.

Inhalations with 7% NaCl solution were accompanied by a tendency to decrease the average bronchial patency compared with the initial data (from 86.1±4.7% to 82.1±4.9%, p<0.1). At the same time, a decrease in FEV1 in the range from 10 to 20% was observed in 17.7% of patients and a decrease in FEV1 more than 20% – in 11.8% of patients. It was also found that the decrease in FEV1 by more than 20% correlated with clinical symptoms of bronchospasm (r= +0.39, p<0.05).

An analysis of the restoration of spirometric indicators in 11 children with a decrease in FEV1 after inhalation of a short-acting β2-agonist was performed. Reversibility of bronchial obstruction by 12% or more was recorded in only 5 children, which confirms the presence of provoked bronchospasm.

Interestingly, from a scientific and practical point of view, in 11.8% of patients inhalation of 7% NaCl solution caused a bronchodilator effect (increase in FEV1 more than 12%), which coincides with the data of some authors [5, 13] and probably indicates increase in the level of moistening of the airway surface, improvement of rheological properties of sputum and mucociliary clearance against the background of the absence of general bronchial hypersensitivity. It is in this group of patients with CF that significant both mucolytic and bacteriostatic effects should be expected. The obtained data need further study and updating.

The use of the method of induced sputum secretion in a subgroup of young children without CF according to the developed method allowed to obtain a sufficient amount of biomaterial from the lower respiratory tract for cytological examination in 90.2% (n=25) patients. The duration of sputum collection averaged 15-20 minutes. In 37.0% (n=10) children it was sufficient to inhale 0.9% NaCl solution, others to increase secretion additionally used GVHD. Clinical signs of side effects were observed in 18.5% (n=5) of children in the form of sore throat and spastic cough. Signs of bronchospasm in the studied children were not detected. There were no significant differences in the activity of induced sputum secretion after inhalation of 3% NaCl solution and 7% NaCl solution (37.1% in both cases, p□0.05), which proves the irrationality of using inhalations of 7% NaCl solution in children only to obtain sputum for laboratory analysis.

Thus, the results of the study showed that in young children without CF 3% NaCl solution is effective not

only as a means of hydrating the bronchial mucosa, but also as one that promotes effective expectoration of sputum. Side effects of 3% NaCl solution are mild and can be easily eliminated.

In children with cystic fibrosis the choice of the concentration of the hypertonic solution should be personalized. Because IHS is known to be a bronchial provoker and may irritate the airways, it is not surprising that some patients have side effects such as sore throat, difficulty breathing, spastic cough, and auscultatory symptoms of bronchospasm. Given this, the first inhalation of IHS in all patients should be performed in the presence of a physician and under the supervision of a spirometric study. To prevent the development of adverse events in patients with airway hyperreactivity, it is recommended to perform inhalations of short-acting β2-agonists before inhalation of IHS.

CONCLUSIONS

1. The activity of induced sputum in children without chronic respiratory diseases after inhalation of 3% and 7% NaCl solutions probably does not differ, which proves the irrationality of using inhalations of 7% NaCl solution in children only to obtain sputum for laboratory purposes. toric analysis.
2. Hypertonic sodium chloride solutions are modern drugs that help to improve sputum production, but their use requires a personalized approach, including in the complex mucolytic therapy of patients with cystic fibrosis.
3. The administration of hypertonic sodium chloride solutions to children requires trial inhalations under the control of a spirometric study at the onset of treatment to determine the individual sensitivity of the patient and to predict a positive therapeutic effect.

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

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