Isotonic Saline Nebulization and Lung Function in Children With Mild Respiratory Ailments

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Summary

Nebulization with saline solution, although commonly used to alleviate respiratory symptoms, particularly in children, is often questioned concerning its effectiveness. In this study, we investigated the effects of isotonic saline nebulization on lung function in 40 children (mean age of 14±1 years) suffering from different types of airway disorders. Measurements were carried out directly before and up to 15 min after nebulization, for six days in a row, always on the same day time in the morning. The children were divided into two study groups according to the baseline ratio of forced expired volume in one second/forced vital capacity (FEV1/FVC), below and above 80 %. We found significant improvements after saline nebulization in FEV1, mid-expiratory flow at 50 % and 75 % of FVC (MEF50 and MEF75), and peak expiratory flow (PEF) in the group with the baseline FEV1/FVC less than 80 %. In contradistinction, children with an index greater than 80 % displayed no appreciable changes in the lung function variables when compared with the baseline level before saline nebulization. We conclude that isotonic saline nebulization might mitigate the functional signs of threatening pulmonary obstruction and as such may be clinically useful in pediatric patients with mild respiratory problems.

Key words

Children • Isotonic saline • Nebulization • Spirometry • Respiratory tract

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Introduction

Nebulization is a therapeutic approach comprising the inhalation of aerosolized drugs, which is a suspension of fine particles or liquid droplets in a gas. The administration of solutions in this form is possible with the use of pneumatic or ultrasonic devices. The effectiveness of this method is related to the size of the dispersed substance - preferably smaller than 10 μm, which enables a good penetration into the bronchial tree and causes a high local concentration of a substance (Karolewicz *et al.* 2009). Nebulization is used for the treatment of acute laryngitis, bronchitis, acute recurrent bronchiolitis, cystic fibrosis, asthma, immotile cilia syndrome, and pneumonia (Wabnitz and Wormald 2005). The most important practical advantage of this method is its simplicity, which renders it particularly useful in the treatment of children.

Spirometry is the most often used diagnostic tool for the assessment of lung function. Spirometry results vary depending on the anthropometric factors such as age, gender, height, and weight of a patient (Quanjer *et*

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al. 2010). In general, these factors increase until the age of 20 years and then slowly decline (Chadwick *et al.* 1997). The ratio of forced expiratory volume in one second (FEV1)/forced vital capacity (FVC), called the Tiffeneau-Pinelli index, is a variable that correlates strongest with the patient age, while peak expiratory flow (PEF) and FEV1 depend on gender, height, and ethnicity. Despite age-related changes in spirometry variables, the FEV1/FVC ratio below 80 % is indicative of threatening obstructive symptomatology.

Many studies show that saline nebulization is a helpful adjunctive treatment in respiratory diseases. Khan and O'Driscoll (2004) have reported improvement in sputum expectoration and alleviation of dyspnea in nebulized patients. There are studies comparing the use of hypertonic and isotonic solutions for nebulization in patients with asthma or with cystic fibrosis, showing similarly good outcomes, particularly concerning cough, regardless of a solution tonicity (Mainz *et al.* 2016). It less clear if and how clinical outcomes relate to changes in spirometry variables, which could help optimize the use of nebulization in a verifiable manner. Therefore, in this study, we set out to define whether isotonic saline nebulization would have an influence on spirometry variables in children suffering from respiratory tract diseases.

Methods

Participants and study protocol

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2000 Helsinki Declaration of the World Medical Association and its later amendments. The study protocol was approved by the Ethics Committee of Wroclaw Medical University in Poland. It was carried out in July 2018 at the Granit Rehabilitation Center in Szklarska Poręba, Poland, where it was part of a sanatorial stay for combating frequent respiratory disorders in children from rural areas. Forty consecutive children (F/M, 23/17, mean age 14±1 years), were included in the study. The children suffered from a variety of respiratory tract disorders (Table 1). They were stratified into two groups, below and above 80 % of FEV1/ % FVC at baseline. The groups comprised 23 and 17 children, respectively, with about half-and-half participants from either gender. All children underwent a routine physical examination that included weight, height, tympanic temperature, and arterial blood pressure assessments. Nebulization was performed once daily in the morning, with a volume of 3 ml of isotonic saline for 10 min each for 6 consecutive days, using a classical Respironics InnoSpire Deluxe 1110057 nebulizer (Philips Polska, Warsaw, Poland). Spirometry measurements were performed twice, before and 15 min after the nebulization. The following variables were recorded and expressed as percentage of the reference values, according to the ERS recommendations for standardized lung function testing (Quanjer *et al.* 1989): forced expired volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio (Tiffeneau-Pinelli index), mid-expiratory flows (MEF) at 25 %, 50 %, and 75 % of FVC (MEF25, MEF50, and MEF75), and peak expiratory flow (PEF). All patients were prepared for lung function testing in the following way: fasting condition without breakfast, no prior physical activity, and no prior use of any medications for at least 12 h. Tests were performed according to the guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Miller *et al.* 2005), using a Lungtest spirometer (MES, Cracow, Poland), equipped with a built-in test compatibility check.

Table 1. Demographic and clinical features of the study population

		Baseline FEV1/FVC < 80 %	**Baseline FEV1/FVC ≥ 80 %**
Population		23	17
Age, years (range)		14±1 (13-15)	14±1 (13-15)
Illness:	*bronchial asthma*	2 (5.0 %)	9 (22.5 %)
	bronchitis	13 (32.5 %)	4 (10.0 %)
	allergic rhinitis	7 (17.5 %)	4 (10.0 %)
	sinobronchitis	1 (2.5 %)	0
Weight, kg (range)		56.7 (90-38)	64.2 (80-45)
Height, cm (range)		163.6 (150-178)	172.3 (161-197)
BMI, kg/m^2 (range)		21.1 (17-28)	21.7 (17-28)

Statistical elaboration

Continuous data were expressed as medians, interquartile ranges (IQR), and minimum-maximum range. Categorical data were expressed as counts and percentages. Data distribution was checked with the Shapiro-Wilk test. The Wilcoxon signed-rank test, Chi-squared test, and Mann Whitney U test were used, as

required, for the assessment of differences in lung function measurements before and after saline nebulization. A p-value <0.05 defined statistically significant differences. Microsoft Excel 2017 was used to prepare the database. Statistical analysis was performed using a commercial Statistica package (StatSoft Inc, Tulsa, OK).

Results

There were no appreciable gender-related differences in spirometry variables depending on the baseline FEV1/FVC level below or above the 80 % cut-off, type of clinical respiratory disorders, body mass index, or anthropometric features. Therefore, the results of lung function tests were evaluated without consideration for gender. Children in a group with baseline FEV1/FVC <80 % showed significant improvements after isotonic saline nebulization in the following lung function variables: FEV1, PEF, and MEF50 and MEF75 (Table 2). The median value of FEV1/FVC in this group increased from 73 % to 82 % after nebulization (Fig. 1a), with the minimum value being increased from 38 % to 44 %. In contradistinction, saline nebulization failed to significantly influence respiratory function in children with baseline FEV1/FVC ≥80 %. In fact, in this group of children, there was a tendency for decreases in lung function values (Table 2, Fig. 1b). An outstanding difference appeared between the magnitude of FEV1/FVC augmentation in children with the baseline FEV1/FVC <80 % when compared with a lackluster alteration in children with the baseline FEV1/FVC ≥80 % after isotonic saline nebulization. This difference, expressed as the means of individual medians of the pre-post inhalation values (Δ) in the two groups of children, amounted to +8.7 ±6.0 % and -5.5 ±7.1 %, respectively (p <0.001) (Fig. 1c).

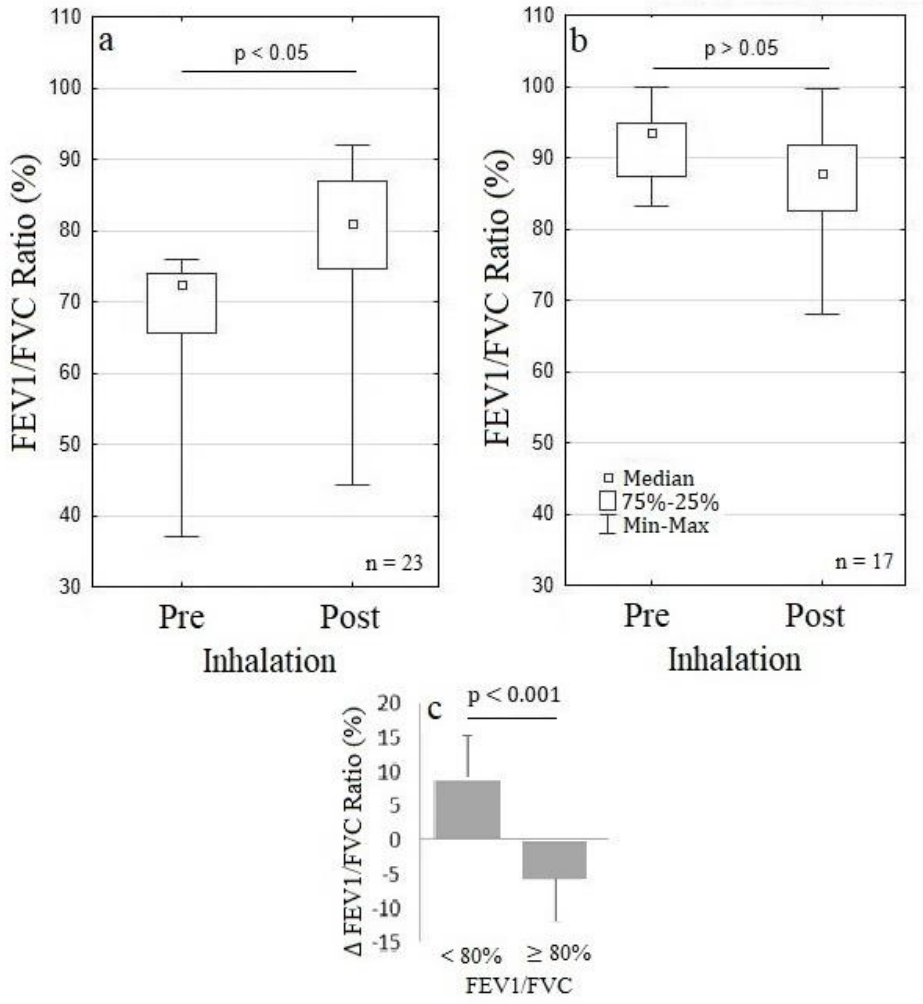

Fig. 1. Changes in FEV1/FVC ration before (Pre) and after (Post) isotonic saline nebulization in children with respiratory ailments depending on the baseline FEV1/FVC below and above 80 %: (**a**) baseline FEV1/FVC <80 %, (**b**) baseline FEV1/FVC ≥80 % of the reference value, and (**c**) means ±SD of the individual medians of the pre-post inhalation difference (Δ) in the two groups of children.

Table 2. FEV1/FVC ratio before (Pre) and after (Post) isotonic saline nebulization in children with respiratory ailments, subdivided into the groups with the ratio below and above 80 % of the reference value

Variable		FEV1/FVC <80 % (n = 23)			FEV1/FVC ≥80 % (n = 17)		
		Pre	Post	Wilcoxon signed-ranks	Pre	Post	Wilcoxon signed-ranks
FEV1 (L)	*Median*	2.24	2.85	p<0.01	2.95	2.90	p>0.05
	IQR 75-25	3.03-2.14	3.87-2.48		3.41-2.49	3.26-2.38	
	Min-Max	1.26-3.81	4.11-2.10		3.95-1.87	3.85-1.02	
FVC (L)	*Median*	3.69	3.18	p>0.05	3.29	3.23	p>0.05
	IQR 75-25	4.28-3.01	4.65-3.06		3.78-2.65	3.83-2.77	
	Min-Max	2.96-5.19	5.12-2.97		4.30-2.09	4.38-2.22	
PEF (L/min)	*Median*	3.22	4.40	p<0.05	5.28	4.56	p>0.05
	IQR 75-25	3.75-2.23	5.18-3.27		6.34-3.84	5.87-3.75	
	Min-Max	1.32-8.30	7.78-2.57		8.30-2.52	7.33-1.00	
MEF75 (L/s)	*Median*	3.04	3.99	p<0.05	4.67	4.33	p>0.05
	IQR 75-25	3.33-2.05	4.69-2.96		5.94-3.80	5.49-3.45	
	Min-Max	1.03-7.24	7.03-1.94		7.14-1.87	7.16-0.73	
MEF50 (L/s)	*Median*	2.41	3.20	p<0.01	3.61	3.66	p>0.05
	IQR 75-25	2.75-1.95	4.05-2.54		4.49-2.87	4.19-2.52	
	Min-Max	1.03-3.65	4.80-1.60		6.08-1.69	5.80-0.79	
MEF25 (L/s)	*Median*	1.37	1.58	p>0.05	1.84	1.73	p>0.05
	IQR 75-25	1.89-1.08	2.06-1.11		2.51-1.47	2.21-1.05	
	Min-Max	0.67-2.45	2.90-0.76		3.28-0.15	3.23-0.43	

FEV1, forced expired volume in one second; *FVC,* forced vital capacity; *PEF,* peak expiratory flow; *MEF75, MEF50,* and *MEF25*, the mid-expiratory flow rate at 75%, 50%, and 25% of FVC, respectively; *IQR,* interquartile range; *Min-Max,* minimum-maximum range

Discussion

The use of isotonic saline nebulization to moisturize the upper respiratory tract, decrease cough, ease congestion, and help deliver inhaled medications is a routine practice, in particular, in respiratory infections in the pediatric population. However, the efficacy of nebulization has not yet been conclusively verified, so that the validity of this procedure is questionable and remains rather empiric. The present study demonstrates that nebulization was effective in improving airway patency in children with respiratory disorders when there was a disease-related modest decrease in the FEV1/FVC ratio below the norm, a sign of possibly threatening airway obstruction. Nebulization then helped normalize the ratio, the effect was significant. Nebulization also improved other spirometry variables such as FEV1, PEF, and MEF50-75. The present findings are generally in line with a study of Poole *et al.* (1998) who have compared the effects of nebulized saline *versus* nebulized terbutaline, a beta-agonist, in patients with severe COPD. Those authors notice that both saline and terbutaline cause a significant and equal improvement in the feeling of breathlessness. The latter drug, however, was somehow superior in that it also slightly but significantly increased FEV1. The authors conclude that saline nebulization may be judged advantageous as adjunctive, but not replacement, therapy to bronchodilators.

There appear other ways to use the advantageous potential of isotonic saline nebulization in respiratory conditions. Wark *et al.* (2001) have used saline nebulization for sputum induction in the diagnostics of airway inflammation in asthmatic patients. The authors demonstrate that nebulization is an effective way to sample airway secretion in asthma exacerbation. Bronchoconstriction that may occur in some patients during the nebulization procedure is easily reversible with beta-agonists. Khan and O'Driscoll (2004) have attempted to differentiate the placebo effect of isotonic saline nebulization from clinical effectiveness in the enhancement of sputum expectoration and relief of breathlessness in COPD patients with severely decreased FEV1 (down to 30 % of the reference value). The authors use active and sham nebulization in a single-blinded manner. They report a significant improvement in clinical outcomes, but not in FEV1. Therefore, studies most often

point to improvements in expectoration and in a subjective feeling of breathlessness after isotonic saline nebulization. However, mucus liquefaction, tracheal lubrication, and better mucociliary clearance and expectoration after isotonic saline nebulization streamline airflow and also enhance signaling of airway cytokines, all of which is liable to improve spirometry variables (Wen *et al.* 2016, Wabnitz and Wormald 2005, Sutton *et al.* 1988).

A study by Elkins *et al.* (2006) has compared the effects of hypertonic and isotonic saline nebulization on the frequency of exacerbations and on lung function assessed from changes in FVC and FEV1 in patients with cystic fibrosis. The authors find that both types of saline significantly improve lung function, although hypertonic saline is superior regarding a reduction in exacerbations. In contrast, Chadwick *et al.* (1997) have compared the effects on FEV1 of hypo-, iso-, and hypertonic solutions used for nebulization in cystic fibrosis patients stratified into those with basal FEV1 below and over 70 % of the reference value. The authors notice a significant decrease in FEV1 after isotonic, but not hypo- and hypertonic saline nebulization in the group with FEV1 <70 %, and an insignificant decrease in FEV1 in the group with FEV1 >70 %. These findings contradict a need to make the saline solution for nebulization as close as possible to isotonicity, a rather common attempt, at least for cystic fibrosis patients. The discrepant findings concerning the effects of isotonic saline nebulization on lung function variables may likely depend on the pathology of the underlying airway disease, differences in the way the tests are performed, and the availability of saline aerosol to the epithelial layer of airways which, for instance, in cystic fibrosis is hampered by mucus plugging.

In the present study, isotonic saline nebulization had no appreciable effect on spirometry variables in children with asthma. However, the asthmatic children, all but one, were grouped with those having the baseline FEV1/FVC above 80 %, whose spirometry variables showed no change in response to isotonic saline nebulization other than a mild insignificant tendency for a decrease (Fig. 1b, c). Our results are in line with the notion of the futility of using saline nebulization for the relief of asthma exacerbation in both inpatient and emergency settings. We extend this notion to a lack of improvement in lung function in response to saline nebulization also in stable mild pediatric asthma. Nebulization may actually cause harm due to a delay in the implementation of the first-line bronchodilator treatment. Nonetheless, a review of the literature reveals that saline nebulization is often empirically used in asthma despite lacking recommendations (Hassan *et al.* 2018). The issue, however, remains open whether nebulization of an active bronchodilating drug in isotonic saline solution would provide more optimal results than either saline or the drug alone. The question also arises of whether any potential difference between the two would be due to the presence of saline *per se* and not due to greater drug's accessibility to the airways caused by the nebulizing mode of administration. There is a lack of comparative studies using various vehicles for nebulization to conclusively resolve this issue.

In the present study, we failed to substantiate any association between BMI and lung function assessed from changes in FEV1 and FVC. In particular, there was no influence of overweight on the results of nebulization in terms of the spirometry variables, within a modest range of overweight we had in the study children. In non-asthmatic non-smoking healthy patients, obesity, assessed from BMI, does not significantly correlate with spirometry function variables (Al Ghobain 2012). Likewise, Ghabashi and Iqbal (2006) have found that although obesity is prevalent in asthmatic subjects, it does not correlate with any of the main spirometry variables. Nonetheless, many asthmatic patients with normal FEV1 have lower mid-airflow rates pointing to the possibility of ongoing airway inflammation, which calls for a search for alternative methods to assess lung function in asthma, particularly in connection with obesity. On the other side, there are studies showing that obesity in children has an impact on bronchial hyperreactivity, assessed by methacholine challenge, which increases more in females than in males (Sposato *et al.* 2013).

There are other potential factors that could have a bearing on the assessment of lung function by spirometry. Body position is one such factor. FEV1 and FVC are significantly larger in the standing *versus* sitting position. This difference is small, in a range of 60-80 ml to the advantage of standing in individuals with average BMI (Townsen 1984) and it becomes negligible in the obese with BMI >30 kg/m^2 (Gudmundsson *et al.* 1997). None of our patients were obese and all were investigated in the sitting position both before and after saline nebulization. Weber and Lengsfeld (2011) have shown that gender may affect the deposition of aerosolized medicines given by nebulization into the lungs, with a better efficiency noted in females. In the present study,

we failed to substantiate the influence of gender on changes in forced expiratory flows after isotonic saline nebulization.

This study had a limited design as it included children with a modest decline in the FEV1/FVC ratio, representing various respiratory ailments at a time of remission, with no signs of overt respiratory insufficiency. Therefore, the results may not apply to respiratory insufficiency or to a specific disease. Despite the limitations, we believe we have shown that isotonic saline nebulization in children with threatening obstructive features has the potential to improve spirometry variables and thus is liable to improve airflow and gas exchange in the lungs. We conclude that saline nebulization may provide some respiratory relief used alone or as an adjunct to more aggressive systemic drug therapy. Taking into account low cost, comfort and ease of application, and avoidance of systemic side effects, usually inherent to pharmacologic agents, isotonic saline nebulization seems an applicative option in children with mild airway conditions.

Conflict of Interest

There is no conflict of interest.

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