Nebulized myo-Inositol increases oxygen saturation and relieves symptoms in patients with airways diseases

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ABSTRACT — OBJECTIVE: *Recent findings have evidenced the beneficial activity of myo-Inositol (myo-Ins) for the treatment of airways diseases. The study was designed to examine its efficacy in counteracting respiratory diseases complications, using nebulization as delivery route.*

PATIENTS AND METHODS: *15 patients with different clinical features of airways diseases were treated for 15 days on average with nebulized myo-Ins. Peripheral capillary oxygen saturation (SpO2) levels and symptoms distribution were analyzed.*

RESULTS: *All the patients experienced a significant increase in the SpO2 levels after the treatment with nebulized myo-Ins [98% (IQR 95-97.5) after the treatment vs 96% (IQR 98-98) before the treatment] ($p<0.05$). Moreover, 67% of patients had a total recovery and did not manifest symptoms after the end of the treatment; the remaining 33% had a regression of the symptoms ($p<0.001$) with a marked improvement of their general health status.*

CONCLUSIONS: *Nebulized myo-Ins relieved symptoms of respiratory diseases thus reducing the related complications.*

KEYWORDS
myo-Inositol, Nebulization, Respiratory diseases, SpO2, Respiratory symptoms.

INTRODUCTION

Respiratory diseases are the second leading cause of death and disability in the world, after cardiovascular disorders, including stroke. According to a recent statistical survey, in the last few years, respiratory diseases were responsible for 339.000 deaths in the European Union (EU), equivalent to 7.5% of all deaths[1]. Airways diseases affect both upper and lower tract of the respiratory system[2] and can be the consequences of complex gene–environment interactions, as asthma[3], or caused by different etiological agents thus manifesting heterogeneity of symptoms including dyspnea, cough, etc. Furthermore, the recent Covid-19 pandemic has led to an unprecedented surge in respiratory problems, with an extraordinary increase in clinical manifestations, ranging from atypical pneumonia, a hyperinflammatory phenotype, respiratory failure, and acute respiratory distress syndrome[4].

In this global scenario, myo-Inositol (myo-Ins) has been studied as possible "non pharmacological" adjuvant therapeutic strategy for the treatment of airways diseases[5]. myo-Ins is a key molecule participating in several intracellular signaling pathways and physiological processes. Respiratory diseases usually involve an inflammatory response and endothelial dysfunction. myo-Ins modulates interleukin-6 (IL-6) levels in chronic inflammatory diseases and possesses endothelial protective properties[6]. Therefore, the aim of this pilot study was to evaluate the efficacy of Myo-Ins in counteracting respiratory diseases and mitigating the related symptoms, using nebulization as delivery route.

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PATIENTS AND METHODS

Between January 2021 and May 2021, a total of 15 patients (8 women and 7 men) were successfully recruited in this non-randomized pilot study. All the participants gave their oral informed consent after explanation of the study purpose. The study was conducted following the Ethical Principles of the Helsinki Declaration and the national law. Patients (women and men, aged between 24-81 years) with a clinical diagnosis of airways diseases were included. The primary outcome of this study was to evaluate if nebulization of myo-Ins could ameliorate clinical symptoms in patients affected by respiratory inflammation resulting from different pathologies. The patients' medical history and concomitant pathologies were obtained from a review of their medical records. Patients were treated with nebulized myo-Ins (400 mg in 3 ml 0.9% saline) (Broncositol®, produced by Farmares, Via Sabatino Gianni, 14, 00156 Rome, Italy and distributed in Italy by Exipharma, Via del Giglio, 40, 35133 Padova, Italy; Class IIb Medical Device) twice a day for 15 days on average.

STATISTICAL ANALYSIS

Statistical analysis was performed using GraphPad Software 2018 (La Jolla, CA, USA). Wilcoxon signed rank sum test was performed to compare changes from T0 (baseline) to T1 (after myo-Ins treatment) for peripheral capillary oxygen saturation (SpO2) levels; data are presented using box plots as median and interquartile range (IQR). The level of statistical significance was achieved with a p-value < 0.05. Fisher's exact test was used to analyze categorical variables.

RESULTS

The concomitant pathologies that affected patients of the study in addition to airways diseases are listed in the Table 1.

The age range of the selected patients was 24-81 years, with a median value of 50 years (IQR 28-64). Among patients, 33.3% had chronic obstructive pulmonary disease (BPCO); 20% was affected by asthma and recurrent tonsillitis, each; COVID-19 was predominant in 13.3% of patients; pulmonary emphysema, bronchitis and otitis recurred in 6.7% of patients, respectively.

Table I. Concomitant pathologies in addition to airways diseases.

Concomitant pathologies	Recurrence rate (%)
Obesity	13.3
Diabetes	6.7
Dysmetabolic syndrome	6.7
Hypertension	6.7

SpO2 levels significantly increased after the treatment with myo-Ins, 98% (IQR 95 - 97.5), compared to those at the time of the enrollment, 96% (IQR 98-98) (p<0.05) (Figure 1). Concomitantly, 67% of patients had a total recovery and they did not manifest symptoms of airways diseases after the end of the treatment; the remaining 33% had a regression of the symptoms (p<0.001) with a marked improvement of their health status (Figure 2). Before the treatment with myo-Ins, 46.7% of the patients suffered from dyspnea, which disappeared in 71.4% of patients and was reduced in 28.6% after the treatment. Before the treatment, long-term respiratory complications of COVID-19 were present in 26.7% of total patients: they disappeared in 75% of patients and they were reduced in 25% of patients after the treatment. At the enrollment, 33.3% of the patients suffered from coughing, which totally disappeared in 80% of them and improved in 20%. Among patients, 6.7% had fever before the treatment, which disappeared in all the observed cases after the treatment with myo-Ins.

DISCUSSION

Nebulization represents the preferred route for the administration of drugs to treat respiratory disorders such as asthma and chronic obstructive pulmonary disease[7,8]. It offers several advantages in the treatment of these diseases compared to other routes, due to the direct delivery to the target site, rapid onset of action, high and long-term pulmonary efficacy, and reduced risk of systemic side effects [9]. Our data indicate that nebulized myo-Ins reduces symptoms in patients affected by different respiratory problems and significantly increases SpO2 levels.

Some of the patients (33.3%) were affected by chronic obstructive pulmonary disease (BPCO), a long-term lung pathology that causes persistent and progressive respiratory symptoms, including difficulty in breathing, cough, and/or phlegm production[10]. Asthma and recurrent tonsillitis (20% each) were also two prevalent airways diseases of our study population. Pulmonary emphysema, bronchitis, and otitis were present in the 6.7% of cases. Covid-19 affected 13.3% of patients.

All the patients recruited in our study exhibited several constrictive symptoms: dyspnea was one of them and it affected 46.7% of our population. Dyspnea is a subjective experience of breathing discomfort akin to suffocation and one of the worst symptoms experienced by critically ill patients, including those who are mechanically ventilated[11].

Cough, the most common chronic, non-communicable disease in children and adults character-

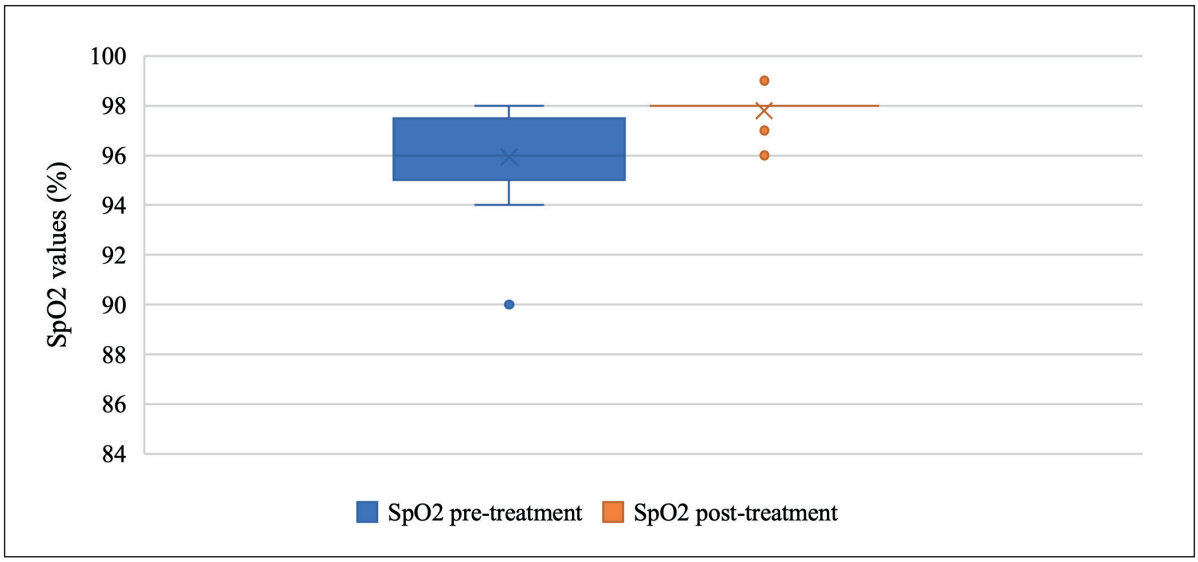

Figure 1. Box plot showing the SpO2 levels before and after the treatment with nebulized Myo-Ins. Data are expressed as median values and interquartile range (IQR); (*p<0.05 by Wilcoxon signed rank sum test).

ized by variable respiratory symptoms and variable airflow limitation[3], was present in the 33.3% of the study population; 26.7% of patients reported long-term effects of Covid-19 and 6.7% had fever. This report is to our knowledge the first that investigates the efficacy of nebulized myo-Ins in counteracting complications of several respiratory pathologies. myo-Ins is a naturally occurring polyol involved in several critical physiological processes in cells[6]. In the lungs, it promotes the maturation of the surfactant phospholipids, such as phosphatidylcholine and phosphatidylinositol (PI)[12]. Indeed, the synthesis of PI in type II pneumocytes appears to be dependent on extracellular myo-Ins concentrations[13]. Myo-Ins treatment significantly reduces short-term adverse neonatal outcomes and the incidence of bronchopulmonary dysplasia in preterm infants[14,15], acting as a substrate that enhances the synthesis and secretion of surfactant phospholipids in immature lung tissue[16].

Intravenous infusion of myo-Ins is used in pulmonology for the therapy of respiratory tract affections, asthma, and chronic obstructive pulmonary disease and for the treatment of respiratory distress syndrome (RDS) in premature babies[14] or acute respiratory distress syndrome (ARDS), hypovolemia, ascites, edema, and thrombosis. In these patholog-

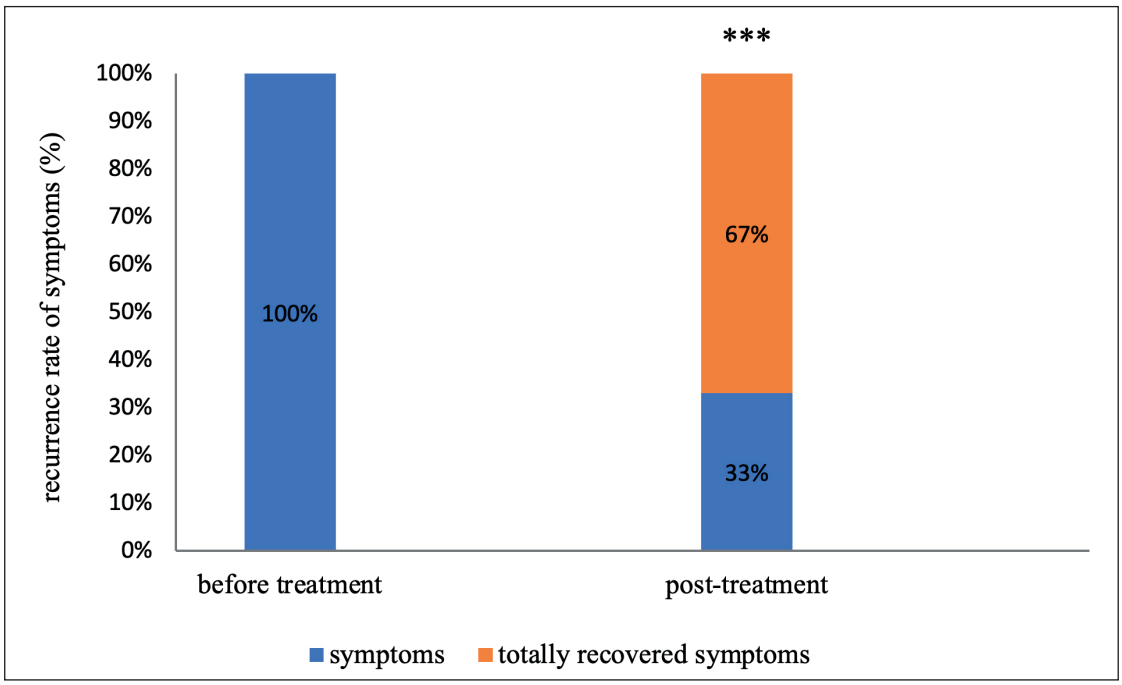

Figure 2. Recurrence rate of symptoms before and after the treatment with nebulized Myo-Ins. ***p<0.001 by Fisher's exact test.

ic conditions myo-Ins counteracts the main clinical disease features, and significantly reduces several inflammatory pathways[17]. In the present study, myo-Ins was administered for the first time through nebulization, leading to total recovery and to the disappearance of the clinical features of respiratory diseases in 67% of the cases. The remaining 33% had a statistically significant regression of the symptoms ($p<0.001$). Recovery was associated with a significant increase in SpO2 levels. Inflammatory response is a physiological protective mechanism to cellular and tissue injury. When such response is deregulated, failure to neutralize acute inflammation occurs, leading to augmented risk of developing chronic inflammation which can lead to a worsening especially in presence of metabolic disorders already existing, as obesity, type 2 diabetes and cardiovascular disease[18]. In the case of chronic inflammation in the lungs, pneumocytes release inflammatory mediators and cytokines/chemokines, such as IL-1ß, IL-6, IL-8, and TNF-α in response to oxidative stress[19]. IL-6 is a cytokine that regulates humoral and cellular responses and plays a key function in inflammation and tissue-damaging during infections. Its levels are higher in patients affected by cardiovascular disease[20], hypertension[21], diabetes[22] as well as in other relevant diseases or viral infections[23]. Compelling evidence reports that clinical presentation of COVID-19 begins with acute respiratory distress and patients undergo a detrimental overreaction of the immune system known as a "cytokine storm", in which high levels of IL-6 persist[24]. Researchers demonstrated that myo-Ins specifically down-regulates IL-6 levels[25] and it has endothelial protective and restoring properties[26,27]. In our study, 13.33% of patients had a SARS-CoV2 infection (Covid 19) and 26.67% had long-term respiratory complications of COVID-19 at the time of the enrollment and before the treatment with nebulized myo-Ins. After the treatment, these patients had total recovery of the symptoms, and a significant increase in the SpO2 levels. Although this is a pilot study with a limited sample size, we must acknowledge that the enrolled population was widely heterogeneous. However, future RCTs with larger cohorts of patients are necessary to confirm our findings.

CONCLUSIONS

Myo-Ins acts as a pivotal molecule in several intracellular signaling pathways. Compelling evidence reports that its oral and intravenous dosing are beneficial in metabolic diseases and inflammatory states. In our pilot study, we demonstrated for the first time that its delivery through nebulization exerts a beneficial activity in patients affected by respiratory diseases. Thus, this new route of administration should be considered to use myo-Ins as "non-pharmacological" therapeutic strategy in several respiratory inflammatory states and new studies should be planned to verify this promising option.

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Conflict of Interest:
The author declares that there are no conflicts of interest.

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