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Use of helium-oxygen mixture (Heliox®) in the treatment of obstructive lower airway disease in a pediatric emergency department

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Abstract

Objective: To determine whether the use of salbutamol, in a helium-oxygen mixture (80:20), can modify outcome and risk of hospitalization of pediatric patients.

Methods: A controlled cohort study including patients aged 2 months to 12 years with diagnoses of asthmatic crisis or viral bronchiolitis. Intensity was characterized from moderate to severe, as measured by clinical score (pulmonary index, PI) for obstructive disease. Scores > 8 were considered eligible. The Heliox® group was composed of 20 patients and the Oxygen group of 40 patients. Patients received sequentially, at 20-min intervals, until six nebulization cycles were completed (2-h period): salbutamol 0.15 mg/kg/dose (maximum 5 mg). The nebulized drug was driven either by Heliox® mixture (80:20) or 100% oxygen. Patients diagnosed with acute asthmatic crisis received, additionally, prednisolone (2 mg/kg) orally.

Results: Eleven patients in the Heliox® group still required treatment at 6 h, against 38 patients in the group receiving oxygen-driven nebulization ($p = 0.034$). At 12 h, 7 patients in the Heliox® group remained under observation, against 27 in the Oxygen group. Differences regarding the need for supplemental oxygen were observed only at 6 h of treatment ($p = 0.02$).

Conclusions: Heliox® (80:20), for salbutamol administration, is effective in the treatment of pediatric obstructive disease that responds to bronchodilator therapy. Compared to usual aerosol delivery technique, Heliox®-driven salbutamol nebulization is associated with shorter stay in the observation room after 6 h of treatment.

J Pediatr (Rio J). 2010;86(5):424-428: Asthma, bronchiolitis, helium, oxygen, salbutamol.

Introduction

The first-line treatment for some childhood obstructive pulmonary diseases is fundamentally based on the administration of inhaled bronchodilators. Within this context, it is believed that, in patients with an important degree of airway obstruction, deposition of aerosol medication is often difficult to accomplish and, consequently, a minor clinical response to the use of such medication is expected. Thus, a gas mixture composed of helium and oxygen (Heliox®) has been used as a promising therapeutic alternative in these obstructive diseases resulting from many different

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etiologies. However, over the last 20 years, this gas mixture has been more frequently used in bronchial asthma and acute viral bronchiolitis, both in the emergency department and intensive care unit.[1-3]

Helium has a threefold lower density than room air or 100% oxygen. The low density of helium can turn a turbulent airflow into a laminar flow and, consequently, decrease airway resistance, resulting in decreased inspiratory pressure and work of breathing.[4] Moreover, helium increases carbon dioxide diffusion and can improve alveolar ventilation.[5] These properties make Heliox® an alternative to be considered in the treatment of patients with asthma and other conditions of severe airway obstruction.

Kim et al.,[4] using Heliox®-driven albuterol, showed better clinical response in the treatment of pediatric patients with acute severe asthma, when compared to oxygen. Similarly, a 70:30 helium-oxygen mixture has been used for treatment of acute viral bronchiolitis.[6] Martinón-Torres et al.,[7] in a clinical trial, observed favorable outcome (improvement in clinical score, heart rate, and respiratory rate, and decreased length of stay in intensive care unit) in 19 patients who used the gas mixture (Heliox®). All patients had bronchiolitis (moderate-to-severe intensity) and their controls were managed conservatively (supportive measures associated with oxygen-driven nebulized epinephrine).

Although bronchial asthma and acute viral bronchiolitis are prevalent diseases, accounting for a significant number of pediatric hospitalizations, both in the emergency department and intensive care unit, the use of Heliox® has been little studied in our field.[8,9] Therefore, the present study was designed to determine whether the use of salbutamol, administered intermittently, in a frequent manner, and driven by a helium-oxygen mixture (80:20), can modify outcome and risk of hospitalization in a group of pediatric patients.

Methods

Study design

This is a controlled cohort study including patients aged 2 months to 12 years. All patients had a clinical diagnosis of acute asthmatic crisis or viral bronchiolitis established by the medical team providing care to each patient. Intensity should be from moderate to severe, as measured by the pulmonary index (PI) for obstructive disease.[10] Scores > 8 were considered eligible.[2,11]

All patients with asthmatic crisis and acute viral bronchiolitis assisted in the emergency department who received bronchodilators driven by Heliox® were considered for inclusion in the study. Controls were patients with the same diagnoses (assisted in the emergency department), matched for similarities (physical and temporal), who received conventional bronchodilator therapy (with oxygen).

All patients were prescribed bronchodilator solutions, according to the unit's routine care. The medical team selected the patients who would receive Heliox®, whereas the research team was limited to follow outcome of patients (throughout their stay in the observation room). The identification of patients receiving conventional therapy (selected by severity, sex, and age) was the responsibility of the research team, which also followed these patients throughout their stay in the observation room. The population selected as a control was obtained sequentially for every case using Heliox®, always trying to identify the next patient to be treated in the unit with the clinical characteristics established for inclusion in the study.

The use of Heliox® was established by the medical team, in a process of convenience sampling, without any intervention by the research team. The research team established the criteria for composition of the control group (similarity matching).

In both populations, patients with congenital heart disease, bronchopulmonary dysplasia, bronchopneumonia, tracheostomized patients or patients with facial dysmorphism were excluded.

For study purposes, the diagnosis of acute asthmatic crisis was established by the presence of recurrent respiratory symptoms (coughing, wheezing, and/or chest tightness) associated with previous, unequivocal clinical response to inhaled bronchodilator therapy.[1] The diagnosis of viral bronchiolitis considered patients under 18 months of age, with first clinical manifestation of obstructive airway disease (wheezing and/or rales associated with signs of respiratory distress).[3] All patients had prodromal illness suggestive of upper airway viral infection (evolution not exceeding 72 h) and chest radiological investigation supporting the hypothesis of viral bronchiolitis, established by a pediatric radiologist not participating in the study.

Administration of medication

Once patient eligibility clinical criteria were met and the inhaled bronchodilator therapy was indicated, the patients received sequentially, at 20-min intervals, until six nebulization cycles were completed (2-h period): salbutamol 0.15 mg/kg/dose (maximum 5 mg). The nebulized drug was driven either by a helium-oxygen mixture (Heliox®) at a ratio of 80:20 (cases) or 100% oxygen (controls). Heliox® was delivered through a mixer (Heliomix®, White Martins, Brazil) administered in a closed system, with an adjustable face mask and a one-way inspiratory valve. Patients diagnosed with acute asthmatic crisis received, additionally, prednisolone (2 mg/kg) orally. For patients diagnosed with bronchiolitis, once the first nebulization cycle was completed, the medical team responsible for reassessing patients determined the continuation or discontinuation of therapy. Suspicion of worsening of clinical

conditions, related to the use of bronchodilator substance, was an indicative of discontinuation of nebulization and the patient could not be included in the study. The therapeutic approach (drugs used, doses and intervals established, besides the possibility of discontinuing bronchodilators in bronchiolitis) constitutes the routine established by the unit for initial treatment both of asthmatic crisis and acute viral bronchiolitis. The need for supplemental oxygen therapy was determined by levels of oxygen saturation (O_2 sat. < 95%). Patients were assessed, after each nebulization, by one of the researchers, and their clinical data were entered into a standardized form for establishing a clinical score: respiratory rate, presence and characteristics of wheezing, inhalation/exhalation ratio, levels of oxygen saturation, and use of accessory muscles. Once the 2-h period was completed (six nebulization cycles), the patient was reassessed. Patients with a PI ≥ 3 were admitted to the observation room, where they remained under treatment, following the unit's routine care. During this period, patients were reassessed hourly (up to 12 h) for the same variables. At the end of this period (12 h), the unit's medical team defined the need for hospitalization or the possibility of discharge.

For study purposes, the need to stay in the observation room and the need for supplemental oxygen were evaluated at 6 and 12 h. Additionally, the need for hospitalization (after 12 h) and the need for admission to pediatric intensive care unit were compared between groups. The general characteristics of the sample were described as mean and standard deviation. Quantitative data were compared using Student's *t* test. Differences < 95% were considered to be significant ($p < 0.05$). McNemar's chi-square test was used for intragroup comparisons and Pearson's chi-square test or Fisher's exact test for comparisons between groups.

The risk estimate to remain in the observation room and require supplemental oxygen therapy was determined by calculating the odds ratio (OR) and its 95% confidence interval (95%CI) for time points 6 and 12 h. The data were entered into an Office Excel® spreadsheet (Microsoft, USA) and analyzed using the Statistical Package for the Social Sciences (SPSS, IBM, USA) version 12.

The research project was approved by the Research Ethics Committee of Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Brazil, protocol no. 626/08.

Results

Between September and October 2008, 60 patients were selected. The Heliox® group was composed of 20 patients and the Oxygen group of 40 patients. The demographic characteristics of each group are shown in Table 1. As for length of stay in the observation room, 11 patients in the Heliox® group still required treatment at 6 h, against 38 patients in the group receiving oxygen-driven nebulization ($p < 0.01$). Regarding the need to stay in the observation room at 12 h, 7 patients in the Heliox® group were still under treatment, against 27 patients in the Oxygen group ($p = 0.02$). Intragroup comparison showed statistically significant differences in the Heliox® group between time points 0 and 6 h ($p = 0.004$) and 0 and 12 h ($p = 0.002$), but not between time points 6 and 12 h ($p = 1.000$). In the Oxygen group, there was no difference between the three time points: 0 and 6 h ($p = 0.500$), 0 and 12 h ($p = 0.063$), and 6 and 12 h ($p = 0.250$) (Figure 1).

Compared to conventional nebulization with oxygen, the Heliox® group showed a protective behavior against the need to remain in the observation room, both for 6 and 12 h – OR: 0.06 (95%CI 0.01-0.34) and OR: 0.25 (95%CI 0.07-0.91).

Regarding the need for supplemental oxygen therapy at 6 h, 7 patients in the Heliox® group were still using oxygen, against 27 patients in the oxygen-driven salbutamol group ($p = 0.017$). At 12 h, only 3 patients in the Heliox® group still required oxygen therapy, against 14 in the oxygen-driven salbutamol group ($p = 0.1$). Intragroup comparison showed statistically significant differences in the Heliox® group between time points 0 and 6 h ($p < 0.001$) and 0 and 12 h ($p < 0.001$), but not between time points 6 and 12 h ($p = 0.125$). The Oxygen group also showed differences at the same time points: 0 and 6 h ($p = 0.004$) and 0 and 12 h ($p < 0.001$), but not between 6 and 12 h ($p = 0.063$) (Figure 2).

Table 1 - Demographic characteristics of the study population

Characteristics	Heliox® (n = 20)	Oxygen (n = 40)	p
Male	11	22	1
Mean age ± standard deviation (months)	21.8±24.1	22.3±28	0.946
Diagnosis of asthmatic crisis	9	17	0.853
Clinical diagnosis of bronchiolitis with response to bronchodilator therapy	11	23	0.853

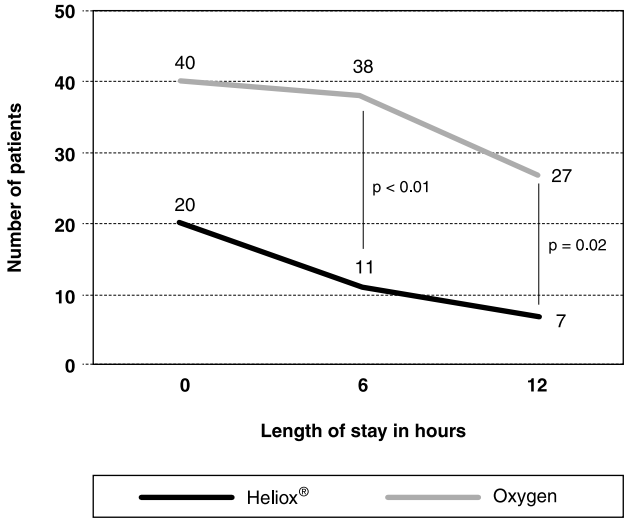

Figure 1 - Length of stay in the observation room of patients using oxygen vs. Heliox®

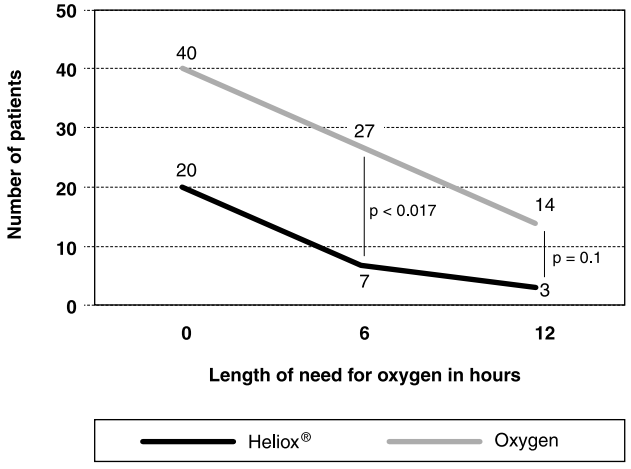

Figure 2 - Need for oxygen therapy in patients using oxygen vs. Heliox®

Compared to conventional nebulization with oxygen, the Heliox® group showed a protective behavior against the need to remain on supplemental oxygen, both for 6 and 12 h – OR: 0.26 (95%CI 0.07-0.91) and OR: 0.32 (95%CI 0.05-1.45).

Once the observation phase was concluded, at the end of 12 h, 6 patients in the Heliox® group required hospitalization, against 19 in the Oxygen group (p = 0.195). One patient in each group had unfavorable clinical outcome, and admission to intensive care unit was indicated.

Discussion

Our results indicate that a balanced helium-oxygen mixture (80:20), used in a closed system for administration of salbutamol, is effective for treatment of childhood obstructive disease.

Compared to the conventional technique of administration of inhaled bronchodilator drugs, the use of the gas mixture showed a lower risk of staying in the observation room after 6 and 12 h of treatment. Likewise, the gas mixture also showed a lower risk of requiring supplemental oxygen, mainly in the first 6 h of treatment.

These more favorable responses, observed in the first hours of treatment, may be related to an optimization of drug deposition within the airways. The benefits resulting from the physical properties of gas mixtures balanced with up to 40% helium are well described in the literature.[12] Within this range (21 to 40% oxygen), it is possible to preserve the benefits of a gas mixture of lower density and lower coefficient of resistance while maintaining a more constant gas flow through the airways. It is therefore possible that patients with severe obstructive conditions, secondary to bronchospasm, debris or cellular residues, may benefit from this therapy.[13]

Although the physical properties of helium are well known for decades, its ability to drive bronchodilator substances has not always been accepted. Only in recent years this ability has been clearly evidenced, associated with the fact that the control of gas flow and concentration requires specifically adjusted equipment.[5] Although a fixed concentration of the gas mixture (80:20) was administered to all patients, the device used (Heliomix®) allowed adjustments in helium and oxygen delivery. This is important because some studies employ techniques of continuous nebulization when using the gas to drive nebulizer therapy.[14] Thus, Heliomix® could ensure up to 40% oxygen in the mixture, or even deliver 100% oxygen if hypoxemia was determined.

In our study, we decided to test some benefits resulting from the early administration of Heliox® (in the first six nebulization cycles, performed within the first 2 h of treatment). This strategy was devised for some reasons. The first was based on the principle of not changing the routine treatment employed in the department concerning administration of bronchodilator substances (both in asthma and bronchiolitis), considering dose and administration intervals. The second resulted from the observation of some discomfort in using the closed system with adjustable face mask, mainly in younger patients and for longer periods of time.

Although studies using this strategy can be found in the literature,[15,16] we believe that, even for a 2-h period, we would have great difficulty in maintaining the nebulizer system adapted in a continuous manner to the patient's face in a significant number of cases.

Our study has some limitations. The most important one is related to the small sample size. We cannot confidently establish that the lack of benefits found after 6 h has not been determined by the combination of an insufficient number of patients with a less marked effect of the gas mixture. Taking into consideration the significant differences found between groups at 6 h, we believe that this therapy is useful in these patients.

Regarding the use of a bronchodilator substance (salbutamol) in patients with bronchiolitis, a disease with variable clinical response to this therapy, it is important to reinforce some considerations. Its use was only indicated for patients with established diagnosis of bronchiolitis in whom initial nebulization showed some signs of clinical benefit for the patient. The literature reports that 20 to 50% of patients with bronchiolitis might benefit from such therapy.[17-20] This criterion minimizes a potential selection bias; however, some studies using Heliox® in the treatment of bronchiolitis have not employed this strategy.[7,20] More robust designs, such as clinical trials, have used randomization in order to minimize, among other reasons, a potential effect of variability in bronchodilator response among patients with acute viral bronchiolitis. The study design used herein lacks the power a randomized clinical trial or the possibility to control potential limitations inherent in its own conception. However, we cannot fail to mention that matching and similarity between the two groups can minimize potential biases.

Although investigation of respiratory viruses by immunofluorescence of nasopharyngeal aspirates is part of the routine care of patients with a clinical diagnosis of acute viral bronchiolitis, this technique is only indicated in our emergency department for patients who meet criteria for hospitalization. Thus, such data cannot be added to the clinical diagnosis of bronchiolitis. A significant number of patients allocated in the study showed clinical improvement, not meeting the criteria that would justify their hospitalization. As already mentioned, the research team did not interfere with practices determined by the medical team, despite recognizing that such information could provide more security to the clinical diagnosis of the disease.

Thus, we found that the use of helium-oxygen mixture (Heliox®) may be useful in the clinical management of pediatric patients with obstructive airway disease that responds to bronchodilator therapy. Its use appears to be associated with a lower risk of staying in the observation room and a decreased need for supplemental oxygen during the first hours of treatment for obstructive disease responsive to bronchodilator therapy.

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