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The effect of albuterol with heliox versus albuterol nebulization in acute asthma exacerbation: a randomized controlled clinical trial

Abstract

Introduction: Asthma is one of the most common chronic disorders of the respiratory tract. Thus, this study intended to evaluate the clinical effects and the peak flow metric effects of nebulized albuterol with heliox versus albuterol nebulization in acute asthma exacerbation.

Material and methods: In this randomized clinical trial study, 109 patients with acute asthma attacks admitted to the emergency departments (EDs) in Golestan Hospital were enrolled. The patients were divided randomly into two groups: the intervention and control groups. The intervention group was nebulized with heliox (helium/oxygen-70: 30) plus albuterol with a 10 mL/min dose for 20 minutes three times, which lasted 60 minutes. The control group received standard treatment (albuterol in combination with oxygen).

Results: The results showed that the mean scores of FEV1 and PEFR after 20 minutes were significantly different in the two groups, as FEV_1 scores in the intervention group were 2.76 and 3.01 at 20 and 60 minutes, respectively, while FEV_1 scores in the control group were 1.99 and 2.64, respectively ($p < 0.001$). In addition, PEFR scores in the intervention group at 20 and 60 minutes were 299.24 and 310.57, respectively. However, these scores in the control group were 237.98 and 274.56, respectively ($p < 0.001$).

Conclusion: The results showed that the use of heliox in t eating severe asthma attacks could be regarded as a different standard treatment that can lead to significantly better control of asthma attacks in the short term.

Key words: respiratory tract, asthma, heliox, PEFR, FEV_1, emergency medicine

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Introduction

Asthma is one of the most common chronic diseases around the world. Currently, there are about 300 million patients with asthma globally, and it is predicted that 100 million people will be added to the population of asthma patients by the year 2025 [1]. Since the past 30 years, the prevalence of asthma in developed countries has increased so that about 10–12% of adults and 15% of children in these countries are suffering from this disease. However, the prevalence of asthma in developing countries was much less than in economically developed countries over the past years. Still, now it appears to be rising with increasing urbanization [2, 3]. Asthma is currently considered a common cause of visits to emergency departments (EDs) and urgent care clinics. In the United States, from 2001 to 2003, asthma was, on average, responsible for about 4210 deaths per year, and about 504000 hospitalizations, and 1.8 million emergency room visits a year [4].

In the Global Burden of Asthma report released in 2003, the prevalence rate of asthma in the total population of Iran was estimated to be about 5.5%. Since no definite cure has been already found for asthma, most sufferers of this disease can control it by following doctors' instructions and taking the prescribed anti-inflammatory and soothing drugs [5]. However, asthma attacks are dangerous and may be life-threatening. The high concentration of oxygen through a mask intended to achieve oxygen

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saturation above 90% and prescribed high doses of the short-acting inhaled β2-agonists form the basis of the treatment regime for asthma [1]. Interest in the use of heliox as a mixture of helium-oxygen was raised in the early 1980s when deaths from asthma attacks began [6]. During asthma attacks, all patients do not give an appropriate response to bronchodilators and corticosteroids. However, due to its low density, heliox is believed to work more efficiently than oxygen and a mix of oxygen/air through the airways [7]. Heliox's low density and viscosity aid in promoting larger and smoother gas movement, lowering airway resistance, and lowering work of breathing in some individuals [8]. Results of several studies conducted by Dorfman et al. [9], Henderson et al. [9], and Kass et al. [7] showed that after the conventional treatment of intravenous prednisolone and albuterol and record PEFR and FEV_1, a group of patients receiving Heliox gas and during the breathing gas, also again PEFR, FEV_1 and the evaluated clinical symptoms showed that and the other group of patients breathed oxygen-free helium, and again PEFR and FEV_1 were recorded and clinical symptoms that some were followed by the improvement of respiratory function and others did not show any change in respiratory function.

This study intended to evaluate the effects of heliox gas on treating patients with acute exacerbation of asthma referring to EDs in Golestan Hospital. The outcomes are expected to be used for faster treatment, fewer hospitalizations, and improved life quality of asthma patients.

Materials and methods

Trial design

This prospective clinical trial study included all patients with acute asthma attacks referring to EDs in Golestan Hospital in 2015. At first, the patients were visited, assessed clinically, and examined physically by a physician. The patients' vital signs were recorded in their files, and rehabilitation equipment was ready at the patients' bedside before any test.

Participants

Inclusion criteria

Patients at the minimum age of 18 and maximum age of 55 years with acute bronchospasm symptoms referred to EDs in Golestan Hospital.

Exclusion criteria

Smokers with the consumption of over ten packs of cigarettes per year, patients with chronic bronchitis, acute medical problems, heart and coronary artery diseases, cardiac arrhythmia, pregnant women, and those patients with the beta-agonists nebulizer treatment over the last 6 hours. The procedure taken to conduct the study was explained to all the patients, and accordingly, those who did not confirm their agreement in writing to the study's terms and conditions were excluded.

Interventions

Before the intervention began, based on the patients' history, physical examination of the patients by talking on the sentence or phrase or word, *GCS status*, use of sub-breathing muscles, wheezing, and parameters of respiratory rate, heart rate, blood pressure, and arterial blood oxygen and clinical status were assessed. Based on Borg Dyspnea Scale, degrees of the patient's difficulty in breathing were estimated to be 17: from 0 to 10 (0 = lack of difficulty in breathing, 0.5 = completely low, 1 = very low, 2 = low, 3 = medium, 4 = relatively intense, 5 = intense, 6 = very intense, 7 = very intense, 8–9 = completely intense, and 10 = maximum amount of difficulty in breathing). PEFR and FEV_1 were recorded in the minutes of zero. Then, based on the severity of the asthma attack, the patients underwent the standard treatment for asthma, considering the protocols of reference books [1]. Those patients with mild to moderate severity of the attacks were treated with nebulized albuterol 2.5 mg over 20 minutes in three doses and with ipratropium bromide (in case they were previously treated with this drug and responded positively) 0.5 mg over 20 minutes at three doses and 50 mg of oral prednisolone (in the absence of a direct response to albuterol). At the same time, those patients with extremely severe attacks were treated with nebulized albuterol 5 mg over 20 minutes in three doses and ipratropium bromide (if they responded positively to the treatment with this drug) 0.5 mg over 20 minutes at three doses and 50 mg of oral prednisolone.

In the case group, heliox (a mix of helium/oxygen 30:70) plus albuterol in 10 mL/min was nebulized for 20 minutes three times in 60 minutes. It was then measured and recorded in all patients in 20, 40, and 60 minutes after the start of the intervention of PEFR and FEV_1. Similarly, for 60 minutes while clinical status [1] based on clinical symptoms of *GCS status*, speaking, breathing rate, heart rate, paradoxical pulse, use of auxiliary respiratory muscles and wheezing, were re-evaluated, and compared.

Outcomes

Clinical parameters, PEFR and FEV_1, were measured before the treatment and within minutes 20, 40, and 60. Respiratory rate, heart rate, blood pressure, and the percentage of oxygen saturation were recorded, and finally, the difference between these parameters in the two groups was statistically analyzed. If the patients in both groups did not respond appropriately to the therapeutic intervention and suffered a general deterioration and worsening dyspnea, the intervention was repeated, or other lines of the treatment were used. If it was done before the 60 minutes, the patient was excluded from the study. Finally, patients with a history of clinically and paraclinical confirmed asthma or a history of asthma diagnosed by spirometry for two weeks remained in the study. Otherwise, they were removed from the analysis.

Randomization

According to the inclusion and exclusion criteria, a sample size of patients was randomly assigned to two groups: the case and control groups.

Blinding

All gases were provided from independent tanks and a mask. Unlike doctors, the patients did not know what gas they had breathed.

Statistical methods

All the data about the patients, including demographic factors, clinical symptoms, was recorded on the checklist made by the executor and was entered into the SPSS version 22. Then, the statistical analyses were performed in two parts: descriptive and analytical. All demographic and clinical properties of the patients were then reported based on descriptive criteria. In the analytical part, based on the statistical assumptions, proportional parametric and non-parametric tests were conducted. The Chi-square test was used to analyze the qualitative data, while to compare the quantitative data, the independent t-test was used. In case of lack of normality assumption, the Mann-Whitney was used. All tests were examined at the level of 5%.

Results

This study was conducted on 109 patients who were admitted to EDs. The patients were randomly divided into two groups of 55 and 54 (Figure 1). Of the 109 patients studied, 47 (43.1%) were male, and 62 patients (56.1%) were female. The mean age of the patients in the study was 37.6 ± 71.10 years, as the lowest age was 18 years, while the highest age was 55 years (Table 1).

It was also found that the mean FEV_1 was significantly different in the two groups after 20 minutes. In effect, the mean FEV_1 in the standard treatment group plus heliox in 20 minutes was 2.76, while in the standard treatment group, it was 1.99. As the mean values showed, the difference was statistically significant ($p < 0.001$). Furthermore, the mean FEV_1 in the 60th minute in the standard treatment group plus Heliox was 3.0176, while in the standard treatment group, it was 2.64. As the mean values showed, this difference was also statistically significant ($p < 0.001$) (Figure 2). In addition, from 20 minutes later, the mean difference of PEFR in the two groups was statistically significant. In the standard treatment group plus Heliox after 20 minutes, the mean PEFR was 299.24, while in the standard treatment group, it was 237.98. As the mean values showed, the difference was statistically significant ($p < 0.001$). Moreover, the mean difference of PEFR after 40 minutes in the standard treatment group plus Heliox was 310.57, while in the standard treatment group, it was found to be 274, which the difference was statistically significant ($p < 0.001$); however, the mean difference of PEFR was not significant in the 60^{th} minute (Table 2, Figure 3).

In the examination of hemodynamic variables, it was found that the difference between heart rate, respiratory rate, systolic and diastolic blood pressure, and arterial blood oxygen during the first 60 minutes was not statistically significant between the two groups ($p > 0.05$) (Table 3). It was also found that the frequency of the intensity of wheezing within 60 minutes was similar between the two groups. The type of talking and dyspnea after 20 minutes between the two groups was also found to be the same, and 40 minutes later, all the patients were able to talk using the sentence (Table 4).

Discussion

Initially, Barach et al. in 1935 showed the usefulness of heliox in treating patients with respiratory tract obstruction [10]. After that, in 1980, heliox was used as a treatment for patients with severe asthma. Heliox reduced lung inflammation and also ameliorated asthma complications [11].

This study showed that the mean FEV1 and PEFR after 20 minutes in the treatment group

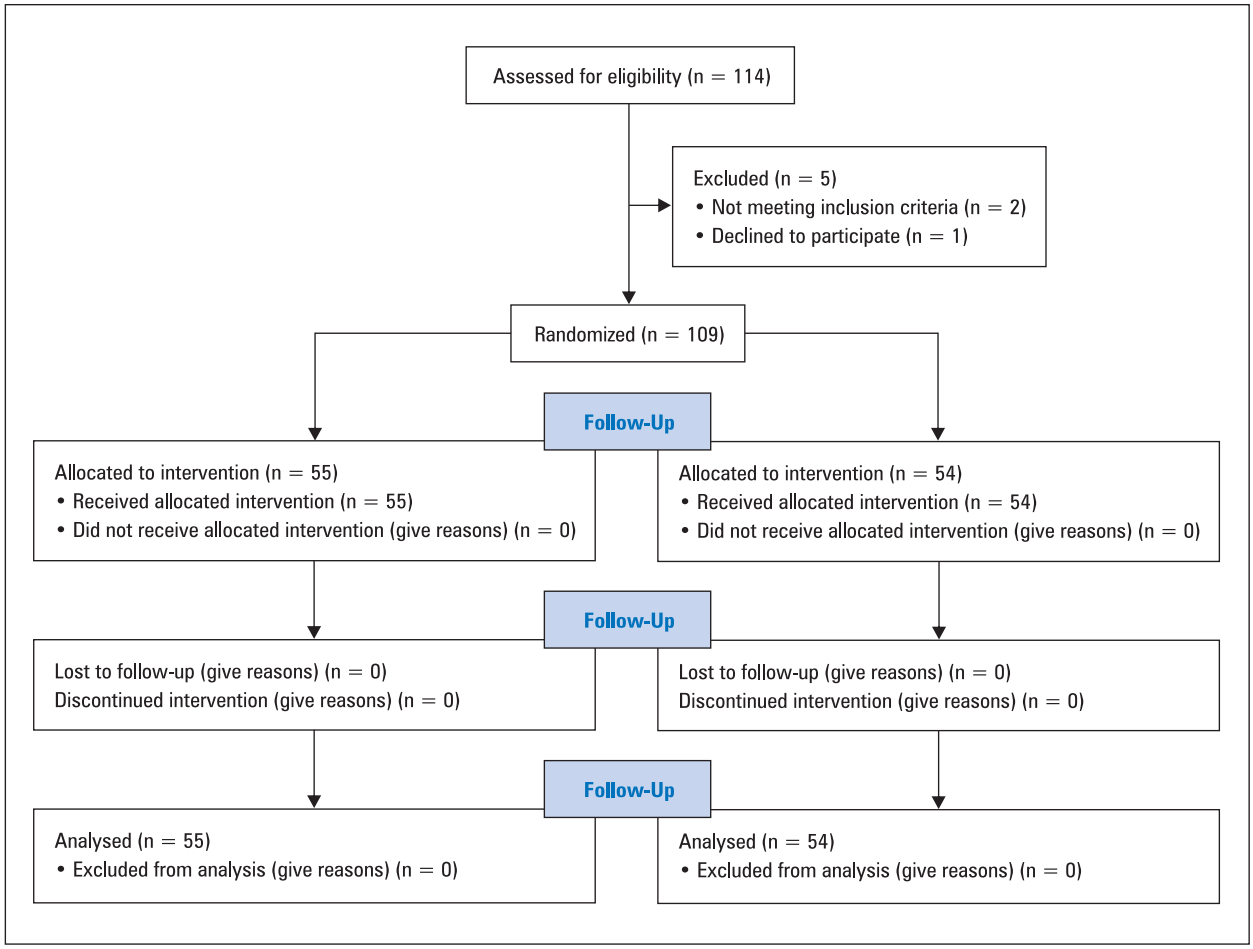

Figure 1. Flow diagram chart

Table 1. Frequency of demographic variables and clinical symptoms on arrival in the two groups of patients

Group / Variables		Standard treatment plus heliox	Standard treatment	P-value
Age (years)		36.11 ± 3.37	37.81 9 ± 0.41	0.836
Gender	**Male**	23 (42.6%)	24 (43.6%)	0.912
	Female	31 (57.4%)	31 (56.4%)	
Duration of catching (year)		4.24 ± 1.83	4.2 ± 1.86	0.909
Type of talking	**Phrase**	26 (48.1%) 26(48.1%)	28 (50.9%)	0.773
	Sentence	28 (51.9%)	27 (49.1%)	
Wheezing		24 (44.4%)	30 (54.5%)	0.292
Dyspnea		17 (31.5%)	18 (32.7%)	0.889

with heliox significantly increased. However, the mean difference of PEFR after 60 minutes between the two other groups was not significant. It was also found that there was not a statistically significant difference between the two groups in vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and arterial blood oxygen at different times. Dispense severity between the two groups was found not to be statistically significant when discharging. No significant difference was found between the two groups

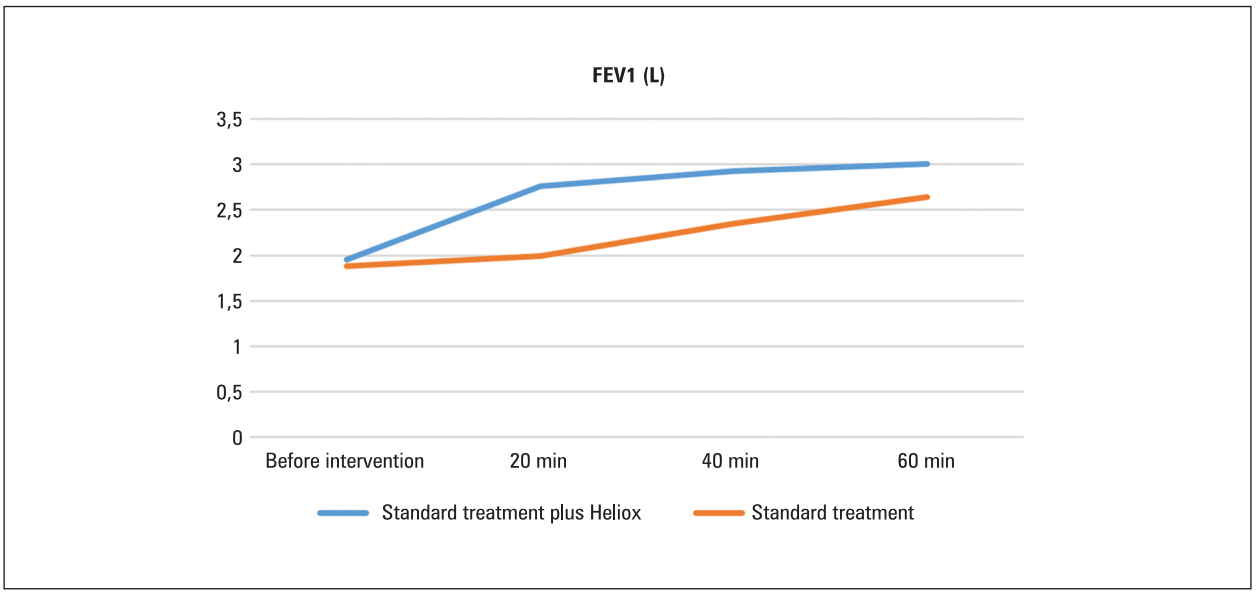

Figure 2. FEV_1 (L) trend during study time points in both groups

Table 2. Peak flow metric variables in the two groups of patients studied during the 60 minutes

Group / Variables		Standard treatment plus heliox	Standard treatment	P-value
FEV_1 (L), Mean ± SD	Before the intervention	1.95 ± 0.49	1.88 ± 0.40	0.424
	During 20 minutes	2.76 ± 0.64	1.99 ± 0.38	< 0.001
	During 40 minutes	2.93 ± 0.6	2.35 ± 0.45	< 0.001
	During 60 minutes	3.01 ± 0.59	2.64 ± 0.46	< 0.001
PEFR (L/min), Mean ± SD	Before the intervention	213.74 ± 93.26	213.54 ± 41.97	0.989
	During 20 minutes	299.24 ± 78.35	237.98 ± 42.42	< 0.001
	During 40 minutes	310.57 ± 74.72	274.56 ± 49.54	< 0.004
	During 60 minutes	316.55 ± 73.016	303.69 ± 50.076	0.287

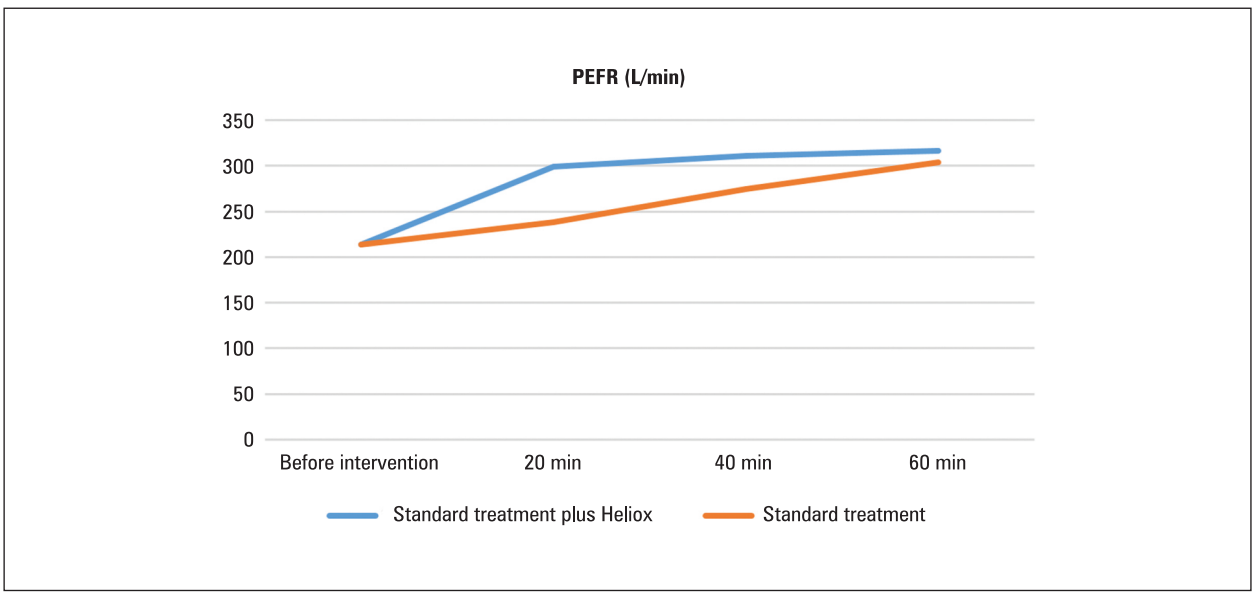

Figure 3. PEFR (L/min) trend during study time points in both groups

Table 3. Hemodynamic variables in the two groups of patients studied during the 60 minutes

Group / Variables		Standard treatment plus heliox	Standard treatment	P-value
Heart rate (per minute)	Before the intervention	85.6 2± 15.01	81.09 ± 10.72	073/0
	During 20 minutes	83.4 ± 15.48	78.94 ± 9.7	0.076
	During 40 minutes	82.53 ± 14.51	77.8 ± 14.43	0.095
	During 60 minutes	80.66 ± 15.41	76.58 ± 11.02	0.114
Respiratory rate (in minutes)	Before the intervention	33.75 ± 7.57	33.9 ± 4.58	0.901
	During 20 minutes	30.98 ± 6.59	30.29 ± 2.89	0.483
	During 40 minutes	29.44 ± 8.44	28.12 ± 4.25	0.305
	After 60 minutes	27.2 ± 7.31	25.83 ± 3.17	0.211
Diastolic blood pressure (mmHg)	Before the intervention	79.9 ± 11	77.67 ± 10.83	0.288
	During 20 minutes	81.01 ± 11.94	77.67 ± 10.83	0.128
	During 40 minutes	82.66 ± 10.63	81.34 ± 8.72	0.48
	During 60 minutes	83.38 ± 12.33	81.34 ± 8.72	0.321
Systolic blood pressure (mmHg)	Before the intervention	128.83 ± 20.49	121.52 ± 15.81	0.039
	After 20 minutes	130.77 ± 21.14	124.7 6± 18.24	0.115
	During 40 minutes	131.51 ± 19.81	124.76 ± 18.24	0.067
	During 60 minutes	134.35 ± 22.4	131.18 ± 19.82	0.436
Arterial blood oxygen%	Before the intervention	94.07 ± 2.21	93.85 ± 2.17	0.602
	During 20 minutes	94.48 ± 1.77	94.47 ± 1.6	0.979
	During 40 minutes	95.01 ± 1.75	95.07 ± 1.53	0.864
	During 60 minutes	95.96 ± 1.84	95.89 ± 1.73	0.834

Table 4. Frequency and clinical symptoms in the two groups of patients during 60 minutes

Group / Variables		Standard treatment plus heliox	Standard treatment	P-value
Wheezing	During 20 minutes	9 (16.7%)	6 (10.9%)	0.383
	During 40 minutes	2 (3.7%)	0	0.15
	During 60 minutes	2 (3.7%)	0	0.15
Type of talking after 20 minutes	Phrase	4 (7.4%)	3 (5.5%)	0.678
	Sentence	50 (92.6%)	52 (94.5%)	
Dyspnea during 20 minutes		0	1(1.8%)	0.32

in terms of the symptoms like wheezing and talking at discharge.

In a randomized control study conducted on the effect of heliox (70:30) compared with O_2 30% on acute exacerbation of asthma in 1999, Kass and Terregino reported that 9 out of 23 adult patients with exacerbation of acute asthma in the treatment group improved more than 25% in PEFR after 20 minutes compared to 2 patients in the control group. They also found that treatment with heliox rapidly reduced dyspnea compared with the control group [7]. The results of PEFR reported in this study agree with our findings, but in dyspnea, a significant difference was not found between patients receiving heliox and albuterol. Moreover, Kress et al. studied the effect of albuterol nebulized with heliox in ameliorating asthma exacerbations during emergency room visits. The results showed that during asthma exacerbations, albuterol nebulized plus heliox significantly increased more spirometric parameters than albuterol nebulized

plus oxygen [10]. These findings are also in line with our results.

In 2000, in a randomized prospective controlled study comparing the use of a helium-oxygen mix of 80:20 and the air in addition to continuous nebulizer of albuterol and ipratropium in 40 patients, Dorfman et al. concluded that there was no significant difference between the treated and control groups. In effect, no significant differences were seen in respiratory rate changes, systolic and diastolic blood pressure, oxygen saturation, and PEFR [9]. The findings of this study regarding vital signs and oxygen saturation were similar to our research findings. Still, the results of PEFR were different from our findings, which might be due to the diverse populations examined in the two studies and the other sample sizes used. The sample size in our study was three times more than the sample size used in their research.

On the other hand, an important cause of the difference in the results of our study and the study conducted by Dorfman et al. is the different doses and combinations of drugs used in the two studies. A mix of heliox albuterol was used in our research, and favorable results were observed in PEFR and FEV_1 indicators. Still, in the survey, helium and oxygen mix of 80:20 and the air were used together with a continuous nebulizer of albuterol and ipratropium.

In 2010, in a review study looking at ten studies conducted on 544 patients with acute asthma (7 studies conducted on adults and three studies on children with pulmonary function test recorded from 15–60 minutes), Rodrigo and his colleagues found that the use of heliox improved pulmonary function only in a subset of the patients with severe defects of pulmonary function [12].

Rodrigo and colleagues in 2013 showed that nebulizer heliox (70:30) and β2 agonists used for children and adults with acute asthma led to a statistically significant average change in the peak expiratory flow rate (PEFR). The subgroup analysis showed that patients with severe and very severe asthma had a noticeable improvement in the peak expiratory flow compared to mild to moderate acute asthma patients. Heliox also significantly reduced the risk of hospitalization and the severity of asthma attacks. These data support the use of heliox just as nebulizer β2 agonists in the usual treatment of patients with acute asthma [13]. The results of this study are consistent with the findings of our research.

In a study in 2014 conducted to compare the effects of heliox and nebulizer air-driven in the treatment of asthma, El-Khatib MF et al. showed that changes in FVC, FEV1/FVC, FEF (25–75%), FEF MAX, FEF25%, FEF50%, FEF 75% compared with baseline in patients with $FEV_1 <$ 50% and receiving Heliox is more than another that this indicates that Heliox is better in the treatment of acute asthma [14]. Moreover, other studies in different parts of the world confirm our results. For instance, Kim et al. showed that nebulized albuterol delivered by heliox significantly improved clinical complications of patients with asthma as more than albuterol produced by oxygen [15]. Besides, El-Khatib et al. (2014), Lee et al. (2005), and de Boisblanc et al. (2000) reported findings similar to our results [14, 16, 17].

Conclusion

As the results showed, it can be concluded that the beneficial effects of heliox in severe asthma attacks can be considered as an adjuvant treatment in addition to the standard treatment for patients with severe asthma attacks admitted to EDs. It is believed that heliox can lead to considerably better control of asthma attacks in the short term.

Conflict of interest

None declared.

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