



Contents lists available at ScienceDirect



Heliox-driven β_2 -agonist nebulization for children and adults with acute asthma: a systematic review with meta-analysis

Gustavo J. Rodrigo, MD^{*}; and Jose A. Castro-Rodriguez, MD, PhD[†]

^{*} Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay

[†] Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

ARTICLE INFO

Article history:

Received for publication July 21, 2013.

Received in revised form September 17, 2013.

Accepted for publication September 27, 2013.

ABSTRACT

Background: The effect of heliox as a nebulizer β_2 -agonist driving gas in acute asthma remains controversial.

Objective: To perform a systematic review with a meta-analysis of randomized trials designed to evaluate the efficacy of heliox versus oxygen in driving β_2 -agonist nebulization in patients with acute asthma.

Methods: A search was conducted of all randomized controlled trials published before August 2013. Primary outcomes were change in spirometric measurements and severity composite score (pediatric studies); secondary outcomes were hospitalizations and serious adverse effects.

Results: Eleven trials from 10 studies (697 participants) met the inclusion criteria (7 included adults and 3 included children). The mean duration of heliox therapy was 120 minutes and the most common helium–oxygen mixture used was 70:30. Patients receiving heliox presented a statistically significant difference for mean percentage of change in peak expiratory flow (17.2%; 95% confidence interval 5.2–29.2, $P = .005$). Post hoc subgroup analysis showed that patients with severe and very severe asthma showed a significant improvement in peak expiratory flow compared with those with mild to moderate acute asthma. Heliox-driven nebulization also produced significant decreases in the risk of hospitalizations (odds ratio 0.49, 95% confidence interval 0.31–0.79, $P = .003$) and severity of exacerbations (pediatric studies; standard mean difference -0.74 , 95% confidence interval -1.45 to -0.03 , $P = .04$). There were no group differences for serious adverse effects.

Conclusion: This review suggests that heliox benefits in airflow limitation and hospital admissions could be considered clinically significant. Data support the use of heliox as a nebulizing β_2 -agonist driving gas in the routine care of patients with acute asthma.

© 2013 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Inhaled rapid-acting β_2 -agonists (continuously or at regular intervals), systemic corticosteroids, and supplemental oxygen are the treatment of choice for acute severe asthma.^{1–3} During the past 10 years, β_2 -agonist heliox-driven nebulization has gained wider use in acute care settings. The latter is based on the fact that heliox (a helium–oxygen mixture) increases the deposition of inhaled particles to the distal airways in patients with severe asthma. This fact presents the potential benefit of being able to deliver aerosols deeper into the distal airways and alveoli during severe airway obstruction compared with oxygen or air.^{4,5} Patients with acute severe asthma could be better assisted by the delivery of aerosolized medications with heliox rather than room air or oxygen.^{6,7}

Thus, the objective of this study was to evaluate the efficacy of heliox versus oxygen in driving β_2 -agonist nebulization in patients with acute asthma. The authors hypothesized that patients with acute asthma treated with nebulized β_2 -agonists driven by heliox would show greater clinical improvement.

In the more than 60 years since its use was first proposed, the role of heliox in treating patients with acute asthma remains controversial because the evidence arises from small randomized trials or uncontrolled studies. Furthermore, systematic reviews of randomized trials published to date have included different applications and indications of heliox, which obscures their conclusions.^{8–10} To the authors' knowledge, there have been no systematic reviews comparing heliox-driven nebulized β_2 -agonists with standard care in asthma exacerbations.

Methods

The authors adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this systematic review.¹¹ A protocol was prospectively developed

Reprints: Gustavo J. Rodrigo, MD, Departamento de Emergencia, Hospital Central de las Fuerzas Armadas, Av 8 de Octubre 3020, Montevideo 11300, Uruguay; E-mail: gustavo.javier.rodrigo@gmail.com.

Disclosures: Authors have nothing to disclose.

Funding Sources: This work was funded solely from the salaries of Drs Rodrigo and Castro-Rodriguez.

detailing the study objectives, primary and secondary outcomes, criteria for study selection, approach to assessing study quality, data synthesis, and statistical analysis. This study was registered with the International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO/>; identifier, CRD42013003842).

Search and Selection Criteria

The authors identified published studies from MEDLINE, EMBASE, CINAHL, SCOPUS, and the Cochrane Controlled Trials Register (CENTRAL; August 2013) databases using the terms *heliox* or *helium* or *oxygen*, and *asthma*. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all the following criteria: (1) randomized trials without language restriction; (2) studies including children or adult (>18-year-old) patients presenting to an emergency department for treatment of acute asthma; (3) comparison of heliox-powered β_2 -agonist nebulization with air- or oxygen-powered β_2 -agonist nebulization (control); and (4) report at least 1 of the following outcomes: change in spirometric measurements (peak expiratory flow [PEF] or forced expiratory volume in the first second) and change in asthma evaluation composite scores (pediatric studies) as primary variables and hospital admissions and serious adverse events (SAEs) as secondary variables. The assessment timing was extended from 30 minutes to 4 hours. An SAE was defined as the presence of hypoxemia (oxygen saturation by pulse oximetry <90%) during the protocol.

Data Extraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by the 2 authors (G.J.R. and J.A.C.-R.). From the full text, they independently assessed all studies for inclusion based on criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. Bias was assessed according to recommendations outlined in the Cochrane handbook¹² for the following items: (1) adequacy of sequence generation; (2) allocation concealment; (3) blinding of participants and investigators; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other bias. Each potential source of bias was graded as high, low, or unclear risk of bias. Disagreements were discussed and resolved by consensus.

Data Analysis

Analysis was by intention to treat and included all participants to minimize bias. Outcomes were pooled using mean differences or standard mean differences (inverse variance method) and Mantel-Haenszel odds ratios or risk differences (when there are no events in either group). When effect estimates were significantly different between groups, the number needed to treat for benefit (NNTB) or for harm was obtained. Heterogeneity was measured by the I^2 test¹³ (<25%, absent; 26%–39%, unimportant; 40%–60%, moderate; 60%–100%, substantial). Because selected studies differed in the mixes of participants and interventions, a random-effects model was performed to address this variation across studies for all outcomes.¹⁴ As an a priori subgroup analysis, the authors explored the influence of the following factors: nebulizer flow rate adjustment to ensure equivalent aerosol output (yes vs no), use of a system that ensured delivery of a high helium concentration (yes vs no), age (children vs adults), and acute asthma severity (moderate to severe [PEF $\geq$ 50% of predicted] vs severe to very severe [PEF <50% of predicted]). Subgroups were compared using the residual χ^2 test from the Peto odds ratios.¹⁵

Predefined sensitivity analysis was performed to explore the influence of the statistical model (fixed vs random effects), sample size ($n \leq 40$ vs $n > 40$), and methodologic quality (high vs low) on the size effect. Potential publication bias was analyzed through the use of a funnel plot and the Egger test.¹⁶ A P value no greater than .05 (2-tailed test) was considered significant except for the Egger test ($P < .1$, 90% confidence interval [CI]). Meta-analysis was performed using Review Manager 5.2.5 (Cochrane IMS, Cochrane Library, Oxford, United Kingdom).

Results

Eleven trials from 10 ten studies^{17–26} (697 patients) met the entry criteria (Fig 1). Seven studies ($n = 584$) included adults^{17–21,23,26} and 3 included children ($n = 113$; Table 1).^{22,24,25} One study included 2 different trials.²³ Most studies enrolled children and adults with acute severe asthma. Four studies used a helium–oxygen mixture of 80:20,^{18,19,23,26} 6 used a 70:30 mixture,^{17,20–22,24,25} and 1 used a 79:21 mixture.²¹ In 5 studies, β_2 -agonists were administered in a continuous form.^{18,22,24,25} Four studies used a protocol designed to ensure delivery of a high concentration of heliox to patients' airways,^{19,22,23,25} and in 3 studies the nebulizer flow rate was adjusted to warrant equivalent aerosol output.^{22,23,25} Inhaled albuterol and systemic corticosteroids were used in almost all trials. The mean duration of heliox

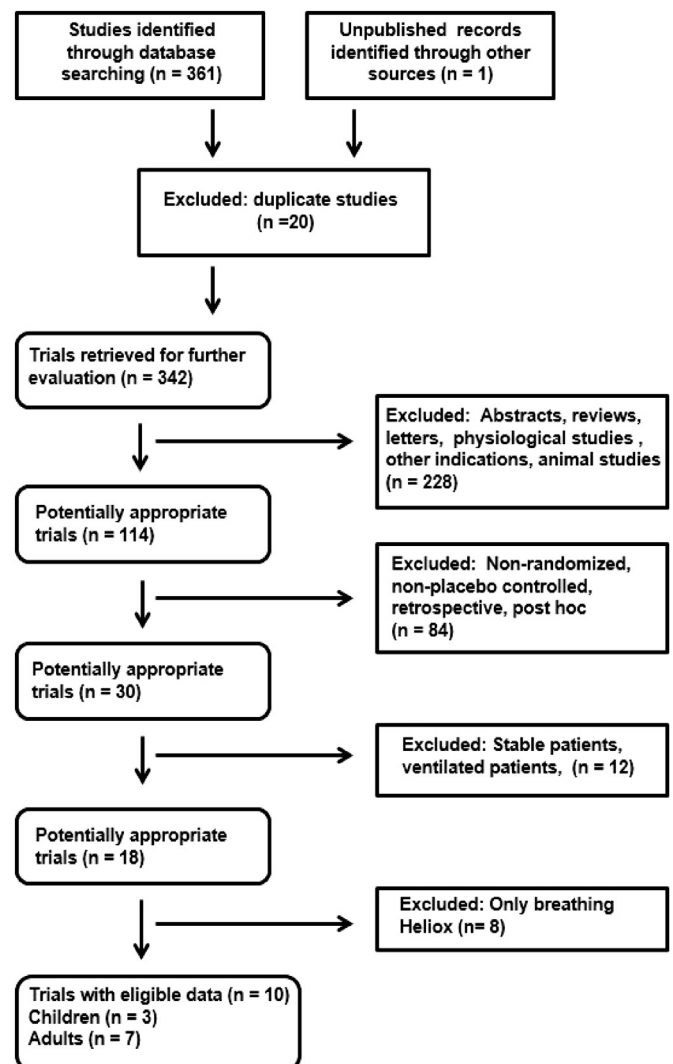


Figure 1. Flowchart for identification of included studies.

Table 1
Characteristics of included studies

Study	Design	Randomized patients, n (% female)	Age (y), mean (range)	Severity of exacerbation	Primary outcome	Protocol
Henderson et al ¹⁷	R, SB	205 (53)	44 (18–65)	mild–moderate	PEF, FEV ₁	70:30 helium–oxygen- vs 100% oxygen-driven ALB nebulization (5 mg) × 3
Dorfman et al ¹⁸	R, CT, UB	40 (51)	29 (?)	moderate–severe	PEF	80:20 helium–oxygen- vs 21% oxygen-driven ALB continuous nebulization (45 mg/kg) + IB 1.0 mg
Kress et al ¹⁹	R, CT, SB	45 (64)	34.5 (18–50)	severe	FEV ₁	80:20 helium–oxygen- vs 100% oxygen-driven ALB nebulization (2.5 mg) × 3; SCS in all patients; protocol designed to ensure delivery of high concentration of heliox
Rose et al ²⁰	R, CT, SB	39 (78)	37 (2–21)	severe	PEF, FEV ₁	70:30 helium–oxygen- vs 30% oxygen-driven ALB continuous nebulization (15 mg/h)
Xie et al ²¹	R, CT, UB	24 (73)	41 (26–58)	mild–moderate	PEF, FEV ₁	79:21 helium–oxygen- vs 21% oxygen-driven FEN nebulization (0.5 mg) × 3
Kim et al ²²	R, CT, UB	30 (50)	7.3 (2–18)	moderate–severe	pulmonary index score	70:30 helium–oxygen- vs 100% oxygen-driven ALB continuous nebulization (15 mg/h); IB + SCS in all patients; protocol designed to ensure delivery of high concentration of heliox; heliox flow rate adjusted
Lin Lee et al ²³ (trial a)	R, CT, DB	80 (72)	33.6 (18–50)	severe	PEF	80:20 helium–oxygen- vs 21% oxygen-driven ALB nebulization (2.5 mg) × 3; protocol designed to ensure delivery of high concentration of heliox; heliox flow rate adjusted
Lin Lee et al ²³ (trial b)	R, CT, DB	80 (72)	33.6 (18–50)	very severe	PEF	80:20 helium–oxygen- vs 21% oxygen-driven ALB nebulization (2.5 mg) × 2; SCS in all patients; protocol designed to ensure delivery of high concentration of heliox; heliox flow rate adjusted
Rivera et al ²⁴	R, CT, DB	41 (39)	7.5 (3–16)	moderately severe	dyspnea	70:30 helium–oxygen- vs 30% oxygen-driven ALB continuous nebulization (15 mg/h); SCS in all patients
Bigham et al ²⁵	R, CT, DB	42 (64)	7.7 (2–21)	severe	LOS	70:30 helium–oxygen- vs 30% oxygen-driven ALB continuous nebulization (15 mg/h); SCS in all patients; protocol designed to ensure delivery of high concentration of heliox; heliox flow rate adjusted
Arias Ortiz et al ²⁶	R, CT, UB	71 (63)	21 (?)	moderate–severe	LOS	80:20 helium–oxygen- vs 20% oxygen-driven ALB nebulization (1 mg) × 3; SCS in all patients; treatment at discretion of treating physician

Abbreviations: ALB, albuterol; CT, controlled trial; DB, double blinded; FEN, fenoterol; FEV₁, forced expiratory volume in first second; IB, ipratropium bromide; LOS, length of hospital stay; PEF, peak expiratory flow; R, randomized; SB, single blinded; SCS, systemic corticosteroids; UB, unblinded.

therapy was 120 minutes (range 30 minutes to 4 hours). All were randomized controlled trials. Five studies were judged to have a low risk of bias^{20,22–25} (Table 2). With the exception of 2 studies^{17,22} that compared a helium–oxygen mixture of 70:30 with 100% oxygen, the percentages of oxygen used for nebulization were virtually identical in the 2 groups.

Primary Outcomes

The assessment of 7 trials from 6 studies^{17,18,20,21,23,26} including 505 patients with asthma showed that patients receiving heliox presented a statistically significant difference of 17.3% (95% CI 5.2–29.4) for percentage of change in PEF ($P = .005$) compared with

patients receiving oxygen (Fig 2). This increase corresponded to an absolute increment of approximately 20 L/m. Although the result presented heterogeneity, there was no evidence of publication bias (Egger test, intercept -6.47 , 90% CI -38.0 to 50.9 , $P = .78$) among the studies. Heterogeneity was largely explained by a study with a high risk of bias.¹⁷ When this study was removed, heterogeneity was decreased from 73% to 27%. Post hoc subgroup analysis (Table 3) showed that studies that adjusted nebulizer flow rate presented a statistically significant difference for percentage of change in PEF compared with those studies that did not. In the same way, patients with severe and very severe asthma (PEF $<50\%$ of predicted) showed a significant improvement in PEF compared with patients with mild to moderate acute asthma (PEF $\geq 50\%$ of

Table 2
Risk of bias of eligible studies

Study	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting and other sources of bias
Henderson et al ¹⁷	low	low	low	unclear	low	unclear
Dorfman et al ¹⁸	unclear	unclear	high	high	low	unclear
Kress et al ¹⁹	unclear	unclear	unclear	unclear	low	low
Rose et al ²⁰	low	low	low	low	low	low
Xie et al ²¹	unclear	unclear	low	high	low	unclear
Kim et al ²²	low	low	high	unclear	low	low
Lin Lee et al ²³ (trial a)	low	unclear	low	low	low	low
Lin Lee et al ²³ (trial b)	low	unclear	low	low	low	low
Rivera et al ²⁴	unclear	low	low	low	low	low
Bigham et al ²⁵	low	low	low	low	low	low
Arias Ortiz et al ²⁶	low	unclear	high	unclear	low	low

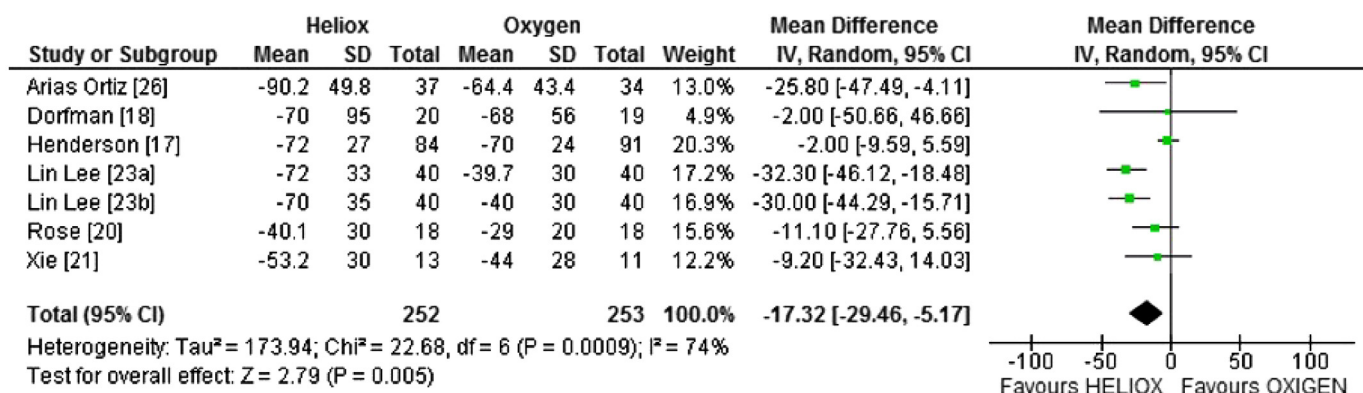


Figure 2. Pooled mean difference with 95% confidence intervals (CIs) of eligible studies comparing oxygen- with heliox-driven β_2 -agonist nebulization for the outcome of mean percentage of change in peak expiratory flow.

predicted). Regarding sensitivity analysis, there were no significant differences in the pooled effect size according to the sample size and statistical model (Table 3). The studies with a low risk of bias^{20,23} showed a significant improvement in pulmonary function compared with high-risk studies.

Data from 4 studies^{17,19–21} indicated that the use of heliox significantly increased the mean percentage of change in forced expiratory volume in the first second (12.7%, 95% CI 0.3–25.9, $I^2 = 66\%$, $P = .04$). Pediatric studies^{22,24,25} used different asthma or pulmonary severity composite scores as the primary outcome instead of spirometric measurements. Their pooled analysis showed that β_2 -agonist heliox-driven nebulization significantly decreased the severity of exacerbations in children (standard mean difference -0.74 , 95% CI -1.45 to -0.03 , $I^2 = 69\%$, $P = .04$).

Secondary Outcomes

Seven trials with a total of 405 adults and 71 children with acute asthma reported hospital admissions.^{17–20,22–24} Beta-2-agonist heliox-driven nebulization significantly lowered the rate of hospital admissions. The overall cumulative incidence was 25% in the heliox group and 36% in the oxygen group (Fig 3). Treatment of 9 patients with heliox prevented 1 patient from undergoing hospitalization compared with oxygen-driven nebulization (NNTB = 9, 95% CI 5–34). The result was homogeneous. A visual inspection of the funnel plot and the Egger test (intercept 0.33, 90% CI -0.39 to 1.06 , $P = .39$) did not show any asymmetry, suggesting the absence of publication bias. There was no significant difference in the rate of admissions between adults and children. In addition, there were no group differences in SAE (episodes of hypoxia requiring increased oxygen concentration; Fig 4). The result was homogeneous and without evidence of publication bias (Egger test, intercept 0.09, 95% CI -0.17 to 0.35 , $P = .41$).

Table 3

Post hoc subgroup and sensitivity analysis for percentage of change in peak expiratory flow

Comparison	MD (95% CI)	P value
Adjusted nebulizer flow rate ^{22,23} vs did not adjust ^{17,18,20,26}	23.8 (11.0–36.5)	.00025
Severe ^{20,23} vs mild to severe acute asthma ^{17,18,21,26}	17.2 (0.4–33.9)	.044
Sample size ($n \leq 40$ ^{18–21} vs $n > 40$ ^{17,23,26})	9.7 (–15.5 to 35.1)	.44
Statistical model (fixed vs random effects)	4.2 (–8.8 to 17.2)	.52
Methodologic quality (low risk ^{20,23} vs high risk ^{17,18,21,26} of bias)	17.2 (0.4–33.9)	.044

Abbreviations: CI, confidence interval; MD, mean difference.

Discussion

To the authors' knowledge, this is the first systematic review designed exclusively to explore the efficacy and safety of heliox compared with oxygen in driving β_2 -agonist nebulization in patients with acute asthma. The present data indicated that heliox was more effective than oxygen for several outcomes. Concerning the benefits, the use of heliox as a driving gas for nebulizers presented a 17.2% increase in mean change from baseline PEF compared with oxygen. This benefit was greater in patients with acute severe asthma, increasing to approximately 25%. Furthermore, heliox-powered nebulization decreased hospital admissions (NNTB = 9). This is a very relevant finding because hospitalizations account for the largest part of direct health costs for asthma. Regarding pediatric studies, the pooled analysis showed a significant decrease in acute asthma severity during treatment with heliox. Because the studies used 3 different composite score systems, pooled data were expressed in SD units. Concerning risks, patients using heliox showed no difference in SAE rate compared with those who used oxygen. Slightly more than 1% of patients had episodes of hypoxia that forced them to increase the oxygen concentration, and there was no significant difference between groups.

In the past decade, 3 systematic reviews on the use of heliox in patients with acute asthma have been published.^{8–10} However, they offer incomplete information on this topic. Ho et al⁸ analyzed the use of heliox as an adjunct treatment in patients with acute asthma. In contrast, Rodrigo et al⁹ pooled a mix of studies (studies designed to washout the air in the lungs and replace it with heliox and studies that used heliox to deliver nebulized therapy). Colebourn et al¹⁰ examined studies on the use of heliox in patients with acute exacerbations of asthma and chronic obstructive pulmonary disease. In a subgroup analysis, they evaluated the effect of heliox-driven nebulization and found a mean difference of 29.6% (95% CI 16.6–42.6) in percentage of change in PEF favoring heliox (2 studies). Also, there was a positive effect in favor of heliox, with a mean difference of 13.29 L/min (95% CI 3.76–22.81) in the analysis of absolute improvement in PEF from baseline (2 studies).

This systematic review suggests that statistically significant heliox benefits in airflow limitation (mainly in patients with severe acute asthma) and avoidance of hospital admissions could be considered clinically significant. Thus, the minimal clinically important difference in PEF has been established as 18.8 L/min (or 5.39% change from baseline).²⁷ Patients receiving heliox as a driving gas for nebulizers delivering bronchodilators improved the PEF by an average of 17% (~ 20 L/min). In addition, patients using heliox had a greater likelihood of achieving a minimal clinically important difference in hospital admissions (NNTB = 9). Conversely, it was

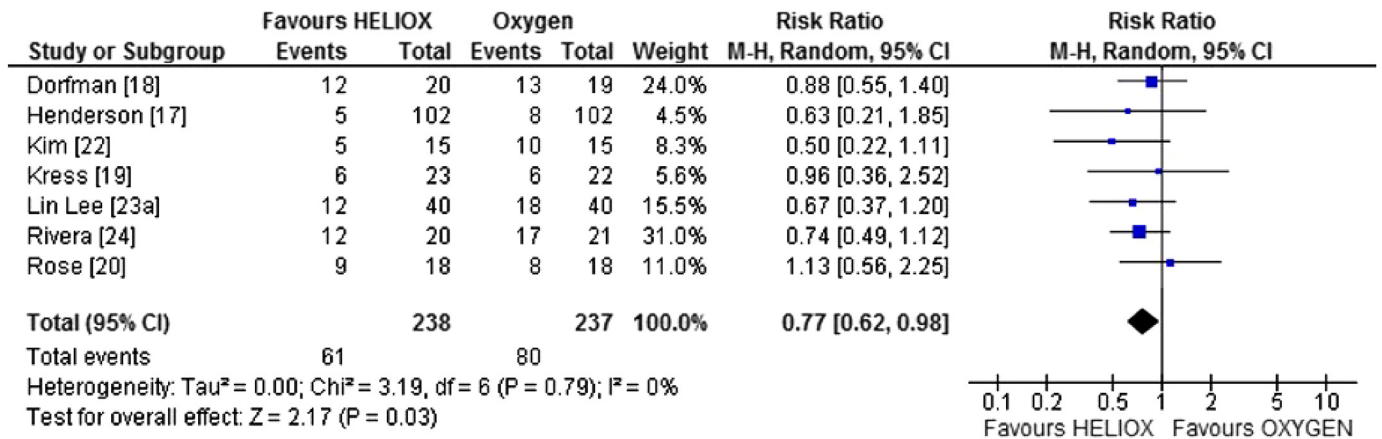


Figure 3. Pooled risk ratio with 95% confidence intervals (CIs) of eligible studies comparing heliox- with oxygen-driven β_2 -agonist nebulization for the outcome of hospital admissions. M-H, Mantel-Haenszel.

difficult to determine the clinical significance of the effect of heliox on pulmonary or asthma severity composite scores. Pooled analysis showed a significant decrease of 0.74 SD.^{22,24,25} If this size effect were interpreted according to the classification of Cohen,²⁸ it would be classified as “medium” effect. However, this labeling is controversial.

There are different methodologic issues of heliox administration that could significantly affect the results. Because inspired fractions of helium delivered with “open” breathing systems result in helium concentrations below approximately 60%, they have no physical or (presumably) biological plausibility for effective gas delivery in a manner that would effectively deliver albuterol. Thus, all patients who are given heliox to breathe should receive this treatment using a high-flow nonrebreathing delivery system.¹⁹ Another source of variability between studies was the difference in flow rate at which the nebulizers were driven. Hess et al²⁹ found that the flow rate necessary to generate an optimal-size respirable particle is higher with heliox than oxygen or air. Thus, this conversion factor is critical, because an unconverted, inaccurate flow may lead to poor generation of aerosol particles and, hence, falsely negative clinical results. Only 4 studies included in this systematic review used a delivery system that ensured delivery of a high helium concentration (ie, minimal or no entrainment of room air).^{19,22,23,25} and 3 studies corrected for heliox use by increasing the flow rate.^{22,23,25} Accordingly, subgroup analysis showed that studies that adjusted nebulizer flow rate presented a statistically significant increase for

percentage of change in PEF compared with those studies that did not.

Heliox-driven β_2 -agonist nebulization therapy has some disadvantages and limitations. Hypoxia can occur during treatment; in that case, the patient may require a higher fraction of inspired oxygen than the 20% or 30% oxygen in the standard available heliox mixtures of 80:20 or 70:30. According to the present data, this event was rarely reported (approximately >1%), suggesting that its use to drive β_2 -agonist nebulization in patients with acute asthma is safe.

This systematic review met most of the methodologic criteria suggested for scientific reviews.¹¹ A comprehensive search of the published literature for potentially relevant studies was conducted using a systematic strategy to avoid bias. Despite the heterogeneity of the studies, the effect sizes were quite consistent. In addition to the issues related to heliox administration, this meta-analysis is limited by the quality and quantity of existing research and how data are reported. Trials with a low bias risk showed a significant increase of PEF compared with those with high bias. Assessment of the consistency of effects across studies is an essential part of the review to determine the generalizability of the findings. Thus, the primary outcome was associated with heterogeneity, explained mostly by a study with a high risk of bias. Moreover, the absence of heterogeneity was particularly important for hospital admissions.

In summary, this systematic review found data to support the use of heliox in the routine care of patients with acute

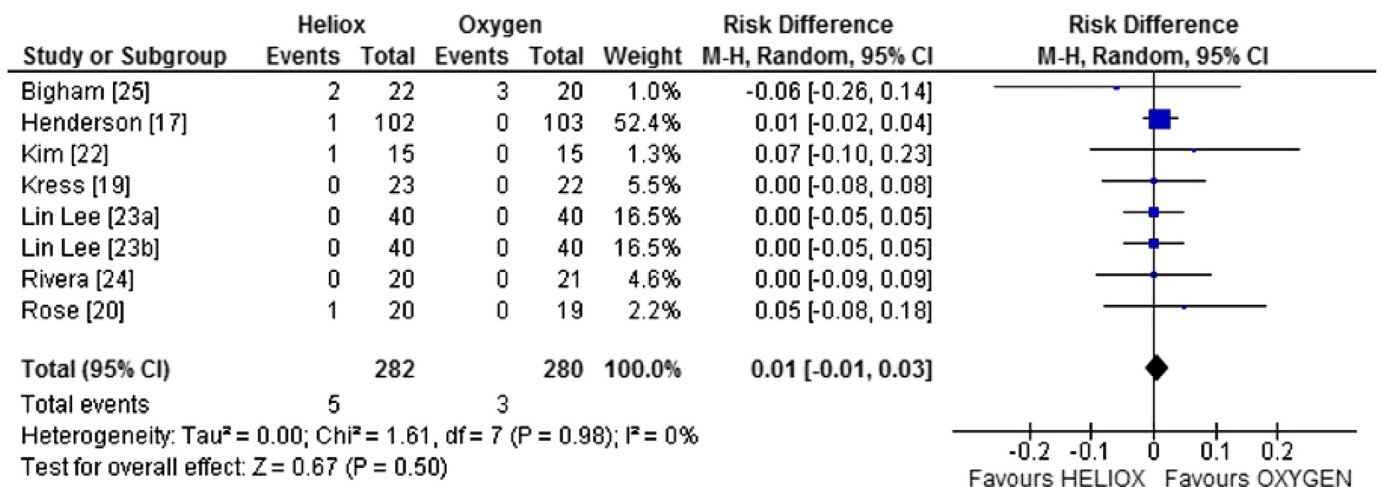


Figure 4. Pooled risk difference with 95% confidence intervals (CIs) of eligible studies comparing heliox- with oxygen-driven β_2 -agonist nebulization for the outcome of serious adverse effects. M-H, Mantel-Haenszel.

exacerbations of asthma as a nebulizer β_2 -agonist driving gas. The evidence from a limited number of small studies suggest that the use of heliox to power β_2 -agonist nebulization in patients with moderate to severe acute asthma is associated with better outcomes in spirometric measurements and hospital admissions. Overall, heliox appears to be safe and well tolerated in the mixtures used. Cost–effectiveness studies should be conducted before generalizing the use of heliox mists in severe acute asthma arising in the emergency department.

References

- [1] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Update 2012. Available at: <http://www.ginasthma.com>. Accessed July 15, 2013.
- [2] National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health 2007. Available at: <http://www.nhlbi.nih.gov>. Accessed July 15, 2013.
- [3] Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults. A review. *Chest*. 2004; 125:1081–1102.
- [4] Piva JP, Menna Barreto SS, Zelmanovitz F, Amantea S, Cox P. Heliox versus oxygen for nebulized aerosol therapy in children with lower airway obstruction. *Pediatr Crit Care Med*. 2002;3:6–10.
- [5] Darquenne C, Prisk GK. Aerosol deposition in the human respiratory tract breathing air and 80:20 heliox. *J Aerosol Med*. 2004;17:278–285.
- [6] Kim IK, Saville AL, Sikes KL, Corcoran TE. Heliox-driven albuterol nebulization for asthma exacerbations: an overview. *Respir Care*. 2006;51:613–618.
- [7] Gentile MA. Medical gases: more to breathe than oxygen. *Respir Care*. 2011; 56:1341–1357.
- [8] Ho AMH, Lee A, Karmakar MK, Dion PW, Chung DC, Contardi LH. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma. A systematic overview. *Chest*. 2003;123:882–890.
- [9] Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for nonintubated acute asthma patients. *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD002884.
- [10] Colebourn CL, Barber V, Young JD. Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. *Anaesthesia*. 2007;62:34–42.
- [11] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151:W1–W30.
- [12] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343. d5928.
- [13] Higgins JPT, Thompson SG, Deeks JJ, Altman D. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
- [14] Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. Chichester, UK: John Wiley & Sons; 2009.
- [15] Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity, combining results from several studies in meta-analysis. In: Egger M, Smith Altman DG, eds. *Systematic Reviews in Health Care: Meta-Analysis in Context*. London: BMJ; 2001:285–312.
- [16] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
- [17] Henderson SO, Acharya P, Kilagbhan T, Perez J, Korn CS, Chan LS. Use of heliox-driven nebulizer therapy in the treatment of acute asthma. *Ann Emerg Med*. 1999;33:141–146.
- [18] Dorfman TA, Burton JH, Jones P, Shipley ER, Mette SA. Inhaled heliox does not benefit emergency department patients with moderate to severe asthma. *Am J Emerg Med*. 2000;18:495–497.
- [19] Kress JP, Noth I, Gehlbach BK, et al. The utility of albuterol nebulized with heliox during acute asthma exacerbations. *Am J Respir Crit Care Med*. 2002; 165:1317–1321.
- [20] Rose JS, Panacek EA, Miller P. Prospective randomized trial of heliox driven continuous nebulizers in the treatment of asthma in the emergency department. *J Emerg Med*. 2002;22:133–137.
- [21] Xie L, Liu Y, Chen L, Hao F, Jin G, Zhao H. Inhaling beta2-agonist with heliox driven in bronchial asthma. *Chin Med J*. 2003;116:1011–1015.
- [22] Kim IK, Phrampus E, Venkataraman S, et al. Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. *Pediatrics*. 2005;116: 1127–1133.
- [23] Lin Lee D, Hsu CW, Lee H, Chang HW, Huang YCH. Beneficial effects of albuterol therapy driven by heliox versus oxygen in severe asthma exacerbation. *Acad Emerg Med*. 2005;12:820–827.
- [24] Rivera ML, Kim TY, Stewart GM, Minasyan L, Brown L. Albuterol nebulized in heliox in the initial ED treatment of pediatric asthma: a blinded, randomized controlled trial. *Am J Emerg Med*. 2006;24:38–42.
- [25] Bigham MT, Jacobs BR, Monaco MA, et al. Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: a randomized, placebo controlled trial. *Pediatr Crit Care Med*. 2010;11: 356–361.
- [26] Arias Ortiz J, Salas Fonseca J, Salas-Segura DA. Uso del heliox en las crisis asmáticas moderadas y severas en el Servicio de Emergencias del Hospital Rafael Ángel Calderón Guardia. Un estudio prospectivo. *Neumol Cir Torax*. 2012;1:21–28.
- [27] Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J*. 1999; 14:23–27.
- [28] Cohen J. A power primer. *Psychol Bull*. 1992;112:155–159.
- [29] Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest*. 1999;115: 184–189.