2 SYNOPSIS

NAME OF SPONSOR: S.E. Carburos Metálicos grupo Air Products, S.A.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(for National Authority use only)*
NAME OF THE FINISHED PRODUCT: Heliox		
NAME OF ACTIVE INGREDIENT(S): Helium and oxygen (He/O2 = 78%/22%)		

Title of Study:

Heliox-driven β2-agonist nebulization for children with moderate to severe acute asthma: a randomized controlled clinical trial.

Investigator(s):

(See Appendix 16.1.4)

Study centre(s):

(See Appendix 16.1.4)

Study period: 2016 to 2020 **Date of first enrolment:** July 4, 2016 **Date of last completed:** January 12, 2020	**Phase of development:** III

Objectives:

Primary Objective

To evaluate the efficacy of heliox (He 78%/O2 22%) for intermittent nebulization of fast-acting beta-agonists bronchodilators (salbutamol), compared with Synthetic Medicinal Air (O2 22%/N2 78%), in children and adolescents with moderate to severe acute asthma in two pediatric emergency departments (EDs).

Secondary Objective

To assess the treatment safety, especially in relation to possible episodes of hypoxia.

Methodology:

This was a prospective, randomized, single blinded, controlled (parallel-group), and balanced pilot study in asthmatic children and adolescents (5 to 16 years) who attended to one of two pediatric Spanish EDs (Hospital La Paz, Madrid, and Hospital General Universitario de Alicante) for a moderate to severe acute exacerbation.

Number of patients (planned and analysed):

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Number of patients planned: 58 patients in total (29 patients per group).

Number of patients analysed: 54 patients in total (27 patients per group).

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. All participants or their parents or guardians gave their informed written consent to participate.
2. Age 5 to 16 years.
3. Diagnosis of asthma according to clinical judgment (GINA 2021) [1].
4. Pulmonary score (PS) of ≥ 4.

Exclusion criteria:

1. Altered consciousness.
2. A pulse oximetry (SaO2) reading of less than 90% in air.
3. Systolic blood pressure greater than 180 mmHg.
4. Requiring non-invasive ventilation, or intubation and mechanical ventilation.
5. Other concomitant diseases than asthma.
6. Having received corticosteroids (CS) in the previous 6 hours.

Test product and comparator, dose and mode of administration:

Irrespective of the group to which the trial patients were randomized, they all received regular treatment for this type of patients with salbutamol and oral CS. All regular basic treatments were permitted except administration of oral CS in the 6 hours prior to presentation at the ED.

Three successive treatments (every 30 min.) with salbutamol (0.15mg/kg/30min) nebulized with heliox (n=27) or Synthetic Medicinal Air (n=27) as a carrier gas. Each treatment was applied (until the nebulizer was dry), followed by a 5 to 10-min. wash-out period. At the end of the treatment (90 min.), patients were discharged when they showed a PS < 3 or hospitalized (PS ≥ 3).

Duration of treatment:

Each treatment was applied (until the nebulizer was dry), followed by a 5 to 10-min. wash-out period. At the end of the treatment (90 min.), patients were discharged when they showed a PS < 3 or hospitalized (PS ≥ 3).

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Criteria for evaluation:

The primary efficacy endpoint was Pulmonary Score (PS).

Secondary endpoints were:

- Percentage of patients who required hospitalization at the end of the treatment (PS ≥ 3).
- Percentage of patients who required intensive care unit (ICU) admission, orotracheal intubation or who die during the protocol.
- Number of hypoxia episodes defined as a SaO2 < 90% during the 90 min of treatment.
- Any serious or mild adverse events (AE).

Statistical methods:

Treatment groups were compared by t test, one way or repeated-measures analysis of variance (ANOVA). In the case of patients lost before the end of treatment (90 min), the LOGRANK test was used, considering patients who obtained a PS = 0 before the end of treatment, as discharges. Also, we used chi-square test with Yates correction or Fisher exact test, for categorical variables. A p value of less than 0.05 using a two-tailed test was taken as significant for all statistical tests. All participants were considered “assessable” for efficacy and safety purposes.

<u>SUMMARY CONCLUSIONS</u>

EFFICACY RESULTS

Fifty-four patients aged 5 to 14 years, 68% male, with moderate to severe exacerbations (PS 4 to 7) were enrolled (27 patients in each group). There were no statistical differences in baseline characteristics between groups, including severity of asthma exacerbation. While the patients treated with heliox appear somewhat more severe at baseline, they subsequently showed a trend to a more pronounced reduction in PS compared to the patients treated with air. However, this difference was not statistically significant. Mean change in PS score from baseline was higher in the heliox group compared with the air group. By 60 and 90 min, changes from baseline levels of PS score significantly favoured the heliox group (-2.8 vs. -2.0, p = 0.04 and 3.6 vs 2.7, p= 0.02 respectively).

Additionally, the LOGRANK estimated curves of the proportion of patients who reached the discharge threshold (PS<3) during the 90 min of treatment showed a significant difference in favour of the heliox group (median time 60 ± 29 min. vs 90 ± 27 min., p = 0.04).

The rate of admission was 11.5% in the heliox group and 14.8% in the air group. This difference was not statistically significant (p = 0.7).

SAFETY RESULTS

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Regarding serious AE, no patient required mechanical/non-invasive ventilation, intubation, and admission to UCI, or experienced hypothermia during the study. Only one patient (treated with heliox) presented an episode of hypoxia (PaO2<90%) after the third nebulization. SAEs reported as hospitalization were due to a PS ≥ 3, which reflects the lack of efficacy of the treatment.

The majority of patients receiving heliox experienced a change in pitch of voice.

Other AE events were: nausea and vomiting (4 patients), anxiety (1 patient), dizziness (2 patients), cold sensation (1 patient), abdominal pain (1 patient), fever (5 patients), thoracic pain (1 patient), somnolence (1 patients) and pre-syncope (2 patients). There were no significant differences between both groups.

CONCLUSION

The evidence from this randomized controlled study suggests that the use of heliox to power beta2-agonist nebulization in children and adolescents with moderate to severe acute asthma is associated with a greater and faster clinical improvement (higher decrease in PS with a higher proportion of patients who reached a significant clinical improvement (PS < 3) during the 90 min of treatment). Overall, the use of heliox appears to be safe and well tolerated in the mixtures used.

DATE OF THE REPORT: January 24, 2022