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Clinical effects of purified air administered to the breathing zone in allergic asthma: A double-blind randomized cross-over trial

C. Pedroletti ^{a,*}, E. Millinger ^b, B. Dahlén ^c, P. Söderman ^d, O. Zetterström ^b

^a Department of Women and Child Health, Karolinska Institutet, Karolinska University Hospital, SE 171 76, Stockholm, Sweden

^b Department of Allergology, Linköping University Hospital, Sweden

^c Department of Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden

^d Children's Hospital, Karolinska University Hospital Huddinge, Stockholm, Sweden

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KEYWORDS

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Summary

Background: Exposure to inhaled allergens is a pathogenetic factor in allergic asthma. However, most studies that previously looked at air cleaning devices have shown little or no effect on patients with perennial allergic asthma.

Aims and objectives: We examined a novel treatment using temperature regulated laminar airflow with a very low particle concentration directed to the breathing zone of teenagers and young adults with mild to moderate allergic asthma during night sleep. We hypothesised that the decreased allergen exposure during the night would have an effect on bronchial inflammation and quality of life.

Method: Twenty-two patients (mean 18.8 years) were randomized to start with active or placebo treatment for 10 weeks. All patients received both active and placebo treatment with unfiltered air, with a 2-week wash-out period in between treatments. Maintenance treatment with inhaled corticosteroids was unaltered during the trial period. Health related quality of life (miniAQLQ) was the primary effectiveness measure. Exhaled nitric oxide (FeNO) and spirometry were also investigated.

Results: Active treatment resulted in an improved miniAQLQ compared to placebo (mean score 0.54, $p < 0.05$, $n = 20$). An effect on bronchial inflammation was also detected with significantly lower FeNO values during the active treatment period (mean -6.95 ppb, $p < 0.05$, $n = 22$). Both effects were evident after 5 weeks. The change in lung function was not statistically significant.

Conclusion: Clean air, administered directly to the breathing zone during sleep, can have a positive effect on bronchial inflammation and quality of life in patients with perennial allergic asthma.

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* Corresponding author. Tel.: +46 73 625 1930; fax: +46 8 5177 773.

E-mail address: christophe.pedroletti@karolinska.se (C. Pedroletti).

Introduction

Asthma is an inflammatory disease. In allergic asthma the inflammation is mainly driven by the exposure to inhalant allergens to which the patient is sensitised.

Minimising the exposure to inhalant allergens, such as animal dander and house dust mites, is a first step in reducing the severity of asthma.^{1,2} Experiences from high altitude studies^{3,4} suggest that long term avoidance of house dust mite allergens leads to a decrease in airway inflammation with consequent symptom improvement.

Most studies that previously used air cleaning devices and other ventilation measures to remove allergen have shown little or no effect on patients with perennial allergic asthma,⁵ suggesting that the allergen reduction had simply not been significant enough to affect airway inflammation. The perennial allergens are widespread and have been shown to be prevalent even in the homes of people who don't own pets.⁶

In this study, we investigated a novel treatment, Airsonett Airshower (AA), that uses a laminar airflow of purified air directed to the breathing zone of a patient during night sleep. We hypothesised that AA treatment on top of inhaled corticosteroids (ICS) medication would lead to a decreased airway inflammation with consequent symptom improvement in patients with allergic asthma.

Materials and methods

Subjects

Perennial allergic asthmatic adolescents and young adults, 12–33 years of age, taking a daily maintenance dose of at least ICS ≥ 400 μ g/day of budesonide or 200 μ g/day of fluticasone and short acting beta 2-agonist treatment on less than 4 days per week, were included into the study. The subjects were recruited at the departments of child allergy Karolinska University Hospital, Stockholm, and at the University Hospital in Linköping. All patients had been examined, diagnosed, and followed by a specialist in allergology with the diagnosis of allergic asthma for many years. The asthma diagnosis had been confirmed by lung function testing and/or bronchial provocation test (metacholine and/or cold dry air). All subjects were sensitive to pet allergen (cat and/or dog), as demonstrated by positive skin prick test (≥ 3 mm) for the allergens. The subjects were also tested for mould spores, house dust mites and birch pollen with positive reactions in most patients (see Table 1). Patients were excluded if they were current smokers, were included in another allergen avoidance program, were in drug trials and if they were on allergen specific immunotherapy.

The study was approved by the regional ethic committee at Karolinska Institutet, Stockholm, Sweden (reference number 2005-1048-31/1) and both the subjects and, if under age, their parents gave informed consent prior to entering the trial.

Study device

The AA treatment is designed to reduce the allergen load in the patients breathing zone by vertically displacing the

Table 1 Individual data for demographics, baseline scores previous to first period, asthma treatment and skin prick test at randomization.

Number of patients	22
No. (%) of female participants	12 (54.5)
Age (years)	18.5 (6.6)
Age range (years)	12–33
No. (%) using daily ICS	
Low dose ^a	13 (59.1),
Medium dose ^a	8 (36.3)
High dose ^a	1 (6.6)
No. (%) using daily LABA	19 (86)
No. (%) using daily LTRA	7 (31.8)
Quality of life score, miniAQLQ (max. of 7.0)	5.18 (1.1)
FeNO (ppb)	32.8 (24.1)
FEV ₁ predicted	77.9 (16.5)
No. (%) pet sensitised	22 (100)
No. (%) of sensitisations pet $\pm$ mite $\pm$ birch	
n = 1	5 (22.7)
n = 2	12 (54.5)
n = 3	5 (22.7)

^a According to GINA. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LTRA, leukotriene receptor antagonist.

allergens, originating from the bed and the ambient room environment, with a temperature controlled laminar airflow (TLA) during night sleep (see Fig. 1). The airflow is filtered through a high efficiency particulate air filter (HEPA), slightly cooled and "showered" over the subject. Due to the higher density, the cooled air descends slowly, and displaces the allergens from the breathing zone. TLA has been evaluated in industrial environments for local control of air pollutants⁷.

The function of the devices in this trial was validated at rest when placed in the patient's bed rooms according to standard ISO 14644-2 Clean rooms and associated controlled environments. In the validation of the clean zone, the active devices had maximum permitted level of 5000 particles/ft³ of particles ≥ 0.5 μ m of the particle count of ambient room air. The reduction in exposure integrated over night was not measured in this trial. Earlier technical studies⁸ have indicated that the exposure is less than 5000 particles/ft³, of particles ≥ 0.5 μ m, but further studies are needed to evaluate this.

In a placebo device the filtration function was disabled. None of the patients reported that they could sense or hear the difference between an active and a placebo device.

Study design

The study was designed as a two-centre, double-blind, placebo-controlled, crossover trial. The patients were randomized into one of two arms starting with either active or placebo treatment followed by a washout period of 2 weeks with no use of the device and ending with a second period of either active or placebo treatment (Fig. 2). Each treatment period was 10 weeks long and all subjects maintained their medication (see Table 1) from

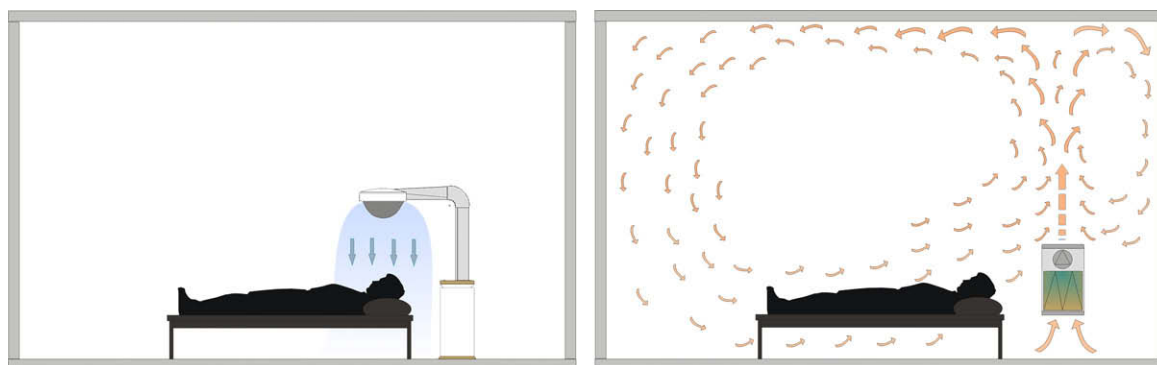


Figure 1 Function of AA treatment (left) compared to traditional air cleaning (right). AA treatment creates an allergen free zone directed to the airways ① whilst traditional air cleaning aims to dilute the allergen levels in the whole room.

randomization throughout the study. Inhaled, short-acting beta 2-agonists were allowed as rescue treatment.

The subjects were monitored at regular visits with spirometry and exhaled nitric oxide (FeNO) measurements at weeks: 0 (randomization), 5, 10 (end of first active/placebo period), 12 (start of second placebo/active period), 17, 22 (end of the trial).

Outcome variables

The primary effectiveness measure for evaluation was the change in quality of life between active versus placebo treatment, assessed by the mini-Asthma Quality of Life Questionnaire (miniAQLQ). The miniAQLQ is a well-known and validated quality of life assessment instrument for use in asthma^{9–11} capable of showing beneficial treatment effects, from the patient's perspective, not captured by objective monitoring. We defined the change in quality of life as the difference in the miniAQLQ summary score from start to end (10 weeks) of each study period. A miniAQLQ scores from 0 to 7, where 7 is no symptoms. A change of 0.5 is considered clinically significant.

Exhaled nitric oxide (FeNO) was measured at each visit followed by spirometry. Single-breath, on-line measurement of FeNO was performed in accordance with the recommendations of the American Thoracic society¹²

(ATS). FeNO was measured with the Aerocrine NIOX (Aerocrine AB, Stockholm, Sweden). Spirometry was performed in accordance with ATS guidelines¹³ to calculate forced expiratory volume in 1 s (FEV₁), and peak expiratory flow rate (PEF). Each patient maintained a daily diary recording of lost school/workdays, quality of sleep and use of medication.

Statistical analysis

The study hypothesis was tested by examining the difference in change of miniAQLQ, FeNO and spirometry during active versus placebo treatment periods. All subjects who completed measurements at both baseline and endpoint of each treatment period were analyzed. Results were summarized by treatment periods as mean scores $\pm$ confidence interval. Changes from baseline within each treatment period (active or placebo) were analyzed using paired *t*-tests. An analysis of variance (ANOVA) model was used to compare the changes (measured as least square mean $\pm$ confidence interval) between the two treatment periods. The country and baseline scores were variates in this model. We calculated that a sample size of 20 would have a 62% power to detect a 30% improvement of miniAQLQ for active treatment vs placebo, with the error set at 0.05 and SD based on a previous pilot study.¹⁴

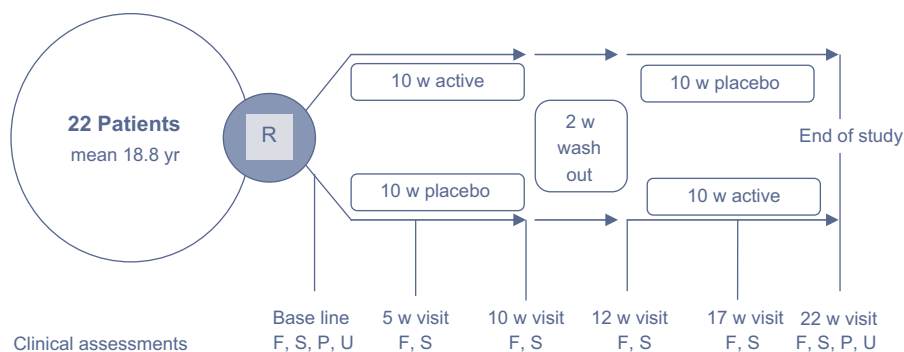


Figure 2 Randomization of subjects into two arms of treatment: active–placebo or placebo–active. Clinical assessments: F, FeNO; S, spirometry; P, physical examination; U, urine sample.

Results

Demographics

In total, 28 patients were enrolled and had AA devices installed in their home bed rooms. Of these, 22 completed measurements at baseline and endpoint of both treatment periods. Two patients withdrew due to pregnancies, one patient due to change of location and failure to complete the protocol, and another two patients withdrew for non medical reasons. One patient was excluded from study analysis due to an incorrectly adjusted study device during the first treatment period. Two of the 22 patients failed to complete the miniAQLQ and therefore could not be included in the miniAQLQ analysis.

The missing data analysis showed only random features of missing data.

Eight episodes of asthma exacerbations were reported with increased reliever medication (beta 2 agonists > 4-days per week). One patient also used a temporary increase in steroid medication. Four of the episodes were during active period, three were judged as being caused by viral infections and one was of no reported cause. Four episodes occurred during placebo treatment, all four were probably due to other viral infections. Three of the eight exacerbations were reported from one subject, two from another, and the remaining three from three different subjects.

Individual data for demographics, baseline scores, asthma treatment and positive skin prick test at randomization are presented in Table 1. The 22 subjects recorded a mean FeNO of 32.8 ppb (95% CI, 22.2–43.5, $n = 22$) and a mean miniAQLQ score of 5.18 (95% CI, 4.67–5.70, $n = 20$) at randomization. Their mean FEV₁ was 92% of predicted.

Change in quality of life and fraction of exhaled nitric oxide

The mean improvement in the overall miniAQLQ score in the active treatment group was greater than in the placebo group (mean difference 0.54; SEM $\pm$ 0.28, $p < 0.05$) (Table 2). The effect seemed to occur already after 2 weeks of treatment and was evident after 5 weeks. The changes in the miniAQLQ score and FeNO values in the two treatment periods are shown in Fig. 3.

FeNO was significantly reduced by 6.4 ppb (SEM $\pm$ 2.5, $p < 0.05$) after 10 weeks of active treatment as compared with placebo (Fig. 3). The reduction was already discernible

after 5 weeks of treatment (first measurement after baseline). The confidence interval of FeNO at the end of the placebo period was greater than at the end of the active period, implying a better control of asthma with an active treatment (Table 2). Patients with more symptoms i.e. a low miniAQLQ score (<5) and high FeNO (>16 ppb) showed greater treatment effect but the sample size was considered too small for subgroup analysis.

Four “drop-out” patients filled the miniAQLQ form before and after at least one study period. Three of them had been given active treatment and demonstrated an increase in two cases (+0.47 and +0.47) and a minor decrease in one case (–0.27). The fourth patient received placebo treatment and showed a minor increase in the miniAQLQ score (+0.27).

FeNO values were obtained at the start and at the end of at least one study period in three excluded patients. All three patients got active treatment but showed small effects on FeNO (+3.6 ppb and –3.4 ppb and –0.9). If these patient data are included in a statistical evaluation a “parallel group design” with lower sensitivity has to be used. The result of such a calculation shows a mean increase in miniAQLQ of 0.73 in the active group and –0.02 in the placebo ($p = 0.056$). The effect on FeNO was smaller (–4.43 ppb active vs –0.25 ppb placebo) and was not significant ($p = 0.25$).

Spirometry

When the changes of FEV₁ and PEF values were considered, small, not significant increases during active periods were observed (mean percentage difference in FEV₁ = 1.14%, mean percentage difference in PEF = 3.44%).

Discussion

There are several phenotypes of asthma and various factors play a role in the pathogenesis and symptom development of the disease. In order to show an effect of allergen avoidance we selected young patients in whom we considered allergen exposure to be of importance for their asthma.

All subjects were sensitive to pet allergen (cat and/or dog), as demonstrated by positive skin prick test (>3 mm). Pet allergen is also the dominating allergen to which young Scandinavian asthmatics are sensitised. High levels of cat allergen are found in homes of non cat owners and it has been shown that allergen is spread via clothing from homes with cats to classrooms, and further to homes without cats.

Table 2 The difference in change, miniAQLQ score and FeNO values, between active and placebo treatment.

Variable	Active treatment (geometric mean (95% CI))		Placebo treatment		Difference in change: mean $\pm$ SEM, p -value, n active–placebo
	Start	End	Start	End	
FeNO (ppb)	29.2 (18.9–39.5)	22.2 (14.8–29.7)	29.0 (18.2–39.8)	28.5 (16.4–40.6)	–6.4 $\pm$ 2.5, $p < 0.05$, $n = 22$
miniAQLQ	5.36 (4.82–5.90)	5.92 (5.56–6.28)	5.69 (5.23–6.14)	5.70 (5.19–6.22)	0.54 $\pm$ 0.28, $p < 0.05$, $n = 20$

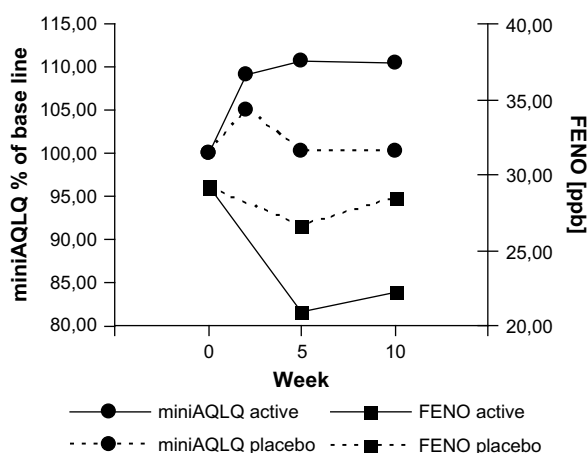


Figure 3 Cross-over variations of miniAQQL and FENO for each time point of the study. Quality of life – miniAQQL ($n = 20$) is presented in % of baseline (week 0). Bronchial inflammation is presented in ppb, forced exhaled nitric oxide ($n = 22$). FENO baseline mean values (week 0) were 29.2 ppb for active treatment and 29.0 ppb for placebo treatment.

For example, it has been shown that the allergen levels in non-cat owners' homes correlate with children's exposure to cat allergen at school.⁶ Cat allergens are small and easily airborne from reservoirs such as beds or other furniture. Movements in bed make the allergens respirable and this exposure may maintain a bronchial inflammation. The fact that avoidance of exposure to indoor allergens could be an important element in the treatment of allergic asthma is shown by studies in mite-allergic children in high altitude environments where a major reduction in mite allergen levels resulted in a significant reduction in bronchial inflammation.³

One limitation of the study is that we did not measure the actual exposure to possible allergens in the breathing zone. Therefore, we cannot assess the impact of a certain amount of allergen reduction on our results. However, the results should not have been skewed by differences in patients' bedroom environments since this investigation was a cross-over study.

Many studies of allergy and asthma have been made with various air cleaning devices in the home setting, showing little or no effect on the disease. In two studies, using clean air delivered directly to the breathing zone showed more promising results.^{15,16} These devices, however, have not been used in clinical settings due to comfort problems such as draft and high sound levels.

Due to air cooling a low flow, more silent fans can be used in the airshower technique. The AA creates a zone of purified air which displaces contaminants from the airspace around the bed environment. The cleaning effect of airborne particles in the breathing zone is accomplished within minutes and the reduction in allergen and particle concentration is significantly reduced⁸ (see Fig. 1). The efficient allergen reduction in the breathing zone is what makes AA treatment different from earlier air cleaning techniques and may explain the positive clinical outcome in this study.

The effect of AA treatment may be due to more dimensions than a decrease in allergen exposure. Apart

from the avoidance of allergens a decreased exposure to airborne particles could be of importance. They may act as irritants or have a proinflammatory effect.

In a recent study of the effects of airshower filtering of the air in the homes of elderly subjects living near major roads in Copenhagen, it was shown that indoor particles affected vascular function.¹⁷ The effect might be caused by inflammatory mechanisms.¹⁸

The Airshower technique has been shown to reduce exposure significantly in workplaces,⁷ is widely used in clean room environments of the electronics industry¹⁹ and is also increasingly used in operating theatres.

Subjective measurements of AQQL showed a clinically meaningful and statistically significant improvement with active AA treatment compared to placebo treatment. Some of the patients also spontaneously reported less nasal symptoms during active treatment. The results from the present study show that the allergen reduction with AA treatment is significant enough to affect the airway inflammation even if the time with clean air is limited to the night.

The fact that exhaled NO levels were lower during AA treatment supports the view that allergen exposure and induced airway inflammation was of importance in our patients.

The decrease in FeNO levels in our patients were significant in spite of the fact that they were on regular maintenance treatment with $\geq 400 \mu\text{g/day}$ of ICS (budesonide or equivalent dose). ICS is well known for its evident lowering effect on exhaled NO,²⁰ thus the medication could mask an effect on FeNO by the AA treatment and a more evident decrease might have been observed if the patients had lower ICS dosages. The findings in this study fit well with the results of comparative studies of young asthmatics in which mite allergen avoidance by living in an alpine resort resulted in reduced FeNO values.^{3,4}

The AA treatment was used as an add-on treatment to ICS and for this reason the daily ICS dose was not altered with randomization. The selection criteria for the study were subjects with partly controlled (the Global Initiative for Asthma, GINA, 2006) moderately severe asthma (GINA, 2002), and for this subject group a recommended step is for example to add on LTRA to the ICS treatment. Our hypothesis was that AA treatment could be considered as an alternative add-on therapy for improved asthma control. Add-on AA treatment is hardly cost motivated in subjects with mild, easily controlled asthma.

The miniAQQL and FeNO were chosen as primary outcome variables to record subjective and objective measures of asthma. The miniAQQL was chosen to measure symptom improvement effects on daily life and FeNO was chosen to acquire objective measures of asthma bronchial inflammation. There is good evidence that exhaled nitric oxide reflects eosinophilic airway inflammation in asthma²¹ and we thought that the nightly reduction of allergen exposure, that AA treatment provides, could be of special importance since both symptoms and eosinophilia tend to be higher at night. Our data is supported by previous findings from Grootendorst and colleagues who also reported an improvement in miniAQQL after 10 weeks of sojourns in high altitude.²²

No significant change in FEV₁ was recorded in the present study. This may partly be explained by the

relatively good spirometry values the recruited patients had at the beginning. The lack of FEV₁ response is in agreement with a high altitude study³ where all subjects were treated with ICS from inclusion. In this study the mite allergen avoidance led to a significant decrease of the residual volume, and to a parallel significant reduction of inflammation, measured by FeNO, implicating improvements in the peripheral airways not reached by ICS medication.

In our study the positive response for QoL was already apparent after the first measurements at 2 weeks and FeNO after the first measurements at 5 weeks, and the improvements were maintained throughout the study. It could have been of value if FeNO had been measured more frequently in the beginning of each period as this marker is known to react rapidly to anti inflammatory treatment.²³ Furthermore, the fact that the FeNO values were similar, the start of each treatment period (see Table 2) indicates a rapid reversal of this parameter since the washout period was only 2 weeks.

The material was not large enough to show a significant correlation between MiniAQLQ and FeNO but did indicate a tendency suggesting that patients with lower QoL score at baseline had the greatest improvement in both QoL and FeNO values.

The patient material of this study was of a selected asthma phenotype, i.e. young adults with typical allergic asthma. In an older group of patients, clinical effects of AA treatment might possibly take a longer time because more chronic asthma is associated with secondary changes.

Finally, there were six drop-outs in our study due to different reasons specified in the Results section. In three of these cases FeNO values could be obtained during at least one study period and in three cases the miniAQLQ form was filled in.

Since these subjects did not carry out both study periods, they could not be part of a cross-over analysis. However, including these patients and recalculating the data as a parallel group study also showed a positive effect of the intervention, but did not reach statistical significance.

Conclusion

In conclusion, improvements in FeNO levels and QoL were significantly greater after AA add-on treatment compared with placebo add-on treatment in this group of adolescents and young adults taking regular ICS ≥ 400 μ g/day of budesonide or 200 μ g/day of fluticasone. Patients with low QoL score at baseline showed greater improvement in both QoL and FeNO values.

The clinical effect of this novel non pharmaceutical intervention shows promising results as an additive measure for the treatment of perennial allergic asthma. However, the clinical relevance of these findings needs to be verified in larger controlled trials to be able to make general treatment recommendations.

Conflict of interest statement

Dr. Christophe Pedroletti has received a few speaker fees from Airsonett AB. Professor Olof Zetterström receives

a scientific consultant fee from Airsonett AB as a member of the steering committee conducting a new AA multi-centre study. Dr. Eva Millinger, Dr. Barbro Dahlen and Dr. Päivi Söderman have no conflict of interest to declare connected to the actual study.

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