Nocturnal Temperature controlled Laminar Airflow for treating atopic asthma: a randomised controlled trial

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METHODS

Mode of action of Protexo

At night airborne particles are carried by a persistent convection current established by the warm body, transporting allergens from the bedding area to the breathing zone. The TLA device Protexo is designed to displace the body convection which leads to persistent exposure to particles and allergen in bed. Ambient room air is filtered, cooled by 0·5-0·8ºC and distributed to the breathing zone by Protexo – the reduced temperature allows the filtered air to descend slowly in a steady laminar stream, displacing particulate and allergen rich air from the breathing zone (fig S4). The method is able to break body convection without creating draught or dehydration, and thereby reduces and controls particle and aeroallergen exposure in the breathing zone (1). A recent study demonstrated >30-fold reduction of cat allergen in the breathing zone with TLA compared to no treatment, and >3000-fold reduction in all particles ≥0.5µm (>3700-fold reduction in particles ≥10µm) [1].

Airborne particle count measurements

Home visits for clean zone validation according to EN-ISO14644-3:2005 standard were performed by technicians at device installation, 3, 6 and 12 months follow-up. Airborne particle count measurements were made using GT-321 Handheld Particle Counters (Met One Instruments Inc, USA).

Dust allergen collection and analysis

Three months after device installation a vacuumed dust sample was collected from participants' beds as previously described [2]. Briefly, mattresses with undersheets left

on were vacuumed for 2 minutes using a vacuum cleaner with sampling nozzle (ALK, Hørsholm, Denmark) according to a standard protocol. Protein was extracted from 100mg dust in 2ml phosphate buffered saline with 0.05% Tween-20 for 2 h at room temperature with rotation. Samples were centrifuged at 4500 rpm for 10 min then 10,000 rpm for 10 min and supernatants stored at -20°C. Allergen levels were determined using a sandwich ELISA kit for cat (Fel d 1) and dust mite (Der f 1 and Der p 1) allergens according to the manufacturer's instructions (Indoor Biotechnologies, Warminster, UK). Allergen concentrations were expressed as ng/g dust with a detection limit of <50 ng/g.

RESULTS

Treatment compliance and efficacy of blinding

In the active group, 136/166 (72%) participants who completed the whole study used their device on at least 80% of expected nights. In the placebo group this figure was 66/79 (71%). At the end of the study 165 patients answered the question which treatment they believed they received, to assess efficacy of masking. In the active group 52/105 (50%) believed they had received an active device; in the placebo group 35/60 (58%) believed they had received a placebo device.

Aeroallergen exposure and relationship with specific IgE levels

The median particle count (particles≥0.5μm diameter) in patients' bedrooms at device validation visits (installation, 3, 6 and 12 months) was 103,804 particles/ft^3 (IQR 56,880 to 193,840; n=1064 measurements). Median counts in the breathing zone a few minutes after turning the device on were 720 particles/ft^3 (IQR 306 to 1,485) for TLA and 117,047 (68,197 to 215,921) for placebo. In view of the finding of lesser increase in cat-specific IgE in active versus placebo treated patients in this study, we also analysed dust samples aspirated from the mattresses of 132 participants (87 active, 45 placebo) at 3 months. Allergen detection rates are shown in table S4 – Der p 1, Der f 1 and Fel d 1 were detected in 20%, 40% and 67% of mattress dust samples respectively, and there was no significant difference in detection rates between active and placebo treated patients. Among sensitized participants, allergen-specific IgE levels were positively correlated with mattress dust

allergen levels for cat (r=0.36, P=0.004), and house dust mite allergens Der f 1 (r=0.37, P=0.001) and Der p 1 (r = 0.57, P<0.001; fig S5 A-C).

Adverse Events

Adverse events affecting ≥5% of patients on ≥1 occasion were upper respiratory tract infection (ICD-9 code 480-488) in 117 (61.9%) participants in active and 62 (66.7%) in placebo group; upper respiratory tract symptoms (ICD-9 code 490-496) in 54 (28.6%) in active and 22 (23.7%) in placebo group; general symptoms (ICD-9 code 780-789) in 43 (22.8%) in active and 19 (20.4%) in placebo group.

REFERENCES

1. Gore RB, Boyle RJ, Hanna H et al. Effect of a novel Temperature controlled Laminar Airflow device on personal breathing zone aeroallergen exposure. *(under review)*.

2. Schram D, Doekes G, Boeve M et al. Bacterial and fungal components in house dust of farm children, Rudolf Steiner school children and reference children--the PARSIFAL Study. *Allergy* 2005;60(5):611-8.

Table S4. Level of asthma medication use during TLA treatment

	Baseline Active	Baseline Placebo	3-12 months Active	3-12 months Placebo	Difference in medication*	P value
Inhaled corticosteroids	0.72 (0.46)	0.77 (0.47)	0.74 (0.53)	0.77 (0.49)	0.03 (0.04)	0.38
Short acting β-2 agonist	0.20 (0.40)	0.22 (0.39)	0.19 (0.25)	0.22 (0.41)	0.02 (0.02)	0.39
Long acting β-2 agonist	0.51 (0.51)	0.53 (0.48)	0.51 (0.48)	0.55 (0.47)	-0.01 (0.03)	0.77
Leukotriene receptor antagonist	0.29 (0.46)	0.24 (0.41)	0.31 (0.53)	0.28 (0.43)	-0.00 (0.02)	0.88

All medication doses are expressed as mean (sd) proportion of the 'Defined Daily Dose', according to World Health Organisation Drugs Statistics Methodology guidelines. * Difference = mean (SE) of [(Active during 3-12 months) – (Active at baseline)] – [(Placebo during 3-12 months) – (Placebo at baseline)]. During the whole study period, systemic corticosteroids for ≥3 days were administered on ≥1 occasion to 25/189 (13.2%) patients in active and 12/93 (12.9%) patients in placebo group (P=0.94), and the mean (sd) number of systemic corticosteroid courses administered per patient was 0.17 (0.53) in active and 0.24 (0.83) in placebo group (P=0.50).

Table S5. Allergen detection in mattress dust samples

	Active	Placebo	P value	Total
Der p 1	18/87 (21%)	8/45 (18%)	0.69	26/132 (20%)
Der f 1	36/87 (41%)	17/45 (38%)	0.69	53/132 (40%)
Fel d 1	57/87 (66%)	32/45 (71%)	0.52	89/132 (67%)

Data shown are the number (%) of mattress samples with detectable levels of house dust mite (Der p 1, Der f 1) or cat (Fel d 1) major allergens. Mattress dust samples were taken at 3 months from study participant bedrooms at UK and some Swedish sites. Detection limit for all allergens = 50ng/g mattress dust. P values are calculated using chi-squared test.

FIGURE LEGENDS

Fig S4. Temperature controlled Laminar Airflow Device - the device draws in ambient air, filters and cools it by 0.5-0.8ºC, then distributes it to the breathing zone of a recumbent patient.

Fig S5. Relationship between mattress dust allergen levels and specific IgE levels to the same allergens in study patients. The data show the relationship between $\log_{10}$ allergen levels as ng/g of mattress dust in samples taken at 3 months (x axis) and $\log_{10}$ specific IgE levels in serum samples taken at baseline for dust mite allergens Der p 1 (A), Der f 1 (B) and cat allergen Fel d 1 (C). Among sensitized participants, allergen-specific IgE levels were positively correlated with mattress dust allergen levels for Der p 1 ($r = 0.57$, $P<0.001$), Der f 1 ($r=0.37$, $P=0.001$) and Fel d 1 ($r=0.36$, $P=0.004$).

Fig S6. Mean ± SEM change in AQLQ during treatment in TLA (blue) and Placebo (red) groups. Proportion (%) of participants in TLA and Placebo groups who completed the study and had a significant treatment response at different timepoints during the study is also shown. Significant treatment response was defined as an improvement in AQLQ ≥0.5 points from the time of randomisation.