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INCENTIVE DEVICE IMPROVES SPACER TECHNIQUE BUT NOT CLINICAL OUTCOME IN PRESCHOOL CHILDREN WITH ASTHMA

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Abstract

Background—Inhaled corticosteroid use reduces respiratory symptoms in young children with recurrent wheeze. Delivery of steroids with pressurised metered dose inhalers and spacers is influenced by children's proficiency/technique in using delivery devices.

Objectives—To investigate the influence of an incentive device, the Funhaler®, on spacer technique and symptom control in young children with asthma and recurrent wheeze.

Methods—Randomised controlled trial where 132 2–6 year old asthmatic children received regular inhaled fluticasone through Aerochamber Plus®, or Funhaler®. The setting was a research clinic at Princess Margaret Hospital for Children, Perth, Australia. Subjects were followed up for a year. The main outcome measure was asthma symptoms. Proficiency in spacer technique was measured as salbutamol inhaled from spacer onto filter. Quality of life was measured three-monthly. Groups were compared in terms of spacer technique, symptoms and quality of life. The relationship between spacer technique and clinical outcome was examined.

Results—There was no difference between Funhaler and Aerochamber groups in wheeze free days, cough free days, bronchodilator free days or quality of life ($p = 0.90, 0.87, 0.74$ and 0.11 respectively). Spacer technique was better in the Funhaler group ($p = 0.05$), particularly in subjects younger than 4 years of age ($p = 0.002$). Drug dose on filter (as the mean of five 100µg doses) ranged from zero to 136µg.

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Conflict of interest statement:

The fluticasone used in the study was supplied by GlaxoSmithKline, Australia. The Funhaler devices used in the study were sponsored by Visioned, Australia. The sponsors did not have access to the data and played no part in the analyses or interpretation of the data.

Scientific meetings & thesis:

Contents of this paper will be presented at the Thoracic Society of Australia and New Zealand Annual Scientific conference in March 2010. Part of this paper was previously presented at the European Respiratory Society Annual Scientific Meeting. All data from this paper stems from a PhD thesis recently completed by the first author at the University of the Free State, South Africa.

Conclusion—Use of Funhaler® incentive device does not improve clinical outcome, but improves spacer technique in children younger than 4 years. Variability in drug delivery is large in young children using pMDI-spacers.

Keywords

Asthma; wheeze; children; preschool; spacer technique; device technique; inhaled corticosteroids

Background

Inhaled corticosteroids are commonly used to treat young children with recurrent wheeze and asthma (1, 2), but can only be effective when delivered to a patient's airways. Pressurised metered dose inhalers (pMDIs) and spacers are widely used for the administration of inhaled corticosteroids to young children. The delivery of medication with pMDI-spacers is strongly influenced by patients' proficiency in using spacers (spacer technique). Spacer technique is often sub-optimal in children with asthma (3). An important part of spacer technique is a patient's breathing pattern. Breathing pattern strongly influences spacer output and drug delivery to the lung (4–8).

The Funhaler is an incentive spacer device with a spinning disk and a whistle attached to its expiratory arm. The Funhaler was designed to give positive feedback to children while they are using the device (9, 10). The rationale for this study was that the incentive toys on the expiratory arm of the Funhaler would positively influence children's breathing, and subsequently improve drug delivery. The hypothesis was that use of the Funhaler would improve clinical outcome in preschool children with asthma, by positively influencing drug delivery through improved inhalation technique.

Objective

To investigate the influence of an incentive spacer (Funhaler), on spacer technique and clinical outcome in young children with recurrent wheeze.

Study design

Two to six year old children in whom asthma had been diagnosed by a doctor, and who were being prescribed inhaled steroids for treatment of their asthma, were included in the study. Children were excluded if they had a known immunodeficiency, chronic lung disease other than asthma, known allergy to study medication, and if they had been administered systemic steroids in the three months prior to the baseline study visit. In the occasional case where the study doctor felt that a particular child's symptoms were likely to be caused by chronic lung disease other than asthma, the child was excluded from the study, and referred to the hospital's respiratory clinic. Children were recruited between May 2005 and October 2006 using local advertising, flyers and direct recruitment from the Emergency Department and clinics at Princess Margaret Hospital for Children in Perth, Western Australia.

At a screening visit eligible subjects who were on inhaled steroids other than fluticasone were changed over to equivalent doses of fluticasone. In subjects who were being treated with combination medication (inhaled fluticasone and salmeterol) the salmeterol was not discontinued. Subjects who were using spacers with face masks were instructed to use the mouthpiece of the spacer instead of using a facemask. Spacer technique was checked, and corrected if necessary. Information about asthma symptoms, personal and family history of atopy and asthma, and tobacco smoke exposure was obtained by standardised questionnaire.

A one month run in period followed to ensure that subjects had no problems with using a spacer mouthpiece instead of a mask, and to ensure that there were no adverse reactions to the use of the study medications. During the run in period, symptoms were monitored as per the rest of the study (see below). After the one month run in period, at the baseline study visit, subjects were randomised, using the block randomisation method, to receive regular inhaled fluticasone through either a conventional valved spacer (Aerochamber Plus®), or a Funhaler®. The Funhaler® and the Aerochamber Plus® have similar *in vitro* drug delivery characteristics (11).

Subjects were followed up three monthly for a year. Asthma control was defined as having daytime asthma symptoms less than twice a week and night time awakenings less than once a month. At each follow-up visit, the dose of inhaled asthma preventer medication was reduced if the subject's asthma was controlled and the parents agreed to it. Conversely, if the subject's asthma was not controlled, the dose of the study medication was increased, if appropriate. Doctors in the community were allowed to change the dose of preventer medication but study participants were instructed to notify the study coordinator if any change in medication dose was made.

Proficiency in spacer technique was measured at the first four visits by measuring the amount of salbutamol inhaled from spacer onto a filter interposed between subject and spacer. Five separate doses of salbutamol (Ventolin, GlaxoSmithKline, Melbourne, Australia) were administered to ensure that a measurable amount of drug was deposited onto the filters.

For one week before every study visit, parents documented symptoms of cough and wheeze, and bronchodilator use on diary cards. .

Quality of life (QoL) was measured with the PedsQL 3.0 Asthma Module® questionnaire, based on parental response at each study visit. The PedsQL, developed by Dr James Varni (12, 13), has been validated as a reliable and responsive measure of health related quality of life in children.

Ethics approval for this study was obtained from the hospital's ethics committee.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0. As data were not normally distributed samples were compared using the Mann-Whitney U test. Spearman linear regression was used to test for correlation between variables. The generalized estimating equation technique (GEE) was used to analyse repeated measures.

Results

Two hundred and twenty eight children were screened for eligibility. Ninety six children were excluded: 47 did not meet the inclusion criteria, and 49 either actively or passively refused to participate. One hundred and thirty two subjects were randomised: Twenty (15%) subjects aged 24–35 months, 37 (28%) subjects aged 36 – 47 months, 32 (24%) subjects aged 48 – 59 months, 20 (15%) subjects aged 60 – 71 months, and 22 (17%) subjects aged 72–83 months. One subject who was due to oversight randomised in the week after his seventh birthday was not excluded from the analysis. Subjects in the Funhaler and Aerochamber Plus groups were comparable in terms of age and gender characteristics and exposure to tobacco smoke, as per parental report (Table 1). Fifty five percent of subjects reported doctor diagnosed eczema, and 88% reporting a first degree relative with atopy

(asthma, eczema, or hay fever). Significantly more subjects in the Funhaler group had previously been diagnosed with eczema ($p = 0.01$).

One hundred and eleven subjects (84%) completed the study. A sub-analysis to determine temporal wheeze pattern, that was performed only on subjects who completed the study, is described elsewhere (14). Significantly more subjects dropped out of the Funhaler group (17 vs. 4; $p < 0.01$). Reasons given by subjects' parents for dropping out of the study were non-specific, with only one subject reporting disliking the Funhaler. A number of subjects were weaned off inhaled steroids during the course of the study, with 67% of subjects in the Funhaler group, and 70% of subjects in the Aerochamber group still being prescribed fluticasone at the final study visit. At no point in the study was there a significant difference ($p < 0.05$) between the Funhaler and the Aerochamber groups in terms of fluticasone dose prescribed, or in terms of salmeterol prescribed. The median daily dose of fluticasone prescribed was 200 μ g at the baseline visit, and decreased to 100 μ g by the 6 month visit. Salmeterol was prescribed in the Funhaler group and the Aerochamber Plus group respectively, for 24 (18%) and 27 (20%) of subjects at the time of the baseline study visit, and 18 (14%) and 25 (19%) of subject at the time of the nine month study visit.

Clinical outcome

At the baseline visit, the Funhaler group reported significantly fewer days without wheeze ($p = 0.02$), significantly fewer bronchodilator free days ($p = 0.03$), and had significantly lower QoL scores ($p = 0.05$) than the Aerochamber Plus group (Table 2).

GEE analysis for repeated measures throughout the study revealed no significant difference in wheeze free days, cough free days, bronchodilator free days or QoL between spacer groups ($p = 0.90, 0.87, 0.74$ and 0.11 respectively). After correcting for age and gender, and quality of life at the baseline visit, there was still no significant difference between spacer groups.

Spacer technique

After correcting for age and gender, the Funhaler group demonstrated significantly higher proficiency in spacer technique as determined by filter dose ($p = 0.05$, all subjects, all visits combined using GEE analysis). The improved proficiency in spacer technique in the Funhaler group was limited to subjects younger than 4 years of age at the time of randomisation ($p = 0.002$, all subjects < 4 years, all visits combined using GEE analysis).

In the Aerochamber Plus group subjects younger than four years of age at time of randomisation "inhaled" significantly less drug onto filter than subjects older than four years of age. In the Funhaler group there was no significant difference between subjects younger than four years of age, and subjects older than four years of age in terms of filter dose "inhaled". (Table 3).

Throughout the study, there was large inter-subject variation in proficiency in spacer technique, as measured by drug dose deposited on filter (Figure 1). Mean drug dose recovered from filters ranged from zero to 136 μ g (as the mean of five 100 μ g doses), with measurements above 100 μ g accepted as a combination of the known 25 percent variability in the nominal dose emitted from the pMDI (15), and an approximate ten percent margin of error in measurements.

Conclusion

Use of the incentive spacer device, the Funhaler®, did not improve clinical outcome in preschool aged children. Use of the Funhaler® appeared to improve spacer technique and

subsequent drug delivery. The improvement in spacer technique was only seen in children two to four years of age. In the Funhaler group spacer technique was similar in subjects younger than four years of age and subjects older than four years of age, whereas in the Aerochamber Plus group younger subjects “inhaled” significantly less drug onto filter. Use of the Funhaler® could therefore be a small step towards reducing variation in aerosolised drug delivery in young children, and improving spacer technique and subsequent medication delivery in very young children, who are especially vulnerable to poor spacer technique.

In order to quantify how well each subject used their pMDI-spacer device, we measured salbutamol delivered to a filter positioned between subject’s mouth and their inhalation device. This approach accurately quantifies drug delivered to the airway opening (6, 16–18), but clearly cannot partition the doses delivered to the upper and lower airway. Factors that determine drug deposition on airways are complex and include, amongst others, drug particle size distribution, rate of inhalation, inhalation volume and time, individual subjects’ airway anatomy. More accurate measurements of drug delivery to the airway would require scintigraphic studies which are not appropriate to perform in large clinical trials (19, 20). Filter dose measurements was considered a more robust measure of spacer technique than scoring the individual steps in spacer use (21) and is an accepted marker of aerosol drug delivery (17, 22).

Use of the Funhaler resulted in improved drug delivery to the filter in children under the age of 4 years, but did not result in a better clinical outcome. The failure of improved spacer technique to translate into an improvement in clinical outcome could be ascribed to other factors that influence symptom control in children with preschool asthma including variation in adherence to prescribed treatment (23), the limited effect of inhaled steroids in preventing viral exacerbations of asthma in this age group (2), and the varying intrinsic severity of preschool asthma (24). The study was not powered to demonstrate a difference in outcome in the subgroup of children who were younger than four years old at the beginning of the study. Additionally, various factors in the study design may have limited the effect of improved spacer technique of translating into improved clinical outcome: Subjects were prescribed different doses of inhaled steroids, and subjects’ doses did not stay constant during the course of the study. Furthermore, limiting symptom reporting to seven days before each study visit could have reduced the strength of the signal.

Despite the random allocation of subjects into each of the two spacer groups, there was a difference at the baseline visit in diary card reporting of asthma symptoms, bronchodilator use and QoL scores. One cannot exclude the possibility that the analysis of the outcomes of the two spacer groups may have been influenced by these significant differences at baseline, in spite of statistical correction for differences in baseline values when analysing the data.

In summary, this study demonstrated that use of the incentive spacer device, the Funhaler®, does not improve clinical outcome in preschool aged asthmatic children, but improves spacer technique and subsequent inhaled drug delivery. In addition, the results illustrate the large variation in inhaled drug dose delivered to individual children using pMDI’s and spacers.

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What is already known on this topic

Inhaled corticosteroid use modestly reduces respiratory symptoms in young children with recurrent wheeze. Medication delivery to patients' airways with pressurised metered dose inhalers and spacers is influenced by children's proficiency/technique in using delivery devices.

What this paper adds

Use of the Funhaler® incentive device does not improve clinical outcome, but improves spacer technique and subsequent drug delivery in children younger than 4 years of age. Variability in drug delivery is very large in young children using pMDI-spacers.

Figure 1.

Table 1

Age, gender and cigarette smoke exposure and atopy.

	Funhaler®	Aerochamber Plus®	p
Age in months Median (range)	51 (24–84)	51 (25–83)	0.94
Male N (%)	42 (31.8)	40 (30.3)	0.59
Smokers living in home N (%)	11 (17)	15 (22)	0.29
Mother smokes N (%)	5 (8)	9 (13)	0.40
Doctor diagnosed eczema N (%)	43 (66%)	30 (45%)	0.01*
1st degree relative with history of asthma, eczema or hay-fever N (%)	60 (92%)	56 (84%)	0.06

Table 2

Symptom free days as reported by diary card for the week before each study visit. Quality of life scores, as determined by PedsQL version 3 (asthma module), completed by parents at every study visit

	<u>Wheeze free days</u>		
	<u>Funhaler</u>	<u>Aerochamber Plus</u>	<u>p</u>
	Mean (95%CI)	Mean (95%CI)	
Baseline	5.92 (5.44–6.39)	6.49 (6.16–6.83)	0.02*
3 month visit	6.46 (6.05–6.86)	6.55 (6.22–6.89)	0.97
6 month visit	6.31 (5.91–6.72)	6.32 (5.89–6.75)	0.93
9 month visit	6.19 (5.68–6.69)	6.25 (5.78–6.72)	0.73
12 month visit	6.26 (5.76–6.76)	6.09 (5.54–6.64)	0.93
	<u>Cough free days</u>		
	<u>Funhaler</u>	<u>Aerochamber Plus</u>	<u>p</u>
	Mean (95%CI)	Mean (95%CI)	
Baseline	4.89 (4.39–5.58)	5.43 (4.89–5.97)	0.15
3 month visit	5.44 (4.81–6.07)	5.85 (5.31–6.38)	0.32
6 month visit	4.79 (3.98–5.60)	6.07 (5.57–6.56)	0.03*
9 month visit	5.79 (5.18–6.41)	5.05 (4.37–5.73)	0.13
12 month visit	6.07 (5.50–6.63)	5.29 (4.63–5.94)	0.11
	<u>Bronchodilator free days</u>		
	<u>Funhaler</u>	<u>Aerochamber Plus</u>	<u>p</u>
	Mean (95%CI)	Mean (95%CI)	
Baseline	5.63 (5.12 – 6.15)	6.28 (5.91 – 6.66)	0.03*
3 month visit	6.08 (5.59 – 6.57)	5.95 (5.44 – 6.47)	0.90
6 month visit	5.83 (5.26 – 6.40)	6.20 (5.73 – 6.68)	0.17
9 month visit	6.25 (5.79 – 6.71)	5.81 (5.24 – 6.38)	0.67
12 month visit	6.17 (5.69 – 6.65)	6.10 (5.65 – 6.54)	0.99
	<u>Quality of life scores</u>		
	<u>Funhaler</u>	<u>Aerochamber Plus</u>	<u>p</u>
	Mean (95%CI)	Mean (95%CI)	
Baseline	2047 (1967–2126)	2157 (2083–2231)	0.05*
3 month visit	2190 (2105–2275)	2231 (2146–2316)	0.5
6 month visit	2268 (2167–2370)	2395 (2329–2461)	0.03*
9 month visit	2340 ((2253–2426)	2365 (2289–2440)	0.66
12 month visit	2372 (2280–2464)	2388 (2280–2464)	0.81

Table 3

Comparison of spacer technique between different age groups and spacers. Spacer technique as measured by drug dose delivered to filter (as % of dose recovered from filter, actuator, and spacer).

	Aerochamber Plus group				Funhaler group				Comparison Funhaler vs. Aerochamber			
	Younger than 4 years		Older than 4 years		Younger than 4 years		Older than 4 years		Younger than 4 years		Older than 4 years	
	median (25 th , 75 th percentile)	n	median (25 th , 75 th percentile)	n	median (25 th , 75 th percentile)	n	median (25 th , 75 th percentile)	n	p	p	p	p
Baseline	33 (21, 41)	28	36 (20, 49)	37	33 (25, 44)	25	36 (25, 53)	35	0.41	0.70		0.37
3 months	23 (14, 33)	26	38 (25, 49)	30	36 (26, 43)	25	36 (24, 45)	28	0.66	0.04*		0.86
6 months	24 (21, 31)	19	32 (25, 46)	28	35 (23, 41)	18	36 (25, 46)	25	0.47	0.11		0.55
9 months	26 (17, 33)	20	33 (27, 39)	29	34 (23, 62)	17	29 (23, 37)	18	0.32	0.04*		0.26