ACADEMIC: ORIGINAL RESEARCH

The effect of mode of inhaled salbutamol delivery on measures of small airways obstruction in asthma: a comparison of treatment delivered via spacer and nebuliser

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Abstract

Background

Conventional clinical respiratory tests tell us little about the small airways of the lung (less than 2 mm in internal diameter). Patients with asthma affecting the small airways may respond differently to inhaled bronchodilator treatment (salbutamol) depending on the method of administration.

Aims

In this study, we aimed to assess if there was a difference in the effect of salbutamol treatment via metered-dose inhaler (MDI) and spacer compared to via nebuliser on measures of small airways function. It was hypothesised that the nebulised salbutamol would have a greater effect on the outcome measures due to the particle size being more appropriate for penetrating the smaller airways.

Methods

Two visits were completed by 14 participants with stable asthma. At both visits, lung function tests were completed both before and after administration of 1 mg salbutamol to measure airway obstruction (spirometry), mechanical load to ventilation (impulse oscillometry), and ventilation heterogeneity (multiple breath nitrogen washout). At visit one, seven participants were randomized to take salbutamol via MDI and spacer, and seven via nebuliser. At visit two, all participants took salbutamol via whichever method they had not been given at visit one.

Results

Results indicated that participants given salbutamol via MDI and spacer (compared to via nebuliser) showed a greater improvement, which was statistically significant, between the pre- and post-salbutamol values for most lung function tests.

Discussion

This result was unexpected and may have been due to greater wastage of drug via nebuliser than via MDI and spacer, and differing inhalation patterns. Tidal breathing during nebulised administration, and deep inhalation during use of MDI and spacer, could have affected the delivery of the drug.

Conclusion

This study implies that taking salbutamol via MDI and spacer would be beneficial if higher doses (e.g. 1 mg) were taken.

Introduction

Asthma is a common and potentially serious disease: in New Zealand, it has a high prevalence, with at least one in nine New Zealanders affected.[1] It is an obstructive airways disease characterised by variable airflow limitation associated with symptoms of wheezing, breathlessness, chest tightness, and coughing.[2] The aetiology of asthma is usually allergic and is associated with a T helper 2 cell and eosinophilic inflammatory process; it is considered to be an exaggerated hypersensitivity response which is IgE-mediated (also known as type 1 hypersensitivity).[3] The mainstays of treatment are inhaled corticosteroids and bronchodilators.[4] Asthma is sometimes described as a syndrome rather than a disease, encompassing a group of diseases with heterogeneous patterns and locations of inflammation within the airways. Small airways inflammation and dysfunction has been proposed as a distinct clinical asthma phenotype among those that have been described in the literature.[5,6] These phenotypes may respond differently to treatment, therefore the approach of "one treatment fits all" may not be appropriate.

The small airways (internal airway diameter less than 2 mm) are identified as a "quiet zone" because conventional clinical respiratory tests, such as spirometry, tell us little about this region of the lung[7,8]; for instance, forced expiratory volume in one second (FEV_1) has been shown to be normal despite the presence of disproportionate distal airway inflammation.[8] In contrast, asthma affecting large and medium sized airways is characterised by reduced FEV_1 and reduced FEV_1/forced vital capacity* (FVC) ratio.[4,9] Furthermore, patients with the small airways asthma phenotype often have suboptimal disease control that is not being effectively targeted or controlled by current therapies.[8,10] Most inhalers, such as conventional pressurised metered-dose inhalers (MDI), contain drug particles too large to sufficiently reach the small airways.[11] There are important associations between airway hyperresponsiveness, and airway remodelling, long-term decline in lung function, and asthma severity, which highlight the importance of research on small airways disease.[12] Recently, extra-fine particle sized hydrofluoroalkane solutions, with mass mean aerodynamic diameter of less than 2 μm delivered via MDI, have become available and may

benefit these patients, emphasising the value of identifying those with small airways disease.[9,12]

There is need for a better investigative approach to the small airways phenotype. Non-invasive techniques that might have clinical utility in the assessment of small airways disease include impulse oscillometry* (IOS) and multiple breath nitrogen washout (MBNW), which measure airways resistance and reactance, and ventilation heterogeneity, respectively.[11,13–15] In addition, the forced mid-expiratory flow between 25% and 75% (FEF_{25-75}) is believed to be more reflective of small airways obstruction than FEV_1 or FEV_1/FVC are,[12] and the change in the fraction of exhaled nitric oxide (FE_{NO}) with bronchodilation has also been proposed as a biomarker of small airways disease.[16,17]

At present, the Australasian treatment algorithm for acute asthma recommends the use of inhaled salbutamol from an MDI via a spacer for mild to moderate episodes, and nebulised salbutamol for severe episodes.[18] No attempt is made to differentiate between predominantly small versus large airways disease. This is potentially important as different inhaled asthma treatments have different penetration of the small airways: only particles that are less than 2 µm in diameter can penetrate the small airways.[19]

The differential effects of salbutamol via MDI and spacer compared to via nebuliser on the small airways are unknown. It may be that one of these delivery modes is superior to the other in penetrating the small airways and relieving acute obstruction. If so, there would be a case for changing treatment algorithms for acute asthma to incorporate diagnosis and/or tailored treatment of small airways obstruction.

This study aimed to examine the effects of different modes of salbutamol delivery on the small airways using the measures of small airways resistance mentioned above. It was hypothesised that the nebulised salbutamol would have a greater effect on the outcome measures due to the particle size being more appropriate for penetrating the smaller airways.

Materials and methods

Study participants

Fourteen participants were recruited for this study who were above 18 years of age, gave written informed consent, and had physician-diagnosed asthma requiring a minimum of treatment with regular inhaled corticosteroid. The following were exclusion criteria: a diagnosis of chronic obstructive pulmonary disease (COPD), bronchiectasis, lung cancer, or any other co-morbidity that would have likely affected participation; current smoking; previous ICU admission(s) for acute asthma; or poor asthma control according to 2016 NZ asthma guidelines.[20] Participants were also excluded if they had had a cold or flu within the past two weeks, as this may have affected lung function.[21]

Study protocol

All participants completed two visits at the Otago Respiratory Research Unit. At visit one, seven participants were randomized to take salbutamol via MDI and spacer, and seven via nebuliser; at visit two, all participants took salbutamol via whichever method had been not been given at visit one. All procedures were followed according to the manual of procedures, which was written before any experiments began. Before each visit, all participants were asked to withhold β_2-agonist inhalers for the recommended times, have no alcohol or caffeinated drinks, and do no vigorous exercise for eight hours prior.[22]

The first visit included conducting the four baseline lung function tests in the following order: (1) FE_{NO}, (2) IOS, (3) MBNW, and (4) spirometry, which are detailed below. Salbutamol was then given either via MDI and spacer, or via nebuliser. After administration, the four lung function tests were conducted again after fifteen minutes. At visit two, the same process was repeated, with the only change being the mode of delivery of salbutamol. We aimed to conduct the visits at the same time on both days, with a minimum of 48 hours between both visits in order to "washout" the effect of the treatment given in the first visit.

Mode of delivery of salbutamol

One mg of salbutamol was administered via the nebuliser, or the MDI and spacer. For the latter, the salbutamol was given as ten puffs, which were counted aloud by the experimenter as they were given (Salair, Salbutamol 100 mcg, REX Medical, Auckland). For the nebuliser, 1 mg of salbutamol (Asthalin, Salbutamol, 2.5 mg / 2.5 mL, REX Medical, Auckland) was diluted with 2.5 mL of 0.9% saline and delivered via a mask using air at 8 L/min driving gas flow for five minutes, which is when mist production tended to cease.

Lung function tests

EXHALED NITRIC OXIDE (FE_{NO})

FE_{NO} was the first test and was conducted using a chemiluminescence analyser (Niox Vero, Circassia, Sweden) at an expiratory flow rate of 50 mL/s as per American Thoracic Society (ATS) guidelines.[23] The measurement, recorded in parts per billion, was taken through a single breath of ten second exhalation.[24] If the participant was unable to adequately complete the test, it was repeated until a valid FE_{NO} measurement was made.

IMPULSE OSCILLOMETRY (IOS)

IOS was carried out using Masterscreen IOS (Carefusion, Höchberg, Germany) which was calibrated daily using a 3 L syringe. IOS required the participant to breathe normally (tidal breathing) into a mouthpiece through which impulse-shaped pressure signals were sent into the respiratory system by a loudspeaker. The tests were repeated until at least three reproducible manoeuvres were completed. SentrySuite software (Carefusion, Höchberg, Germany) was used to calculate measures of small airways resistance: resistance at 5 Hz (R5), reactance at 5 Hz (X5), difference between R5 and resistance at 20 Hz (Di5-20), area of reactance (AX), and resonant frequency (Fres.).

MULTIPLE BREATH NITROGEN WASHOUT (MBNW)

MBNW was conducted using a pulmonary function testing device (Eco Medics Ag Exhalyzer® D, Duernten, Switzerland) in accord with the current consensus.[25] As aforementioned, the inert marker gas was the resident N_2. At least two trials were undertaken for every participant; if the within-trial coefficient of variation (CV) of the functional residual capacity (FRC) was greater than 5% for two trials, a third trial was not undertaken. It was aimed to have a CV of 10% or less for three trials. Spiroware software (Eco Medics Ag, Duernten, Switzerland) was used to calculate the following measurements: lung clearance index 2.5% (LCI 2.5%), lung clearance index 5% (LCI 5%), conductive ventilation heterogeneity (Scond*VT), and acinar ventilation heterogeneity (Sacin*VT). The flow/volume calibration was carried out daily using a 3 L syringe. The gas/channel calibration was completed and saved for the first eight participants (for both visit one and visit two) and then was carried out daily for the remainder of the participants; this was not ideal but there were technical issues with the flow of room air from the wall. We consider that this did not alter the results appreciably.

SPIROMETRY

Spirometry was conducted as per the current guidelines using Masterscreen Spirometry (Carefusion, Höchberg, Germany), which was calibrated daily using a 3 L syringe.[26] At least three reproducible attempts were recorded, with the best spirometric measures being used for analysis. The following measurements were analysed by SentrySuite software (Carefusion, Höchberg, Germany): FEV_1, FVC, and FEF_{25-75}.

STATISTICAL ANALYSIS

Microsoft Excel (version 15.3, Microsoft Corp., Albuquerque, NM, USA) was used to analyse the data. Change scores were calculated by subtracting pre-salbutamol values from post-salbutamol values and

p-values were calculated by conducting a paired Student's t-test; the change scores of MDI and spacer and the change scores of nebuliser were then further compared with each other using a paired Student's t-test. A level of $p \leq 0.05$ was considered significant.

Results

All 14 participants were able to complete both the visits, with the exception of two participants, who were unable to complete the MBNW on visit two due to technical issues.

Table 1 shows mean results measured for the four different lung function tests, along with the change scores and p-values for MDI and spacer versus nebuliser; it also shows the overall change score p-value

Lung function test	Values pre-MDI	Values post-MDI	MDI change score	P-value for MDI change score	Values pre-nebuliser	Values post-nebuliser	Nebuliser change score	P-value for nebuliser change score	P-value for MDI and nebuliser change score
FE_NO (ppb)	25.7	25.4	−0.286	0.713	27.6	26.0	−1.60	0.192	0.442
IOS									
Di5-20 (kPa*s/L)	0.0843	0.0821	−0.00214	0.884	0.0979	0.0800	−0.0179	0.230	0.443
AX (kPa/L)	0.871	0.572	−0.299	**0.0385***	0.954	0.854	−0.100	0.455	**0.0450***
R5 (kPa*s/L)	0.434	0.397	−0.0364	0.0891	0.434	0.414	−0.0207	0.258	0.241
X5 (kPa*s/L)	−0.139	−0.106	0.0336	**0.00015***	−0.139	−0.126	0.0136	0.168	0.0880
Fres. (Hz)	17.8	13.8	−4.04	**0.0244***	16.9	15.8	−1.13	0.384	**0.0277***
MBNW									
LCI 2.5% norm.	8.66	8.66	0.00308	0.991	9.19	8.91	−0.274	0.350	0.518
LCI 5% norm.	5.99	5.93	−0.0623	0.587	6.08	6.09	0.01	0.934	0.660
Scond*VT	0.0266	0.0229	−0.00369	0.411	0.0485	0.0525	0.004	0.427	0.242
Sacin*VT	0.115	0.0954	−0.0199	0.110	0.161	0.166	0.005	0.589	0.148
Spirometry									
FEV_1 (L)	3.09	3.36	0.271	**0.00130***	3.07	3.20	0.129	**0.00785***	**0.0261***
FVC (L)	4.31	4.48	0.171	0.0863	4.28	4.38	0.0936	0.246	0.331
FEF_25-75 (L/s)	2.49	2.91	0.422	**0.00091***	2.42	2.75	0.326	**0.0135***	0.507
FEV_1/FVC ratio	0.719	0.752	0.0324	**0.0230***	0.713	0.731	0.0178	0.0970	0.245

Table 1: Mean measured values (3 s.f.) for pre- and post-salbutamol for all four lung function tests for both MDI (and spacer) and nebuliser, along with their respective change scores and p-values. The last column states the overall change score p-value between both MDI (and spacer) and nebuliser. All statistically significant p-values have been bolded and marked with an asterisk (*).

FENO (ppb) = Fraction of exhaled nitric oxide (in parts per billion)

IOS = Impulse oscillometry
Di5-20 = Difference between resistance at 5 Hz and resistance at 20 Hz
AX = Area of reactance
R5 = Resistance at 5 Hz
X5 = Reactance at 5 Hz
Fres. = Resonant frequency

MBNW = Multiple breath nitrogen washout
LCI 2.5% norm. = Lung clearance index 2.5%
LCI 5% norm. = Lung clearance index 5%
Scond*VT = Conductive ventilation heterogeneity
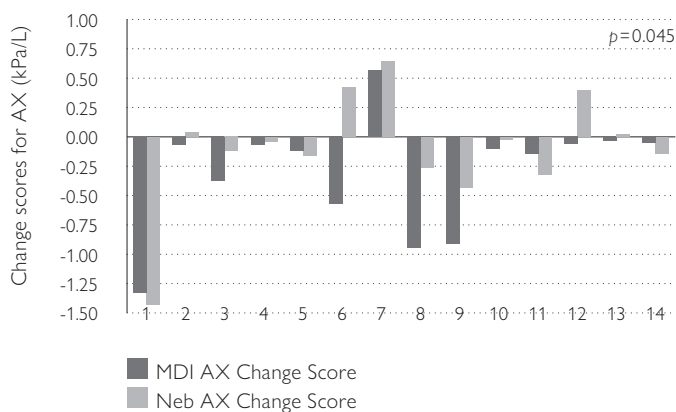Sacin*VT = Acinar ventilation heterogeneity

Spirometry
FEV1 = Forced expiratory volume in one second
FVC = Forced vital capacity
FEF25-75 = Forced mid-expiratory flow between 25% and 75%

Figure 1: Change scores for AX

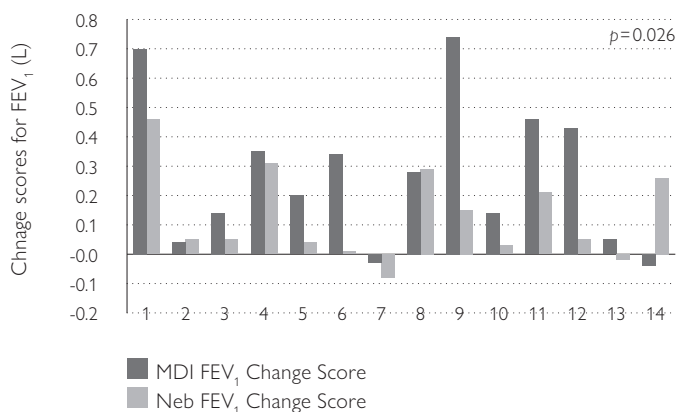*Figure 2: Change scores for Fres.*

Change scores between pre- and post-salbutamol values of area of reactance (AX) for both MDI and spacer, and nebuliser for each of the 14 participants. The statistically significant p-value (p ≤ 0.05) for the comparison of the two change scores is written in the top right corner.
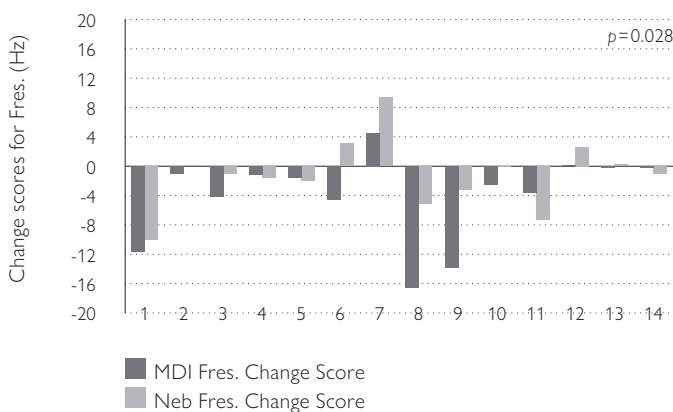
Change scores between pre- and post-salbutamol values of resonant frequency (Fres.) for both MDI and spacer, and nebuliser for each of the 14 participants. The statistically significant p-value (p ≤ 0.05) for the comparison of the two change scores is written in the top right corner.

Figure 3: Change scores for FEV₁

Change scores between pre- and post-salbutamol values of forced expiratory volume in 1 s (FEV₁) for both MDI and spacer, and nebuliser for each of the 14 participants. The statically significant p-value (p ≤ 0.05) for the comparison of the two change scores is written in the top right corner.

between both MDI and spacer, and nebuliser. Figures 1, 2, and 3 graphically show the three statistically significant results, with the dark grey bar representing the MDI change score and the light grey bar representing the nebuliser change score for each of the 14 participants.

Discussion:

The results from this study differed to the hypothesis; participants given salbutamol given via MDI and spacer showed a greater change between the pre- and post-salbutamol values for all lung function tests barring FE$_{NO}$, Di5-20, and LCI 2.5%. The measurements taken for AX, Fres., and FEV₁ showed statistically significant differences between MDI and spacer compared to nebuliser, showing a greater change score for MDI and spacer.

There are several possible explanations to explain why MDI and spacer showed a greater change than nebuliser for measurements of small airways dysfunction, with the first being a shortcoming in the delivery of the salbutamol. An attempt was made to distribute equal doses of salbutamol (1 mg) via both the MDI and spacer and the nebuliser, however 1 mg may not have reached the lungs in both cases. The FEV₁ increase between pre- and post-salbutamol for MDI and spacer was greater than for nebuliser, suggesting that maximal bronchodilation of large airways was not achieved with nebuliser, which may have impacted on the results.

In this study, a jet nebuliser was used to deliver the salbutamol. Although the same jet nebuliser was used for all participants, not all participants may have received the same amount of salbutamol. Jet nebulisers, although useful for paediatric, elderly, non-conscious patients as they do not require patient coordination, can be inefficient in drug delivery.[27] There are multiple factors which contribute to the wastage of the drug, but the factors which may have notably affected the results include residual volume and breathing patterns of the participants. In the jet nebuliser used, there was a small volume of drug remaining, even after mist production had ceased, which meant not all the salbutamol was delivered.[28] Moreover, as this was a continuously operated nebuliser, much of the aerosol would have been lost into the surroundings during exhalation.[27,29] In addition, it has been found that one-quarter of aerosol is exhaled without depositing, leading to greater drug loss.[30] Also, participants with fast inspiration would have had deposition of the particles in the upper airways due to inertial impaction, further reducing the amount delivered into the lungs.[29] Although all participants were instructed to breathe through the mouth for the duration of nebulisation, nose

breathing may have occurred and this would also have further decreased the particles reaching the lungs.[29] Other features that may have affected the effective dose delivered, but were kept constant for all participants, include: driving gas flow, volume fill, concentration of nebuliser solution, solution viscosity and temperature, and nebulisation time.[29]

It is expected that there would have been some inefficiency through the MDI and spacer, however, more controls were in place as compared with the jet nebuliser to minimise drug wastage. Participants were asked to wear nose pegs during the administration of salbutamol, which limited aerosol particle loss through the nasopharynx.[29] The canister was shaken between each actuation, to maximise output.[31] The plastic spacer that was used in this study had been used multiple times before, thereby limiting electrostatic charge.[32] Deposition by impaction in the oropharyngeal region could not be minimised completely and it is stated that the majority of the emitted dose from MDI devices deposits by impaction in these regions.[33] However, using a spacer does reduce the oropharyngeal deposition of a drug substantially.[34] It has also been found that peripheral deposition of a drug is greater when using MDI with spacer, compared with using an MDI alone.[35]

In addition, the breathing pattern was different for the two different delivery methods; participants took deep slow inspirations with the MDI and spacer, whereas they were breathing in a tidal manner with the nebuliser. This brings to the foreground possible further investigation into whether deep slow inspirations with the MDI and spacer aids distribution of the drug to the small airways.

Limitations of this study include the apparent lack of equivalence between the doses given through MDI and spacer compared to through nebuliser. However, this underscores the need for having accessible methods to reduce wastage of drug via nebulisers; it has been reported that the dose of prescribed β₂-agonist is 50 times greater for nebuliser than it is for MDI to overcome the wastage of the drug.[36] Another aspect of this study which could be improved for future investigations is recruitment: relatively mild asthmatics were recruited for assessing the effects on small airways, whereas the ideal participants would be those who already have a significant level of small airways disease. It could also be possible to withdraw participants' ICS inhalers prior to conducting the experiments to a point of loss of control of their asthma.

The results of this study suggest that taking salbutamol via MDI and spacer would be beneficial if higher doses (e.g. 1 mg) were taken. This study also underlines the importance of conducting future experiments in this field with clinically relevant doses (200–400 mcg for MDI and spacer and 1 mg for nebuliser).

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Acknowledgements

Financial disclosures

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