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

Aqeeda Singh, Jan Cowan, Jack Dummer

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.
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 lung injury; or any other co-morbidity that would have likely affected participation. 

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 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 β₂-agonist inhalers for the recommended times, have no alcohol or caffeinated drinks, and do no vigorous exercise for eight hours prior.

The first visit included conducting the four baseline lung function tests in the following order: (1) FE\textsubscript{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\textsubscript{NO})

FE\textsubscript{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. The measurement, recorded in parts per billion, was taken through a single breath of ten second exhalation. If the participant was unable to adequately complete the test, it was repeated until a valid FE\textsubscript{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. SensorySuite 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 reactance at 20 Hz (D5-20), 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 Exhalizer® D, Duernten, Switzerland) in accord with the current consensus. As aforementioned, the inert marker gas was the resident N\textsubscript{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. 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): FE\textsubscript{V1}, FVC, and FE\textsubscript{F25-75}.

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 benefit these patients, emphasising the value of identifying those with small airways disease. 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. In addition, the forced mid-expiratory flow between 25% and 75% (FE\textsubscript{F25-75}) is believed to be more reflective of small airways obstruction than FE\textsubscript{V1} or FE\textsubscript{V1}/FVC are, and the change in the fraction of exhaled nitric oxide (FE\textsubscript{NO}) with bronchodilation has also been proposed as a biomarker of small airways disease.

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. 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.

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.

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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.

**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 (*)**.

<table>
<thead>
<tr>
<th>Lung function test</th>
<th>Values pre-MDI</th>
<th>Values post-MDI</th>
<th>MDI change score</th>
<th>MDI change score</th>
<th>MDI change score</th>
<th>Values pre-nebuliser</th>
<th>Values post-nebuliser</th>
<th>Nebuliser change score</th>
<th>Nebuliser change score</th>
<th>Nebuliser change score</th>
<th>( p )-value for MDI change score</th>
<th>( p )-value for nebuliser change score</th>
<th>( p )-value for MDI and nebuliser change score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV1 (ppb)</strong></td>
<td>25.7</td>
<td>25.4</td>
<td>-0.286</td>
<td>0.713</td>
<td>27.6</td>
<td>26.0</td>
<td>-1.60</td>
<td>0.192</td>
<td>0.442</td>
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<tr>
<td><strong>IOS</strong></td>
<td>0.0843</td>
<td>0.0821</td>
<td>-0.00214</td>
<td>0.884</td>
<td>0.0979</td>
<td>0.0800</td>
<td>-0.0179</td>
<td>0.230</td>
<td>0.443</td>
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<tr>
<td><strong>AX (kPa/L)</strong></td>
<td>0.871</td>
<td>0.572</td>
<td>-0.299</td>
<td>0.0385*</td>
<td>0.974</td>
<td>0.874</td>
<td>-0.100</td>
<td>0.455</td>
<td>0.0450*</td>
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<tr>
<td><strong>R5 (kPa*s/L)</strong></td>
<td>0.434</td>
<td>0.397</td>
<td>-0.0364</td>
<td>0.0891</td>
<td>0.434</td>
<td>0.414</td>
<td>-0.0207</td>
<td>0.258</td>
<td>0.241</td>
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<tr>
<td><strong>XS (kPa*s/L)</strong></td>
<td>-0.139</td>
<td>-0.106</td>
<td>0.0336</td>
<td>0.00015*</td>
<td>-0.139</td>
<td>-0.126</td>
<td>0.0136</td>
<td>0.168</td>
<td>0.0880</td>
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<tr>
<td><strong>Fres. (Hz)</strong></td>
<td>17.8</td>
<td>13.8</td>
<td>-4.04</td>
<td>0.0244*</td>
<td>16.9</td>
<td>15.8</td>
<td>-1.13</td>
<td>0.384</td>
<td>0.0277*</td>
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<td><strong>MBNW</strong></td>
<td></td>
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<td><strong>LCI 2.5% norm.</strong></td>
<td>8.66</td>
<td>8.66</td>
<td>0.00308</td>
<td>0.991</td>
<td>9.19</td>
<td>9.81</td>
<td>-0.274</td>
<td>0.350</td>
<td>0.518</td>
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<tr>
<td><strong>LCI 5% norm.</strong></td>
<td>5.99</td>
<td>5.93</td>
<td>0.00623</td>
<td>0.587</td>
<td>6.08</td>
<td>6.09</td>
<td>0.01</td>
<td>0.934</td>
<td>0.660</td>
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<tr>
<td><strong>Scond*VT</strong></td>
<td>0.0266</td>
<td>0.0229</td>
<td>-0.00369</td>
<td>0.411</td>
<td>0.0485</td>
<td>0.0525</td>
<td>0.004</td>
<td>0.427</td>
<td>0.242</td>
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<tr>
<td><strong>Sacin*VT</strong></td>
<td>0.115</td>
<td>0.0954</td>
<td>-0.0199</td>
<td>0.110</td>
<td>0.161</td>
<td>0.166</td>
<td>0.005</td>
<td>0.589</td>
<td>0.148</td>
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<td><strong>Spirometry</strong></td>
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<tr>
<td><strong>FEV1 (L)</strong></td>
<td>3.09</td>
<td>3.36</td>
<td>0.271</td>
<td>0.00130*</td>
<td>3.07</td>
<td>3.20</td>
<td>0.129</td>
<td>0.00785*</td>
<td>0.0261*</td>
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<tr>
<td><strong>FVC (L)</strong></td>
<td>4.31</td>
<td>4.48</td>
<td>0.171</td>
<td>0.0863</td>
<td>4.28</td>
<td>4.38</td>
<td>0.0936</td>
<td>0.246</td>
<td>0.331</td>
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<tr>
<td><strong>FEF25–75 (L/s)</strong></td>
<td>2.49</td>
<td>2.91</td>
<td>0.422</td>
<td>0.00091*</td>
<td>2.42</td>
<td>2.75</td>
<td>0.326</td>
<td>0.0135*</td>
<td>0.507</td>
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<tr>
<td><strong>FEV1/FVC ratio</strong></td>
<td>0.719</td>
<td>0.752</td>
<td>0.0324</td>
<td>0.0230*</td>
<td>0.713</td>
<td>0.731</td>
<td>0.0178</td>
<td>0.0970</td>
<td>0.245</td>
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</tbody>
</table>

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

**IOS** = Impulse oscillometry

**DIS-20** = Difference between resistance at 5 Hz and resistance at 20 Hz

**AX** = Area of reactance

**R5** = Resistance at 5 Hz

**XS** = 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**

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 (\( p \leq 0.05 \)) for the comparison of the two change scores is written in the top right corner.

**Figure 2: Change scores for Fres.**

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 (\( p \leq 0.05 \)) for the comparison of the two change scores is written in the top right corner.

\( p \)-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.
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 FEV₁-DIS, DiS-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 bronchodilatation 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. 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. Moreover, as this was a continuously operated nebuliser, much of the aerosol would have been lost into the surroundings during exhalation. In addition, it has been found that one-quarter of aerosol is exhaled without depositing, leading to greater drug loss. 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. 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.

**References:**


21. The Johns Hopkins University. Pulmonary function tests [Internet]. Available from: https://www.hopkinsmedicine.org/healthlibrary/test_procedures/pulmonary/pulmonary_function_tests_92,p07759


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