Comparison of the effects of nebulised and inhaled salbutamol on breathlessness in severe COPD

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Summary Background: Patients with chronic obstructive pulmonary disease (COPD) often report greater relief of breathlessness with nebulised bronchodilators than with the same medicine administered from a metered dose inhaler (MDI). This suggests that the nebulised medicines may have an effect on breathlessness over and above changes in lung function resulting from bronchodilatation.

Methods: Twenty-four subjects with COPD and breathlessness at rest participated in this randomised, crossover trial. The mean age was 72 years and the mean FEV1 was 26% of predicted. Subjects were studied on four separate days. On two days they were treated with nebulised salbutamol and on the other 2 days with salbutamol from an MDI and spacer. With each method of delivery, local anaesthetic cream was applied to the face on one day and to the back of the hand on the other.

Results: Five minutes after administration of salbutamol the subjects were significantly less breathless with nebulised salbutamol but by 45 min both treatments resulted in equivalent relief. There was no difference between the treatments in the change in FEV1 or VC and application of local anaesthetic to the face did not influence the response.

Conclusion: There was a small early benefit with nebulised salbutamol but this was not sustained and was not affected by topical anaesthesia. The benefit of nebulisation does not appear to be large enough to warrant the routine, widespread use of nebulised bronchodilators for the treatment of stable COPD.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) often report relief of breathlessness when they have cool air blowing on their face. Many also report greater relief of breathlessness with a nebulised β2 agonist than they do with the same medicine administered from a metered dose inhaler (MDI). A number of studies suggest that mechanical properties of the nebulisation process may play a role in the relief of breathlessness. In a
previous study of subjects with severe COPD, we found that nebulised saline reduced breathlessness almost as much as nebulised terbutaline, even though saline had no effect on lung function. In another study healthy volunteers experienced less breathlessness while exercising if a jet of cold air was directed at the cheek rather than at the leg. Patients with COPD have also been shown to exercise longer, and to report less end-of-exercise dyspnoea, while breathing air at 7°C compared with room temperature.

The present study was designed to investigate the effects of nebulisation on breathlessness in patients with COPD and to answer two questions:

(i) Is there a difference in perception of breathlessness when a bronchodilator is administered from a nebuliser compared with delivery of the bronchodilator administered by via MDI and spacer?

(ii) Is the effect of nebulised bronchodilators on breathlessness modified by anaesthetising the face?

Methods

Subjects were included in the study if they met the ATS criteria for a diagnosis of COPD, had >20 pack-years smoking history and were breathlessness at rest. In addition they had to be clinically stable with no exacerbations in the previous 8 weeks. Subjects were excluded if they had an FEV₁ of greater than 60% of predicted or if their FEV₁ increased by more than 15% and 250 ml following salbutamol. Patients who had heart failure, lung diseases other than COPD, significant cognitive impairment, a change in medication in the previous four weeks, or who were sensitised to local anaesthetics were also excluded. The study was approved by the Auckland Ethics Committee and each subject gave written informed consent.

The subjects were involved in 4 study visits, within a period of 28 days, with each visit being at least 2 days apart. At each visit the subjects received one of the four study treatments (see Table 1). The treatment order was randomised using a computer programme in blocks of 24. With each subject the treatment order was kept in an opaque, sealed envelope that was opened on the first study visit.

Subjects were studied at the same time of the day and under the same conditions. Short-acting inhaled β₂ agonists were withheld for at least 4 h, long-acting inhaled β₂ agonists for at least 12 h, and inhaled ipratropium for at least 6 h prior to each visit.

Breathlessness was measured using both:

1. A 10 cm Visual Analogue Scale (VAS) with the term 'extremely breathless' at one end and 'not at all breathless' at the other.

2. A seven point Likert scale that ranged from 1='extremely short of breath' to 7='not at all short of breath'.

Likert or category scales are as responsive as VAS but have less variability, and because of the limited range of responses they have floor and ceiling effects. For this reason we chose to use both types of scale.

Lung function was recorded with a dry bellows spirometer (Vitalograph, Buckingham, UK). The best of three attempts was used for FEV₁ and slow Vital Capacity.

On arrival at the study centre the subjects rested for 15 min. Following initial recordings, the skin of the face or hand was cleaned with an alcohol wipe, and then a local anaesthetic cream of 2.5% xylocaine and 2.5% prilocaine (EMLA, AstraZeneca PLC, London, UK) was applied. Thirty minutes (min) were allowed for the anaesthetic to take effect. Anaesthesia was determined by loss of skin sensitivity to light touch with a cotton swab. After further recordings of breathlessness and lung function, the bronchodilator was administered. This was either 5 mg salbutamol, in a volume of 2.5 ml, delivered via a nebuliser (Hospitak, Lindenhurst, NY, USA) and mask using compressed air at 6 l/min for 5 min, or 400 mcg of salbutamol, inhaled one puff (100 mcg) at a time, from an MDI and large volume spacer (Volumatic). Subjects were instructed to use tidal breathing while inhaling salbutamol. The subjects remained seated throughout the study. Breathlessness was measured again at 5, 10, 15, 25 and 45 min after the start of administration of salbutamol.

The data was analysed using SAS software (SAS Institute Inc., Cary, NC, USA), using a mixed linear model approach. Treatment was entered as two variables. One variable was whether the salbutamol was delivered by nebulisation or by metered dose inhaler. The other was whether or not EMLA cream was used on the face. Also included in the model was the order of the treatment. Baseline recordings were those taken just prior to salbutamol administration. The five subsequent readings were analysed as repeated measures and the subject as a random effect. For FEV₁ and VC there was only one follow-up measure at 45 min.
Results

There were 24 subjects (16 male) who completed all four days of the study. They had a mean age of 72 (SD 6.64, range 57–83) years, a mean smoking history of 52.5 (27.56) pack-years, and their mean FEV1 was 0.66 (0.38) l, which was 25.9% (14.50) of predicted. All subjects had an FEV1<60% of predicted. On average, the time from the diagnosis of COPD was 8.6 (5.24) years. Four further subjects were excluded after randomisation, three when it was clear on the first or second study day that they were not short of breath at rest, and one who had reversibility of 350 mls (24%).

Visual analogue scale

Applying the local anaesthetic cream to the face had no effect on the change in breathlessness over time as measured on the VAS (P = 0.90) so the use of anaesthetic cream was removed as a variable from the analysis.

A difference was observed in the change in the VAS score over time when nebulised salbutamol was compared with salbutamol from MDI and spacer (Fig. 1). When the individual time points were examined, the VAS scores 5 min after treatment were significantly higher with nebulised salbutamol (P = 0.0006) than with MDI and spacer. This difference had disappeared by 45 min (P = 0.36). The mean improvement in VAS 5 min after the administration of salbutamol was 1.04 cm with nebuliser and 0.47 cm with MDI.

At 45 min, however, there was no difference with mean improvements of 1.30 cm with nebuliser and 1.25 cm with MDI.

Likert score

Similar effects were found when breathlessness was measured using the Likert score. There was no effect of applying the local anaesthetic cream to the face on breathlessness over time (P = 0.56). The Likert scores at 5 min after treatment were significantly higher with nebulisation than with the MDI (P = 0.0002). At 5 min the mean improvement was 0.52 points with nebuliser and 0.02 points with MDI. At 45 min, however, there was no difference with a change of 0.83 points with nebuliser and 0.88 points with MDI (P = 0.92).

There was no difference between nebulised salbutamol and salbutamol from MDI and spacer in the FEV1 measured at 45 min (P = 0.58). The mean improvement in FEV1 was 0.12 l (0.1) with nebuliser and 0.11 l (0.1) with MDI. The FEV1 was not influenced by the presence or absence of local anaesthetic cream (P = 0.54). VAS, Likert and FEV1 were not affected by the order in which the treatments were given.

Discussion

We found that 5 mg of nebulised salbutamol provided more rapid initial relief of breathlessness in subjects with COPD than 400 µg salbutamol, from an MDI and spacer, but that there was no difference in breathlessness scores at 45 min between the two modes of delivery. This suggests that the difference in the initial response to the treatment may be related to the process of nebulisation. The mean

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The four study treatments administered in random order.</th>
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<tbody>
<tr>
<td>1</td>
<td>Nebulised salbutamol 5 mg +local anaesthetic face</td>
</tr>
<tr>
<td>2</td>
<td>Nebulised salbutamol 5 mg +local anaesthetic hand</td>
</tr>
<tr>
<td>3</td>
<td>Inhaled salbutamol 4 x 100 mcg puffs +local anaesthetic face</td>
</tr>
<tr>
<td>4</td>
<td>Inhaled salbutamol 4 x 100 mcg puffs +local anaesthetic hand</td>
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![Figure 1](image-url) Mean change from baseline breathlessness measured on VAS with salbutamol administered either by nebuliser or MDI inhaler with spacer. Treatment was administered between 0 and 5 min. Error bars denote standard errors of the mean.
difference was 5 mm on a VAS and 0.5 on a seven-point Likert scale. These differences are small but likely to be clinically significant. In a study of patients with acute asthma, a change in VAS of at least 5 mm reliably discriminated between those with and without symptom improvement. The additional benefit seen with nebulisation could be the result of having a wet aerosol sprayed on to the face. If so, this could act by cooling the face or through another neurally mediated mechanism. Having said this we would have expected the local anaesthetic cream to reduce the effects of nebulisation and we did not observe this.

Some subjects reported that the moistening and cooling effect that the nebulisation had on their nose and throat was comforting. This may have contributed to the relief of breathlessness. This effect would not have been modified by the local anaesthetic which was only applied to the face. Other studies provide support for this idea. In a study of patients with terminal cancer and breathlessness, the effects of administering oxygen through nasal prongs was compared with air delivered at the same rate through nasal prongs. Air was as effective as oxygen in reducing breathlessness. In another study where oxygen was administered through nasal cannulae to patients with COPD, there was a significant increase in breathlessness following nasal anaesthesia with topical lignocaine. This suggests that the reduction of breathlessness was due to the flow of gas the nose and not to the increased arterial oxygen tension.

Some of our subjects thought that their breathing was more controlled and regular with nebulisation than with the MDI and spacer. It is conceivable that nebulisation does alter the pattern of respiration. In infants, pressure of a mask in the trigeminal nerve distribution reduced ventilatory frequency but other factors such as noise may play a role. The importance of dynamic hyperinflation and its relationship to breathlessness, especially on exercise, is increasingly being recognised. In severe COPD a slower breathing rate could result in more efficient expiration of trapped air and improve symptoms. Despite instructions to the patients to use tidal breathing, we cannot exclude the possibility that a difference in breathing pattern accounted for the early benefit of nebulisation.

Another possible explanation for our findings is that the high dose of salbutamol, delivered by nebulisation, led to a more rapid improvement in lung function and this, in turn, led to more rapid relief of breathlessness, but we think that this is unlikely to be the case. Although we did not measure FEV₁ and VC over the first 15 min of the study, other investigators have made serial measurements of FEV₁ and VC in subjects with COPD following inhalation of different doses of salbutamol. Vathenan et al. compared 400 μg, 1, 2 and 4 mg of inhaled salbutamol delivered from a dry powder inhaler in subjects with stable COPD. FEV₁ was measured at 2, 5 and 10 min after inhaled salbutamol and at subsequent time points out to 6 h. There was no difference in the FEV₁ at the early time points for any of the doses although the higher doses led to more sustained bronchodilation at 4 h. Hansen compared the effects of 2 mg of terbutaline from a turbuhaler and 5 mg terbutaline from a jet nebuliser (Pari Inhalierboy) in 22 subjects with stable COPD. Changes in FEV₁, at 5 and 15 min after inhaled terbutaline were the same for the two treatments. In this study the dose of terbutaline delivered from the dry powder inhaler was similar to that from the nebuliser but the study does illustrate that the process of nebulisation does not in itself lead to a more rapid improvement in lung function. Another study compared the effects of nebulised salbutamol with salbutamol from an MDI and spacer in the treatment of acute exacerbations of COPD. Patients were randomised to receive three doses of 200 mcg salbutamol from an MDI and spacer (in addition to nebulised saline) or 2.5 mg salbutamol via nebuliser (plus placebo MDI) over 15 min. There was no difference in lung function between the treatments at any of the three time points up to 15 min. None of these studies suggest that the more rapid improvement in breathlessness seen with nebulised salbutamol is likely to be due to an effect on lung function.

A potential weakness of our study is that it was not blinded, but the different delivery mechanisms meant it was not possible to conduct a double-blind study. We could not use a double-dummy design because nebulised saline can also reduce breathlessness. The patients were not nebuliser naïve, so it could be argued that they may have had an anticipatory response leading to a more rapid improvement in the breathlessness scores with nebulisation. To minimise this possible bias, subjects were not made aware of the treatment allocation until immediately before administration, and the three investigators who made patient recordings (RS, SB, PP) kept the study conditions as similar as possible in all other respects. Nonetheless we cannot rule out this possibility altogether.

Nebuliser therapy is used in the community by many patients with severe COPD. We have previously found that 40% of patients admitted to our hospital with an exacerbation of COPD were using nebulised bronchodilators at home. There are,
however, drawbacks to this practice including the cost of the machine and the medication, the lack of portability, and need to clean and maintain the machine. Despite the prompt, and clinically significant improvement in breathlessness with nebulised salbutamol, this was not sustained and there was no difference between the treatment groups in their perception of breathlessness at 45 min. The short-lived difference between treatments in their effect on breathlessness would not appear sufficient to justify the widespread, routine use of nebulised bronchodilators in subjects with stable COPD. Eiser and her colleagues conducted a study that was of longer duration and came to a similar conclusion. They studied 19 patients in a cross over study comparing nebulised bronchodilators with bronchodilators from MDI and spacer. Each treatment was administered four times a day for 2 weeks. There were no significant differences between the treatments in dyspnoea or quality of life scores.

We do not believe that our findings should lead to changes in the current recommendations on the domiciliary use of nebulised bronchodilators for patients with stable COPD. However our findings do support the use of nebulised bronchodilators as opposed to MDI (plus spacer) in acute exacerbations where rapid relief of breathlessness is important. It is still not clear, however, why there is greater initial benefit with nebulised bronchodilators compared with the use of an MDI and spacer and this warrants further investigation.

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