Spacers and nebulisers for the delivery of beta-agonists in non-life-threatening acute asthma

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Summary

Background: In asthma exacerbations, higher doses of inhaled beta-agonists are used to overcome acute bronchoconstriction. Traditionally, wet nebulisation has been used, but metered-dose inhaler with a spacer device is an alternative delivery method. Objective: To compare the clinical outcomes in adults and children with acute asthma, presenting in emergency departments or in the community, who have been randomised to beta-agonists given by two different delivery methods. Methods: a metered-dose inhaler with spacer or a nebuliser. Results: A Cochrane review has found no important differences between the two delivery methods in adults. Children may suffer fewer side effects with spacer delivery. Conclusions: Individual response to treatment cannot be predicted, but many studies overcame this problem by using frequent repeated doses of beta-agonists (one respule via nebuliser or four separate actuations of a metered-dose inhaler through a spacer) every 10-15 min, titrated against the clinical response of the patients. This approach is advocated in clinical practice.

KEYWORDS

Acute disease; Adrenergic beta-agonists; Administration and dosage; Anti-asthmatic agents; Administration and dosage; Asthma; Drug therapy; Human; Nebulisers and vaporisers

Background

Acute exacerbations of asthma remain common in spite of the increasing use of prophylactic medication and pose a regular challenge to medical services, both in hospital and in primary care. Treatment with increased doses of inhaled beta-agonists is often required for exacerbations, in addition to other agents such as corticosteroids and oxygen. In order to relieve bronchospasm effectively the beta-agonist needs to be delivered to the peripheral airways. This is made more difficult in acute asthma since the narrowed airways and faster respiratory rate result in increased drug deposition in the throat and large airways.

In order to combat this problem of delivery, two different methods can be employed: wet nebulisation and metered-dose inhaler (MDI) with a spacer (holding chamber). Nebulisation can be accomplished with room air or supplemental oxygen, and requires a supply of compressed gas or a power source. High doses of beta-agonist are put into the nebulisation chamber (typical up to 25 times the dose from a MDI), but much of this dose is lost into the atmosphere and never reaches the patient’s airways.

More recently, beta-agonists delivered via MDIs through a spacer have been used in acute asthma. The inhaler is actuated into the chamber that is then emptied by the patient using either tidal breathing or single breaths. It should however be noted that compliance with the usual instructions to take a deep breath and then hold it for several seconds is not possible for patients with acute exacerbations of asthma.

There is much debate about the relative merits of each delivery method. Whilst nebulisers have traditionally been used in acute exacerbations of asthma, a meta-analysis of trials in adults with asthma or chronic obstructive pulmonary disease (COPD) suggested that MDIs with a spacer are as
effective. In addition, cost and infection control considerations may be important additional determinants of which system is employed. For example, in the community the cost of using a nebuliser exceeds that of a spacer and MDI. In hospital emergency departments, the cost calculations are more complex since disposable nebuliser masks are often driven by piped oxygen; costs may depend on whether or not all patients are sent home with a new holding chamber. Nebulisers represent a potential source of cross-infection, and require regular maintenance.

Whilst nebulisation in hospital is usually oxygen driven, most portable nebulisers used by patients in their homes and carried by general practitioners are air driven. Portable oxygen cylinders can be used to nebulise beta-agonists but a high-flow valve is required for this purpose.

This overview seeks to address some of the practical issues involved in comparing nebulisation and spacers as delivery devices in acute asthma, and uses the Cochrane systematic review (updated in 2001) as source material.

Objectives

The objective of the Cochrane review was to compare the clinical outcomes following the use of beta-agonists in people with acute asthma presenting in the community or in hospital emergency departments. Delivery with MDI and spacer was compared to delivery with nebuliser.

Problems with comparing delivery methods

There are several methodological difficulties in comparing the devices used in delivery of beta-agonists. The main problem is confounding by the dose of beta-agonist administered. An unknown proportion of the nominal delivered dose will reach the lungs of the recipient, and this will vary according to the technique used in inhalation, the severity of the exacerbation and the type of nebuliser or spacer employed. Secondly there are issues relating to a possible placebo response from treatments that patients have found effective in the past (such as nebulised beta-agonists), as acute asthma can be a very frightening experience and accompanied by anxiety that increases the difficulty in breathing. Thirdly there may be differences between children and adults in their use of the devices and response to beta-agonists, and there may be differences between the community and hospital settings.

Deciding which studies to use

Study design and participants

In order to reduce the problems of bias the Cochrane review comparing delivery methods sought out only randomised controlled trials. Trials were not excluded on the basis of being unblinded, but were required to use the same drug through nebuliser or spacer. Children and adults with acute asthma were included who were treated for acute asthma in emergency departments or in the community. Infants were not included, so trials on small children with a mean age of under 2 years were excluded. Also patients who were already hospitalised have not been included in the review at present, but will be incorporated at a future date.

Studies on patients with COPD were excluded, but a meta-analysis of trials in adults with asthma or COPD has been published showing similar results to the Cochrane review.

Outcome measures

The primary outcome measure for the review was hospital admission. This was chosen because it was thought that avoiding admission was important to people suffering acute asthma attacks (and to their families). Secondary outcomes included duration in the emergency department, change in lung function, pulse and respiratory rates, and change in oxygen saturation.

Review methods

The methods used to carry out the review are described in detail elsewhere. A comprehensive search was carried out using the Cochrane Airways group trials register, and no trials were excluded on the basis of language or publication status. The review has been updated twice since it was first published in 1996. Two reviewers independently assessed the full text of papers to check whether the inclusion criteria were met, and to assess the methodological quality of the trials using the method proposed by Jadad et al. This method scores for whether allocation of treatment was adequately concealed during randomisation of the patients, whether there is blinding of the
participants and assessors, and whether withdrawals and dropouts are described. Sensitivity analysis was carried out to check the results if only trials of higher methodological quality were considered, and where heterogeneity between the results of different trials was found this was explored.

Description of included studies

The studies come from all over the world. All studies excluded patients who were suffering from life-threatening asthma. Only one was carried out in the community; all others were conducted in hospital emergency departments. The single pre-hospital study comparing nebulisation to spacer was excluded as there was no randomisation. Different beta-agonists, holding chambers and nebulisers were represented in the studies. The dosage ratio between delivery methods varied from 1:1 to 1:13 in favour of the holding chamber. The dosing schedule also varied from a single treatment to multiple treatments at 10–30 min intervals.

In general, the sample size of individual studies was small (range 18–152 patients). Whilst six of the nine studies in adults were double blind only four of the 13 studies in children was double-blind. Overall, the methodological quality of the included studies was variable. Only two of the included trials commented on the number of potentially eligible patients excluded from the study, but Chou reported that all the eligible children presenting with acute asthma to the emergency department agreed to participate in their study. Many studies did not comment on withdrawals and dropouts, and also did not report whether intention to treat analysis was employed. The hospital admission rate reported in one study was amended using an intention to treat analysis.

Using titrated treatment to overcome confounding by dose delivered

The studies included in this review used dosage ratios varying from 1:1 to 1:13 (lower dose in the spacer). One of the included studies plotted a log dose-response curve; the equivalent dose ratio found in this study was 1:6 with the lower dose in the holding chamber. It should be noted, however, that the dose ratio found in this study cannot be assumed to be identical for other nebulisers and holding chambers. Moreover none of the studies was carried out with the newer inhalers that use CFC-free propellants, which in turn could alter the effective dose ratio between devices.

In clinical practice, the dose of beta-agonist reaching the airways varies depending on the type of nebuliser or holding chamber used, the nominal dose administered and the characteristics of the individual patient’s airways at that time. Uncertainty over the dose of beta-agonists required through any delivery method was overcome in several of the later studies by using short treatment intervals: for example one respule (via nebuliser) or 4–6 puffs (via holding chamber) every 10–30 min until the patient responded to treatment.

This titrated approach neatly overcomes the difficulties of knowing how much beta-agonist is needed for each patient. Each treatment builds on the previous one and as the bronchoconstriction eases the subsequent doses should be better able to reach the airways.

In adults, no additional benefit was found using 6 puffs of Salbutamol (100 mcg each) given at 10 min intervals through a Volumatic Spacer, when compared with 4 puffs at 10 min intervals. A comparison in children between doses of 0.5 and 1.5 mg/kg given at 20 min intervals via nebuliser showed significantly greater improvement in lung function at the higher dose.

The first version of the Cochrane review pooled results from studies that used a single administration of beta-agonist with studies using multiple treatments. In a more recent version of the review these have been separated out, due to concern over dose confounding in the single treatment studies. The latter no longer contribute to the main outcomes of the review.

Results of the review

Of 112 abstracts originally identified from the Airways group database, 44 were selected for possible inclusion in the review. The full text of each paper was obtained and translated when necessary (two from Spanish and one from Portuguese). Studies were excluded for the following reasons: 11 studies on hospitalised patients (these represent a small subset of patients presenting with acute asthma which are not typical of the overall group, they will be incorporated as a separate comparison in a future update of the Cochrane review), 11 studies on non-acute asthma (as the response to bronchodilators may be different), and 10 for other reasons (such as the use of different beta-agonists in each arm of the trial). A total of
12 papers were initially included for this review and nine further papers have now been added so that there are now 880 children and 444 adults in the included trials.

**Spacer vs. nebuliser using multiple treatments**

The primary outcome of the review was hospital admission rates, and the relative risk (RR) of admission did not differ on the basis of delivery method in adults \( \text{RR} = 0.88; 95\% \text{ CI 0.56 to 1.38} \) or in children \( \text{RR} = 0.65; 95\% \text{ CI 0.4 to 1.06} \). Combining the results for adults and children gives an overall relative risk of 0.77 \( (95\% \text{ CI 0.40 to 1.06}) \). The point estimates were stable when studies of lower methodological quality were excluded (although the confidence intervals were wider), and no significant heterogeneity was demonstrated (Fig. 1). Two studies in children did not report admissions but did report data on children whose response to treatment was categorised as poor;\(^5,11\) when these are included the relative risk in children of admission or poor outcome is not significantly different between chamber and nebuliser \( \text{RR} = 0.85; 95\% \text{ CI 0.57 to 1.26} \). In order to check for publication bias a funnel plot was constructed, in which the effect size of each trial was plotted against its weight. The funnel plot did not show obvious asymmetry, so no evidence for publication bias was found. No trials individually showed a significant difference in admission rates between the two delivery methods.

No significant differences were demonstrated between the two delivery methods for lung function, change in respiratory rate, development of tremor and the number of patients given steroids. Interestingly, in the four studies in adults that included analysis of changes in lung function in the most severely affected patients (e.g. \( \text{FEV}_1 < 30\% \text{ predicted} \)), the weighted mean difference (WMD) in \( \text{FEV}_1 \) between the two delivery methods was not significantly different (WMD = \(-1.6\% \text{ predicted}; 95\% \text{ CI } -7.69 \text{ to } 4.49\% \text{ predicted} \)).

Symptom scores are important to patients but could not be combined in the review as no measure of the variance of the mean scores were reported in the primary papers.

### Exploring heterogeneity between trial results

For some outcomes there was significant statistical heterogeneity between the results of different trials. In other words the results between trials differed more than would be expected by chance, starting from the hypothesis that all the trials were sampling the same treatment effect. Fig. 2 shows the duration of time spent in the emergency department for two studies in adults\(^9,18\) WMD \(0.02\text{h} \ (95\% \text{ CI } -0.4 \text{ to } 0.44) \) and one in children\(^6\) where the mean difference is \(-0.62\text{h} \ (95\% \text{ CI } -0.84 \text{ to } -0.44) \) in favour of the spacer.

When these two subgroups are compared, there is significant heterogeneity between them (Chi-square 8.2, degrees of freedom 2, \( P = 0.02 \)), and this cannot be explained on the grounds of study quality as all three studies are of high quality (Jadad score of 3 or more). The heterogeneity disappears when the studies are split as shown in Fig. 2. This could represent a genuine difference between adults and children, especially as other
### Duration in Emergency Department (hours)

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Fig. 2 Meta-analysis of the effect of duration in emergency department of beta-agonist delivered by MDI and spaces compared to nebulisers. The studies have been grouped as adults and children. The intervals show the 95% confidence intervals using a fixed-effect model. N = no. of Patients. Weighted Mean Difference shown are from Ref. [2].

### Rise in pulse rate [% baseline]

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Fig. 3 Meta-analysis of the effect of pulse rate on beta-agonist delivered by MDI and spacer compared to nebuliser. The studies have been grouped as adults and children. The intervals show the 95% confidence intervals using a fixed-effect model. N = no. of Patients. Mean and standard deviation are shown for each area of the study. Weighted Mean Differences shown on from Ref. [2].
outcomes show similar effects with children having less side effects from the use of spacers in terms of pulse rate (Fig. 3). In adults, the rate shows a WMD of 0.82 (95% CI 3.92 to −2.27) per cent of baseline, whilst in children there is a WMD of −7.78 (95% CI −10.21 to −5.34) in favour of the spacer. Heterogeneity between the subgroups is significant (Chi-square 11.98, degrees of freedom 2, \( P = 0.002 \)). However, caution is needed in the interpretation of the findings of differences between subgroups.\(^{30}\) The initial subgrouping into children and adults was not specified in the original protocol and was therefore post hoc when the review was first prepared. It has been tested since by the addition of further trials, which have strengthened the findings of differences in relation to the advantage of spacers in children in terms of pulse rate. A further study in children comparing a homemade non-valved spacer with an oxygen-driven nebuliser in 196 children in Brazil has also shown a shorter duration in the emergency room for the spacer group.\(^ {31}\) The mean duration in the emergency room was 41.1 min for the spacer and 66.9 min for the nebuliser (mean difference 25.8 min, 95% CI 18.6 to 33 min). Moreover, the difference between the ages of participants is only one of several possible explanations for the discrepancy between the results in children and adults. In particular, the children’s study did not use a double-dummy design and was not blinded to the participants (although the clinician assessing patients for discharge did not know which treatment the child had received). All patients in the adult studies were given beta-agonist or dummy treatment via both nebuliser and spacer, and this may have slowed treatment times (as nebulised treatment takes considerably longer to give than spacer treatment). We cannot be sure whether the advantages for the spacer in the children’s study in terms of duration in the emergency department are related to the fact that children were being treated or due to other factors.

**Practical implications**

**Theoretical issues around titration and implications for trial design and practice**

In acute asthma, the lung delivery in individual patients will depend on the degree of bronchoconstriction, and the individual nebuliser or spacer used (as well as the patient technique). For this reason it makes sense to emulate the clinical trials in using beta-agonists frequently (e.g. at 10 min intervals). Used in this way MDIs with spacer can produce equivalent results to nebulised delivery. The optimum average dose and delivery interval for inhaled beta-agonists in acute asthma are unknown, but since no advantage has been shown using doses above 4 separate puffs every 10 min though a spacer,\(^{28}\) this approach is advocated for community use (since nebulisers are more expensive and less convenient than spacers). Oxygen can be administered between spacer usage if required, and the proven benefit of oral steroids in preventing relapse should not be forgotten.\(^{32}\)

Whilst it may be more convenient to use nebulised delivery in the hospital setting, it should be remembered that this raises expectations for future nebulised treatment in the community or for subsequent exacerbations. A recent pragmatic before and after study has confirmed that it is possible to substitute MDI and spacer for nebuliser delivery of beta-agonists in day-to-day emergency department treatment of adults with acute asthma.\(^{33}\) When using an MDI and spacer, patients were initially treated with 5 puffs of albuterol (salbutamol) and then 3–5 puffs every 20 min as needed. Duration of stay fell from an average of 175 min to 164 min, and both peak flow and arterial oxygen saturation improved significantly more with the MDI and spacer. Relapse rates were also lower but this may have been affected by the provision of educational material, a peak flow meter, a spacer and inhaled corticosteroids for the patients’ home use.

**Children and adults**

It is often assumed that adults and children respond in the same way to asthma therapy, however, this should not be taken for granted. It is better to present results in children and adults as separate subgroups. The overall impression gained from this review is that spacers have some advantages in children in reducing side effects such as tachycardia. The reduced duration of stay in the Chou study has been replicated in a further study in children using a homemade spacer.\(^ {31}\) Both studies were unblinded and did not use a double-dummy design, so it remains unclear whether this is a true difference between the way children and adults respond to a spacer and nebuliser, or whether issues of study design confound the results.

**Spacers and nebulisers in chronic asthma**

Two further reviews have addressed the question of spacers and nebulisers to deliver beta-agonists\(^{34}\) and inhaled corticosteroids\(^{35}\) in chronic asthma.
The problem of confounding by dose delivered and the paucity of trial data available make it impossible to draw firm conclusions about the relative efficacy of the delivery methods in these reviews.

Practice points

- In children and adults with non-life-threatening acute asthma beta-agonists administered by MDI and spacer can be as effective as nebulisation in acute asthma.
- In any individual patient with acute asthma, delivery of inhaled bronchodilators to the peripheral airways will depend upon the degree of bronchoconstriction. Since an unknown proportion of the drug will reach its target, it is sensible to administer repeated doses of beta-agonist at short intervals and monitor the patient’s response.
- Optimal delivery doses and intervals are unknown, but the trials typically used one respule via nebuliser or four MDI actuations (given through a spacer and individually inhaled with tidal breathing) at intervals of 10–30 min.
- All the reported studies excluded patients with life-threatening asthma. The conclusions from this review of the available data may not apply in this situation.

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References


