Bronchodilator delivery in acute airflow obstruction: a meta-analysis

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Authors' objectives
To compare the effect of bronchodilators delivery by use of a metered-dose inhaler or wet nebulizer on objective measures of acute airflow obstruction in adult patients.

Searching
MEDLINE was searched from January 1st 1966 to December 31st 1994 using the following MESH terms: ‘lung diseases, obstructive’; ‘asthma or chronic obstructive pulmonary disease’; ‘bronchodilators agents’; ‘nebulizers and vaporizers’; ‘administration, inhalation’; ‘comparative studies or randomized controlled trials’; and the textword ‘bronchodilators’. Additional articles referencing frequently cited articles were sought from SCISEARCH. Searches were conducted of article bibliographies, personal files and files of content area experts in asthma and aerosol therapy.

Letters and reference lists were sent to authors of 5 review articles seeking additional references, information about unpublished studies and studies in progress. A manufacturer of metered-dose inhalers (Trudell Medical Group) was contacted about ongoing research in this field.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with outcome assessed by objective measurement of airflow obstruction using spirometry.

Specific interventions included in the review
The interventions studied include delivery of bronchodilator therapy by metered-dose inhalers with or without a spacer device and by a wet nebulizer. The following bronchodilators agents are included: metaproterenol, albuterol, salbutamol and terbutaline.

Participants included in the review
Adults aged 18 years of age and over with acute airways obstruction caused by asthma or chronic obstructive pulmonary disease (COPD) who were treated in an emergency department or a hospital. One study included two patients under the age of 18 years. The mean age of patients in the included studies ranged from 24 years to 68 years. The review includes 318 patients with asthma, 89 with COPD and 100 with a mixed diagnosis. 5 studies were set in emergency departments and 7 in hospital settings.

Outcomes assessed in the review
The main outcome assessed was the improvement in the forced expiratory volume in one second (FEV1) or peak expiratory flow (PER), after initial treatment with either a metered-dose inhaler or wet nebulizer delivery device.

How were decisions on the relevance of primary studies made?
Three investigators independently reviewed all references that met the inclusion criteria. Disagreement about inclusion was resolved by consensus and, if necessary, further information was sought from the original author.

Assessment of study quality
The validity of the primary studies was assessed on the following criteria: details of method of randomisation, blinding, details of patient characteristics, definition of asthma or chronic obstructive airways disease, details of intervention including comparability of bronchodilators doses, specification of technique, blinding of outcome assessor and details of withdrawals. The included studies were evaluated by three researchers and assigned a methodological score using the validity criteria. The mean score was divided by the total possible score of 16 and expressed as a value from 0.06 to 1.0. Agreement among reviewers was calculated using a weighted $K$ statistic.
Disagreements were resolved by consensus.

**Data extraction**
The following data were extracted in duplicate using a structured data abstraction form: methods of randomisation, assignment to parallel or crossover groups, age, sex and clinical characteristics of patients, study setting, prior calculation of sample size and power, medications compared, delivery systems, outcome measures of airflow obstruction and secondary outcomes including symptom improvement, adverse effects, withdrawals, duration of hospitalisation and economic evaluation. Discrepancies in data abstraction were resolved by a third investigator.

**Methods of synthesis**

How were the studies combined?
The effect size for each study was calculated as the difference between metered-dose inhaler and wet nebulizer treatment groups, following therapy divided by the pooled standard deviation of the outcome measures after treatment for each group. 95% confidence intervals were calculated for each study outcome. The effect size was expressed in standard deviation units and interpreted according to Cohen (0.2 small effect, 0.5 medium effect, 0.8 large effect). The overall effect size was calculated by weighting the contribution from each study by the sample size.

How were differences between studies investigated?
The chi-squared test for heterogeneity was used to assess heterogeneity of effect size among all trials. The relationship between effect size and methodological score was assessed graphically and by linear regression. Sensitivity analysis was performed by including studies initially excluded and by calculating overall effect size separately for open and blinded studies and for studies using equivalent doses, equal doses and standard doses. Subgroup analysis was performed for effect size for patients with asthma compared to those with chronic obstructive airways disease. Post-hoc analysis was used to assess the effect of removing one study with a high effect size from the calculation of the overall effect size.

**Results of the review**

Twelve RCTs (507 patients) were included.

The methodological scores ranged from 0.35 to 0.81 with a mean of 0.61. Agreement among investigators for methodological score was 0.88. The number of positive studies favouring delivery by metered-dose inhaler, that would be required to reject an alternative hypothesis of equivalence with a small effect size of 0.2, was 13 studies.

Overall FEV1 effect size between metered-dose inhaler and wet nebulizer delivery was -0.02 (95%CI: -0.20, 0.16; P > 0.10). Test for heterogeneity P < 0.001. Sensitivity analysis was performed by omitting one study with a high effect size giving an overall effect size, of the remaining studies = 0.09 (95%CI: -0.09, 0.27). Heterogeneity after this omission was no longer present. Further sensitivity analysis was performed by including 5 of 6 excluded studies, giving overall effect size = 0.05 (95%CI: -0.11, 0.20).

A priori hypotheses tested were as follows:

Subgroup analysis of patients with asthma compared to those with chronic obstructive airways disease: effect size for asthma patients (8 studies, N = 292 patients) was -0.17 (95%CI: -0.41, 0.07), compared to effect size for chronic obstructive airways disease patients (3 studies, N = 48 patients) of 0.23 (95%CI: -0.35, 0.81). Comparison of subgroups P > 0.10.

Different doses of beta-agonist: Equivalent doses (3 studies, N= 135 patients) effect size = 0.04 (95%CI: -0.30, 0.37); Standard dose of bronchodilators (6 studies, N = 217 patients) effect size = 0.05 (95%CI: -0.22, 0.33); Equal doses of metaproterenol (1 study, N = 100 patients) effect size = 0.06 (95%CI: -0.34, 0.45).

Double blind studies (6 studies, N = 269 patients) effect size = -0.02 (95%CI: -0.26, 0.23); open studies (6 studies, N = 238 patients) effect size = -0.02 (95%CI: -0.28, 0.24).
Relation of effect size to methodological quality: weak negative correlation ($c = -0.21$).

**Authors' conclusions**
Bronchodilators therapy delivery by metered-dose inhaler or wet nebulizer delivery is equivalent in the acute treatment of adults with airflow obstruction. Spacer devices were used for bronchodilators delivery with a metered-dose inhaler in most studies and should probably be recommended for the treatment of airflow obstruction.

**CRD commentary**
This clearly written and presented review includes rigorous methodology for the selection of included articles according to pre-defined criteria, scoring of studies on defined validity criteria and extraction of data. The likelihood of publication bias is addressed and the number of studies required to reverse the conclusions calculated. Details of the primary studies are tabulated and the treatment effects and overall effect size are presented graphically. There is extensive discussion on the potential sources of heterogeneity and statistical investigation of some of these potential sources. The discussion includes an examination of some of the limitations of the review, including the variability in outcome measures from combined studies, the difference between standard recommended doses from those used in clinical practice, lack of knowledge of optimal doses in initial treatment and dependency of the FEV1 on the initial baseline measure. The authors have suggestions for future research in this area.

Baseline comparability does not appear to have been included in the validity criteria and it is not stated if data were extracted on an intention-to-treat basis or otherwise.

This is a well conducted review which supports the authors' conclusions of equivalence of effect of bronchodilators therapy delivered by metered-dose inhaler or wet-nebulizer. The authors do not give evidence supporting their conclusion that spacer devices "should probably be recommended for the treatment of airflow obstruction".

**Implications of the review for practice and research**
The authors state that future studies should focus on the effect of larger than standard doses of bronchodilators delivered by a spacer type metered-dose inhaler, the benefit of more expedient treatment with a spacer type metered-dose inhaler, the ability of patients to co-operate with treatment, standardised approaches to express changes in airflow obstruction and preferences of patients and physicians in the context of cost evaluations and educational implications.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.