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Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units (Review)

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TABLE OF CONTENTS

[Intervention Review]

Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units

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ABSTRACT

Background

Nebulizers and metered dose inhalers (MDI) have both been adapted for delivering aerosol bronchodilation to mechanically ventilated patients, but there is incomplete knowledge as to the most effective method of delivery.

Objectives

To compare the effectiveness of nebulizers and MDIs for bronchodilator delivery in invasively ventilated, critically ill adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 5); Ovid MEDLINE (1950 to Week 19 2012); Ovid EMBASE (1980 to Week 19 2012); CINAHL via EBSCOhost (1982 to Week 19 2012) and reference lists of articles. We searched conference proceedings and reference lists of articles. We also contacted manufacturers and researchers in this field. There were no constraints based on language or publication status.

Selection criteria

Randomized controlled trials (RCTs), including randomized cross-over trials where the order of the intervention was randomized, comparing the nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients in critical care units.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted study authors for additional information where required. We collected information about adverse effects from the trials.

Main results

This review included three trials, two addressing the primary outcome measure of a reduction of airway resistance (measured as a reduction in interrupter and additional airway resistance) with a total of 28 patients (n =10, n =18) and two addressing adverse changes to haemodynamic observations with a total of 36 patients (n =18, n =18). Limitations in data availability and reporting in the included trials

precluded meta-analysis and therefore the present review consisted of a descriptive analysis. Risk of bias in the included trials was judged as low or of unknown risk across the majority of items in the 'Risk of bias' tool.

Cautious interpretation of the included study results suggests that nebulizers could be a more effective method of bronchodilator administration than MDI in terms of a change in resistance. No apparent changes to haemodynamic observations (measured as an increase in heart rate) were associated with either mode of delivery. Due to missing data issues, meta analyses were not possible. Additionally, small sample sizes and variability between the studies with regards to patient diagnoses, bronchodilator agent and administration technique mean that it would be speculative to infer definitive recommendations based on these results at this time. This is insufficient evidence to determine which is the most effective delivery system between nebuliser and MDI for aerosol bronchodilation in adult patients receiving mechanical ventilation.

Authors' conclusions

Existing randomized controlled trials, including randomized cross-over trials where the order of the intervention was randomized, comparing nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients do not provide sufficient evidence to support either delivery method at this time.

PLAIN LANGUAGE SUMMARY

To assess whether metered dose inhalers or nebulizers are better for delivering inhaled drugs to mechanically ventilated patients

Acute respiratory failure is common in patients with long term breathing problems who have been admitted to hospital for sudden worsening of their symptoms. A large number of these patients require admission to a critical care unit, where a machine can help them to breathe (mechanical ventilation). In addition, medicines are given to help ease breathing problems by opening up the airways of the lungs (bronchodilator drugs). Bronchodilator drugs relax the muscles in the lungs allowing the airways to widen so that more air passes through, making breathing easier. These drugs are mostly given through inhalation, with specially adapted nebulizers and metered dose inhalers (MDIs) being available for patients who are being mechanically ventilated. Which of these delivery methods is more effective is as yet unclear. We carried out a systematic review of the literature by searching five key databases and asking relevant manufacturers for high quality published or unpublished material which compared the effectiveness of these two delivery methods, nebulizers and MDIs.

This Cochrane systematic review included three trials with 46 patients in total (two trials with 18 patients, one trial with 10 patients), and showed that there is insufficient valid research evidence to recommend either delivery method. There is a clear need for more research into which delivery method is more effective.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Metered dose inhalers compared with nebulizers for aerosol bronchodilator delivery in mechanically ventilated adults

Patient or population: mechanically ventilated adults with need for aerosol bronchodilator therapy

Settings: critical care units

Intervention: metered dose inhalers

Comparison: nebulizers

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Impact
Reduction in airway resistance Measured as a reduction in additional effective resistance (Δ*R*rs) and interrupter resistance (R*int*) Assessed before treatment and 30 minutes after the end of each modality of administration	28 (2 studies)	⊕⊕⊕⊖[1] **moderate**	Both studies achieved a greater decrease in airway resistance using nebulizer
Mortality during critical care unit admission Measured using mortality rate in intervention and comparison groups During critical care admission	No studies found	N/A	
Duration of mechanical ventilation Measured as number of days	No studies found	N/A	
Adverse changes to haemodynamic observations Measured as a change in heart rate (beats per minute) Assessed before treatment and 30 minutes after the end of each modality of administration	28 (2 studies)	⊕⊕⊕⊖[2] **moderate**	Neither mode of delivery altered heart rate

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for relatively few patients and events
[2]Downgraded for some selective outcome reporting in one study

BACKGROUND

Description of the condition

Acute respiratory failure is common amongst patients who are hospitalized with an acute exacerbation of their chronic lung disease. Where optimal medical treatment has failed to relieve symptoms, ventilatory support is recommended (Rodriguez-Roisin 2006). Despite advances in non-invasive ventilation strategies (Brochard 1995; Plant 2000), a significant proportion of patients still require invasive ventilation to treat their acute exacerbation. In addition to invasive ventilation, inhaled bronchodilators are an essential component of the treatment and management of this patient group (NICE 2004). Short acting beta2-agonists and ipratropium are widely used to manage symptoms associated with acute exacerbations and are recommended by international guidelines (GOLD 2011).

Description of the intervention

Bronchodilator therapy aims to resolve bronchoconstriction, decrease the work of breathing, potentially relieve dyspnoea (Dhand 2005) and is frequently administered to mechanically ventilated patients(Boucher 1990). Bronchodilators for mechanically ventilated patients may be administered systemically by intravenous infusion, or directly to the lungs through the inhalation of an aerosol (Georgopoulos 2000). There are currently two main methods of delivering aerosol bronchodilation which have been adapted for use in patients receiving mechanical ventilation, the nebulizer and the metered dose inhaler (MDI). Nebulizers deliver bronchodilators to the lower respiratory tract by converting the liquid drug into smaller particle droplets which can then be inhaled. The production of an aerosol may be achieved through the use of compressed gas, ultrasonic sound frequencies, or a vibrating mesh or plate (Dhand 2006a). MDIs contain a pressurized mixture of active drug, surfactants, preservatives and propellants. An aerosol is generated through the actuation of the device, which results in a high speed release of the suspension from the MDI (Jantz 1999). Aerosol delivery offers several advantages over the systemic route, namely painless delivery of the drug directly to the site of action, rapid onset of drug effect, and the resultant reduction in dosage requirements (Dhand 2004; Fink 1999a). As a result, aerosol inhalation is globally recognized as the preferred route of delivery for bronchodilators in chronic lung diseases (GOLD 2011).

Various pharmacological agents with differing modes of action can be deployed for bronchodilation but their overall effect, relaxation of the bronchial smooth muscle, is congruent (Dhand 2006a). Currently, beta2-agonists, anticholinergics and methylxanthines make up the three main pharmacologic classes of agents used for bronchodilation. Methylxanthines can only be administered via enteral or parenteral routes, whereas beta2-agonists and anticholinergics are most frequently utilized through inhalation (BNF 2009) and will therefore be the focus of this review.

Several narrative reviews have attempted to address the issue of which is the most appropriate and effective route of administration of bronchodilator therapy for adult patients receiving mechanical ventilation. Current guidelines endorse either mode of delivery.

The suggested advantages of MDIs have been identified as ease of administration, increased reliability in dosing, cost effectiveness including personnel time to administer the drug, and freedom from contamination risk (Dhand 1996; Dhand 2006a; Dhand 2007a; Fink 1999a; Hess 1991; Hess 2002). Several reviews have concluded that no apparent advantage exists for either MDI or nebulizer if appropriate administration techniques and dose are utilized (Coleman 1996; Dhand 2004; Dhand 2007b; Dhand 2008; Guerin 2008; Jantz 1999; O'Doherty 1997), although the high dose of bronchodilators that is needed for nebulizer delivery may be associated with a higher degree of cardiovascular instability (Dolovich 2005).

How the intervention might work

The success of any aerosol bronchodilation therapy is dependent on satisfactory amounts of active drug reaching the bronchial tree(Dolovich 2005). Aerosol deposition is known to be affected by a number of factors, with specific considerations associated with patients receiving mechanical ventilation that are not present in the ambulatory demographic. These include ventilator, circuit, drug and patient related factors(Dhand 2004). Device related factors are also present, with choice of equipment, position in the ventilator circuit, and timing of drug delivery affecting both nebulizers and MDIs (Fink 1999a).

The efficacy of aerosol drug delivery from nebulizers and MDIs has been shown to be variable in patients receiving mechanical ventilation. Evidence suggests that performance variability is present both in different models of nebulizers (Loffert 1994) and between individual units of the same model (Alvine 1992). The efficacy of bronchodilator delivery from an MDI is also variable, dependent on timing actuation with inspiration (Crogan 1989; Dhand 2003) and rates of inspiratory flow (Fink 1999b). The use of nebulizers for bronchodilator delivery may lead to hypoventilation in mechanically ventilated patients when using older ventilator models (Beaty 1989).

Multi-centre survey data on bronchodilator administration practices in mechanically ventilated neonates highlight variations in practice, with 19% of respondent institutions using MDIs at all times and 43% using nebulizers exclusively (Ballard 2002). Such figures for the adult patient demographic are not available.

Why it is important to do this review

To date, there has not been an international systematic review to determine which method of aerosol bronchodilator delivery system, nebulizer or MDI, is more effective in mechanically ventilated adult patients. This review will therefore attempt to determine which is the most effective delivery system in terms of physiological response and patient outcomes.

OBJECTIVES

To compare nebulizers to MDIs for bronchodilator delivery for invasively ventilated critically ill adult patients in terms of physiological response and patient outcomes. Subgroup analyses were planned according to other ventilation and bronchodilation strategies, ventilator settings and administration variables.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs), including randomized cross-over trials where the order of the intervention was randomized, comparing the nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients.

Types of participants

We included adult patients (as defined by the trialists) receiving invasive mechanical ventilation in critical care units. If no definition was available, we assumed that the participants were adults unless identified as paediatric patients in the studies.

Types of interventions

We excluded studies in which aerosol bronchodilation agents were delivered via the same MDI or nebulizer device simultaneously with another drug group. Combination administration of bronchodilators of differing drug groups (for example beta2-agonists and anticholinergics) was allowed. We excluded any studies in which bronchodilator agents were administered by any route other than aerosol. Other ventilation and bronchodilation strategies such as heated humidification, use of spacer devices, helium oxygen, and nitric oxide mixtures were allowed if equally distributed between the intervention and control groups. We also excluded studies where different bronchodilation agents were used between the intervention and control groups.

Types of outcome measures

Primary outcomes

1. Reduction in airway resistance, measured as a reduction in interrupter resistance (R*int*) and additional effective resistance (ΔRrs)
2. Patient outcome, mortality during critical care unit admission
3. Patient outcome, duration of mechanical ventilation

Secondary outcomes

1. Adverse changes to haemodynamic observations
2. Reduction in wheezing
3. Freedom from contamination
4. Quality of life
5. Practitioner satisfaction including ease of use and convenience

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 5) (Appendix 1); Ovid MEDLINE (1950 to Week 19 2012) (Appendix 2); Ovid EMBASE (1980 to Week 19 2012) (Appendix 3); and CINAHL via EBSCOhost (1982 to Week 19 2012) (Appendix 4).

Searching other resources

We did not limit the search by language or publication status.

We contacted manufacturers of MDIs and nebulizers that have been adapted for use within a ventilator circuit (for example Philips Respironics, Cardinal Health and Trudell Medical) to identify any published, unpublished or ongoing studies which met the inclusion criteria.

We reviewed conference proceedings available online for relevant trials (American Thoracic Society International Conference (2006 to 2012); European Society of Intensive Care Medicine (2003 to 2012); and the Respiratory Drug Delivery Conference (2000 to 2012)).

We screened reference lists within relevant trials to identify any further potential papers worthy of review.

Data collection and analysis

Selection of studies

We undertook the systematic review using the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Two authors (AH and LV) independently examined the titles and abstracts identified by the search strategy to remove any duplicate records and obviously irrelevant reports. We retrieved and evaluated the full text versions of potentially relevant studies identified by at least one author. Two authors (AH and LV) independently assessed each study to determine if they met the eligibility criteria outlined above in the section Criteria for considering studies for this review. We resolved any disagreements by discussion between the authors (AH and LV), with a further author (FS) acting as arbiter. We have provided details of both included and excluded studies in the respective tables of this review.

Data extraction and management

AH and FS extracted data independently utilizing a standardized data extraction form based on the Cochrane Anaesthesia Review Group recommendations (see Appendix 5). We resolved any disagreements by discussion between the authors (AH and FS), with a further author (LV) acting as arbiter. The data extraction form included the following.

- General information: author(s), title, source, contact address, year of study, country of study, language of publication, year of publication.
- Trial characteristics: design (RCT) and risk of bias assessment criteria as outlined below in the section Assessment of risk of bias in included studies.
- Participants: baseline characteristics (including other ventilation and bronchodilation strategies outlined above in the section Types of interventions), inclusion and exclusion criteria, sample size and number of patients allocated to each intervention group, co-morbidity.
- Interventions: detailed description of the comparison devices and administration methods, bronchodilator administered.
- Outcomes. Primary outcomes: reduction in airway resistance, measured as a reduction in interrupter resistance (R*int*) and additional effective resistance (ΔRrs); patient outcome including mortality during critical care unit admission and duration of mechanical ventilation. Secondary outcomes: adverse changes to haemodynamic observations; reduction in wheezing; freedom from contamination; quality of life; and practitioner satisfaction including ease of use and convenience.

- Other: sources of funding, conflicts of interest, unexpected findings.

We used the statistical package Review Manager software RevMan 5.1, utilizing double data entry with two authors (AH and FS) to control and correct data entry errors.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies using The Cochrane Collaboration's tool for assessing risk of bias as outlined by Higgins 2011. The standard components in this tool include adequacy of allocation generation, allocation concealment, blinding, completeness of outcome data, possible selective outcome reporting and any other potential sources of bias. In addition, a further four components were considered as potential sources of bias for cross-over trials; namely appropriateness of the cross-over design, randomization of the order of treatments received, freedom from the bias of carry over effects, and the availability of unbiased data. Each component was judged: 'Yes' for low risk of bias, 'No' for high risk of bias, or 'Unclear'. We have included a 'Risk of bias' table as part of the 'Characteristics of included studies' and a 'Risk of bias summary' figure which details all of the judgements made for all included studies in this review.

Assessment of risk of bias was carried out independently by two authors (AH and FS). We resolved any disagreements by discussion between the authors, with a further author (LV) acting as arbiter.

Measures of treatment effect

We intended to use the risk ratio (RR) as the effect measure for dichotomous data, and to calculate the mean difference (MD) or the standardized mean difference (SMD) with a 95% confidence interval (CI), as appropriate, for continuous outcomes.

Unit of analysis issues

Cross-over trials

If suitable data were available from cross-over trials, we intended to adopt the approach recommended by Elbourne 2002. We intended to include data using results from paired analyses where estimates of within patient differences and means and standard errors were either available, obtainable from the trialists or could be calculated.

Dealing with missing data

Where data were missing, we contacted the original investigators to request the missing data. We intended to perform intention-to-treat (ITT) analysis for dichotomous data. For continuous data we intended to perform ITT analyses if sufficient results were available from the included studies.

Assessment of heterogeneity

We intended to assess clinical heterogeneity using a three step approach. We initially intended to assess graphical depictions of confidence intervals generated by Review Manager software (RevMan 5.1) for the amount of overlap present. Statistical heterogeneity is indicated if there is poor overlap of confidence intervals (Higgins 2011). We intended to explore the presence of heterogeneity formally using the Chi^2 statistic and quantify it using the I^2 statistic (Higgins 2011). We intended to consider meta-analysis if studies were suitably homogenous, in terms of clinical diversity, to provide a meaningful summary.

Assessment of reporting biases

We intended to generate funnels pots using the mean differences and standard errors for each primary outcome to visually assess the impact of study size on treatment estimates. If more than 10 studies were included in a meta-analysis, we intended to also use the regression asymmetry test to test for funnel plot asymmetry, as described by Egger 1997. Where the intervention effect was measured in terms of odds ratios for binary data, we intended to test funnel plot asymmetry using the arcsine test proposed by Rücker 2008.

Data synthesis

We intended to combine data from parallel group and cross-over trials for meta-analysis. In case of bias due to carry over effect in cross-over trials, we intended to incorporate data from the first time period only if the necessary information was available. For cross-over trials when both time periods were used and no standard deviation of the mean difference was available, we intended to impute this using the correlation coefficient from other studies. We intended to calculate this from as many other studies as possible. We intended to analyse the results using inverse variance meta-analysis.

We intended to also meta-analyse data from parallel group and cross-over trials separately. If there was a discrepancy between the two we intended to report the results separately, otherwise the results of the meta-analyses would be reported together.

We intended to employ both a fixed-effect model and a random-effects model to combine data. If there was a discrepancy between the two, we intended to report results from both models. If there was no discrepancy, we intended to report the results from the fixed-effect model if the I^2 was less than 50%, and from the random-effects model if the I^2 was equal to or greater than 50%.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to assess the impact of other ventilation and bronchodilation strategies such as heated humidification, use of spacer devices, helium oxygen mixtures, and nitric oxide mixtures for ventilation. Additionally, we planned subgroup analyses to estimate the impact of differing doses of bronchodilator agents.

We did not perform subgroup analyses as there were inadequate data available from the studies or the study authors to enable the groupings to be made. Additionally, the low number of included studies did not allow for any subgroups to be large enough to enable meaningful analyses.

Sensitivity analysis

We intended to perform a sensitivity analysis comparing the intervention effect in trials judged to have a low risk of bias (that is, trials in which all components of The Cochrane Collaboration's tool for assessing risk of bias have been judged as 'Yes') to trials which have been judged as having a moderate to high risk of bias (that is, trials in which one or more of the components of The Cochrane Collaboration's tool for assessing risk of bias have been judged as 'Unclear' or 'No').

We intended to perform a sensitivity analysis comparing the intervention effect in trials that based the decision to discontinue

mechanical ventilation on pre-specified standardized criteria within the study compared to studies that based this decision on clinicians' judgements alone. This was to estimate the potential for a biased effect when the duration of mechanical ventilation was determined by a subjective judgement.

We intended to perform a sensitivity analysis comparing the intervention effect in trials that used combination administration of bronchodilators of differing drug groups to studies that administered a single bronchodilator agent. This would provide an estimate of the potential for a biased treatment effect when combination bronchodilator therapy was utilized.

RESULTS

Description of studies

The studies were prospective, randomized, cross-over trials conducted on mechanically ventilated adult patients in intensive care units (ICUs). The trials compared nebulizers and MDIs for aerosol bronchodilation, and the order of the interventions were randomized.

Results of the search

Our search identified 2080 titles and abstracts. A total of 18 abstracts were potentially relevant and we obtained the full publications of these. Two authors (AH and LV) independently read the full text publications and referred to a third author (FS) regarding four studies. From this, 11 studies were initially identified as having met the inclusion criteria. The 'study selection algorithm' in the 'Study Quality Assessment and Data Extraction form' (Appendix 5) was then applied to these studies. Eight studies were subsequently excluded (see 'Characteristics of excluded studies' table) and three studies were identified as having met the inclusion criteria (see 'Characteristics of included studies' table). A flow diagram of the search results is shown in Figure 1.

Figure 1. Study flow diagram.

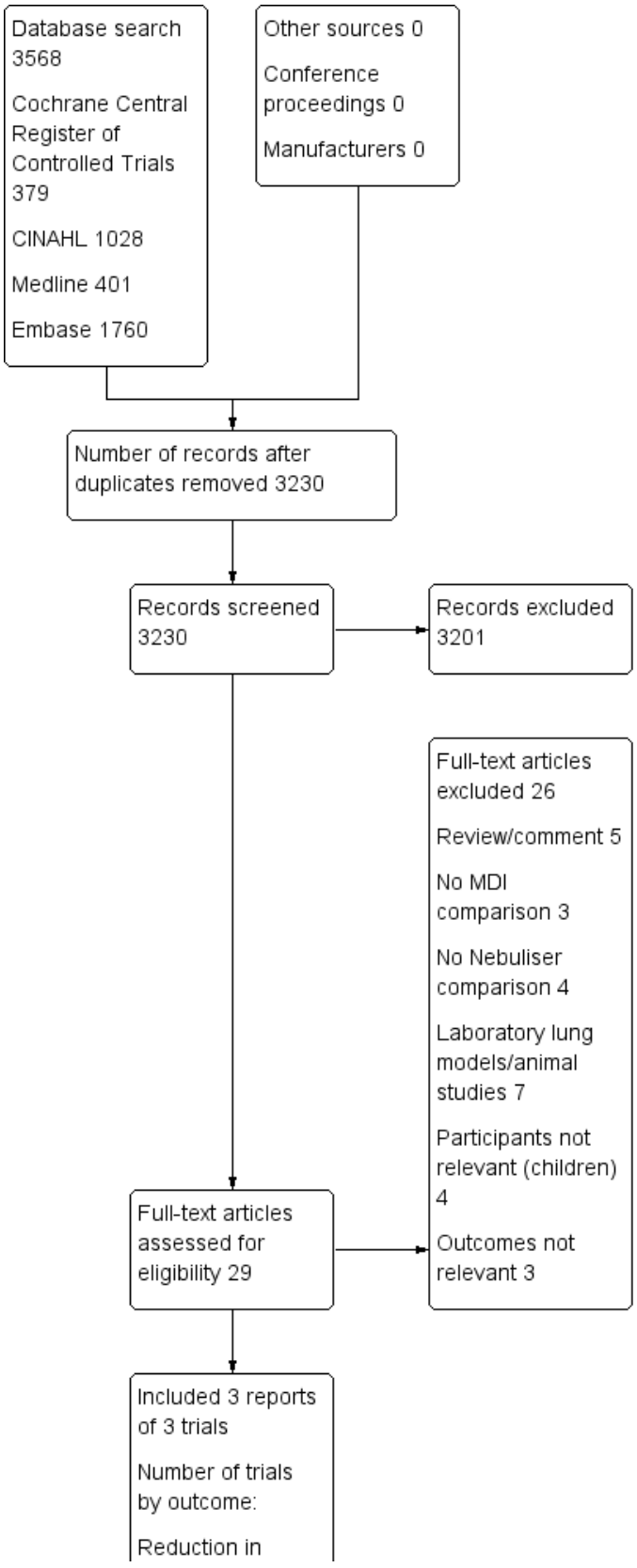
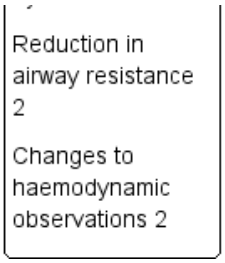


Figure 1. (Continued)



Included studies

We included three studies in this review with a total of 46 patients, which are described in the 'Characteristics of included studies' table. Individual sample sizes of each study were 18 (Gay 1991), 10 (Manthous 1993) and 18 (Guerin 1999) participants, and the studies were conducted in ICUs in America (Gay 1991; Manthous 1993) and France (Guerin 1999) respectively. Participants were recruited from a single medical ICU (Guerin 1999) and multiple ICUs from within a single institution (Manthous 1993). The age range of the participants for the Manthous 1993 and Guerin 1999 studies was 44 to 78 years, with a mean age of 69 years given for the Gay 1991 study. There were a higher number of males (32) than females (14).

The studies compared an MDI and nebulizer for aerosol bronchodilator delivery, with two studies utilizing a single short acting beta2-agonist (albuterol) delivered in either a single dose (Gay 1991) or successively increasing doses (Manthous 1993). The other study used a combination therapy of beta2-agonist and anticholinergic, delivered as a single dose (Guerin 1999). Participants were sedated in one study (Manthous 1993) and sedated and paralysed in another (Guerin 1999). The study by Gay 1991 did not give any information regarding the sedation or anaesthesia of the participants.

Guerin 1999 attached the MDI adapter 15 to 20 centimetres from the Y-piece, actuating the MDI on the onset of the mechanical breath and applying a four second inflation hold. Gay 1991 delivered the MDI bronchodilator dose in three breaths, using a slow manual inflation of the lungs and an inflation hold prior to recommencing mechanical ventilation. Manthous 1993 attached the adapter directly to the endotracheal (ET) tube, timed actuation with inspiration, and did not use an inflation hold. Two studies placed the nebulizer between 10 and 20 centimetres from the ET tube (Guerin 1999; Manthous 1993), with Gay 1991 describing the nebulizer as being placed near the Y junction between the ventilator tubing and ET tube. When stated, gas flows of five (Guerin 1999) and six litres per minute (Manthous 1993) were used to deliver the bronchodilator dose over 20 (Gay 1991) to 30 minutes (Guerin 1999; Manthous 1993). The wash out period between crossing over to the alternative method of administration was four (Gay 1991; Manthous 1993) and 10 hours (Guerin 1999). Respiratory mechanics were obtained using the end-inspiratory interruption technique under constant flow inflation in two studies (Guerin 1999; Manthous 1993). The third study (Gay 1991) obtained recordings during stepwise deflations of a relaxed respiratory system.

The studies by Manthous 1993 and Guerin 1999 both reported on the review's primary outcome measure of reduction in airway resistance, measured as a reduction in additional effective resistance (ΔRrs). All of the studies reported on adverse changes to haemodynamic observations, one of the secondary outcomes of this review. None of the studies reported the patient outcome of mortality during critical care unit admission, or duration of mechanical ventilation.

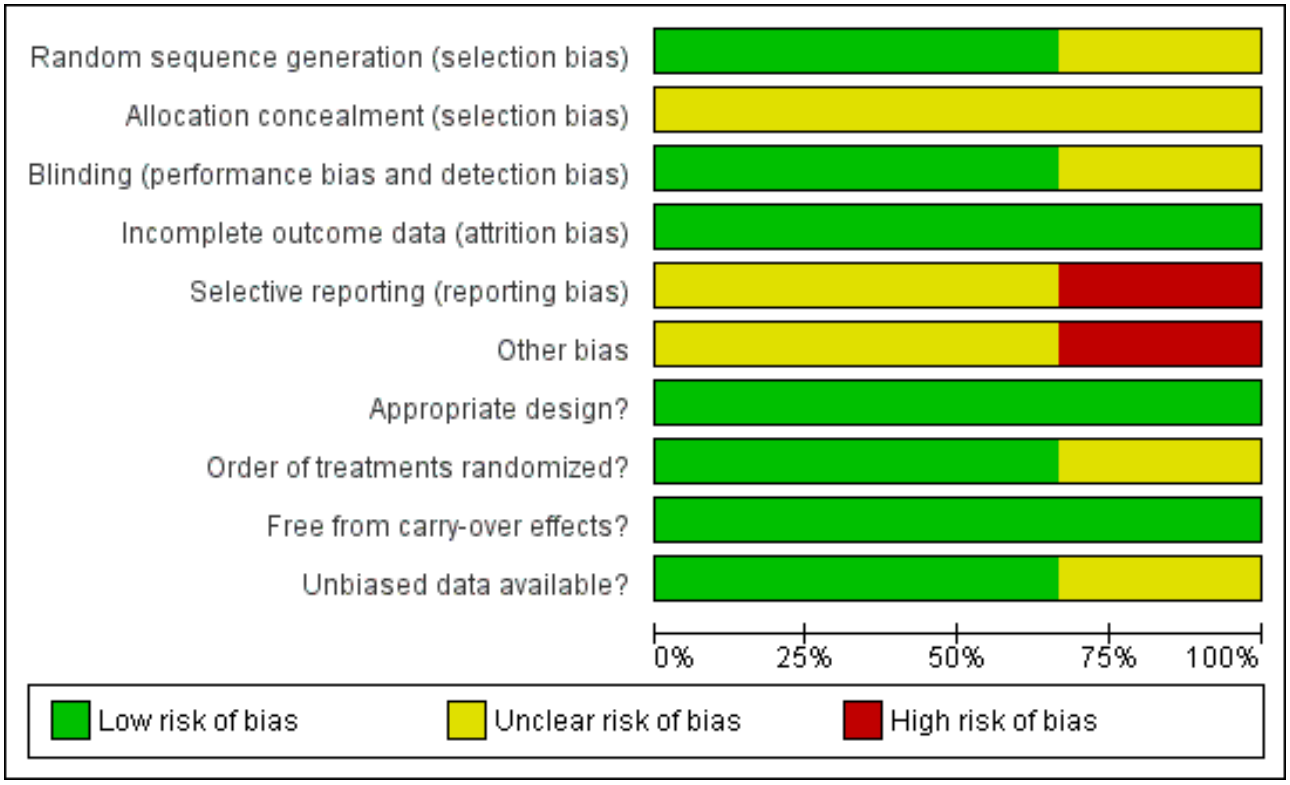
Excluded studies

We excluded eight studies. Three studies did not meet our criteria because they compared different types of MDI with no nebulizer comparison (Fernandez 1990; Fuller 1994; Waugh 1998). A further study by Marik 1999 compared the pulmonary bioavailability of bronchodilators when delivered by MDI and nebulizer using urinary analysis of drug levels, and was excluded as it did not record any of the review's outcomes. Similarly, the study by Fuller 1990, which compared lung deposition of aerosolized bronchodilator therapy administered through MDI and nebulizer, did not record any of the review's outcomes and was also excluded. The study by Duarte 2000 included a participant who had received intravenous bronchodilator in the overall data analysis. One trial was conducted on patients who were breathing spontaneously and not receiving mechanical ventilation (Gervais 1987). The final excluded study by Gutierrez 1988 provided only limited data. We contacted the author but were unable to obtain any further study reports or data.

Risk of bias in included studies

We used The Cochrane Collaboration's domain-based evaluation tool available in RevMan 5.1 for assessing risk of bias. In addition, we added four further domains based on the recommendations outlined by Higgins 2011 for assessing risk of bias in cross–over trials. Most of the trials had a low risk of bias across the 10 domains (Figure 2). Study authors were contacted to supplement information, where needed, to permit judgements on the classification of each risk of bias item. One of the authors did not respond, and for two of the trials the authors responded but the data were not available.

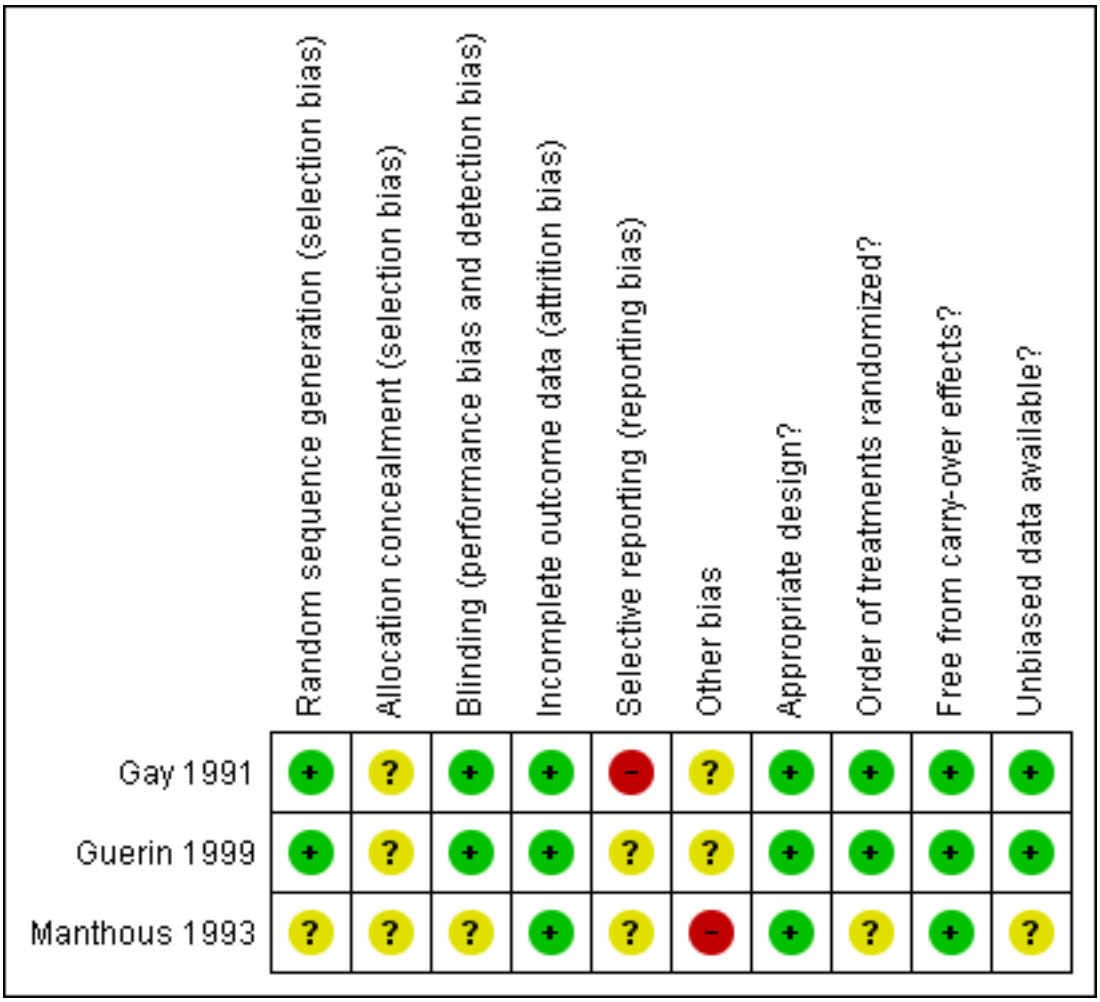
Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation sequence was adequately generated in two of the trials (Gay 1991; Guerin 1999) and was not reported in the third (Manthous 1993). None of the trials reported the methods used to conceal allocation, and we were unable to obtain this information from the authors direct. Given the nature of the intervention, blinding of participants and investigators delivering the interventions was not possible. We therefore assessed the risk of bias based on the blinding of the outcome assessors. In two of the trials, investigators completing post-sampling analysis (Guerin 1999) in addition to data acquisition (Gay 1991) were blinded to treatment modality. Blinding of outcome assessors was unclear in the third study (Manthous 1993). No incomplete data were apparent in any of the studies; however Gay 1991 excluded two participants from the original recruited sample as they did not meet the study inclusion criterion of a diagnosis of airways obstruction. In two trials (Guerin 1999; Manthous 1993) there was insufficient information to enable a judgement. The third study identified and reported on all three pre–set outcomes (Gay 1991). Other potential sources of bias included tracheal suctioning 'as required' prior to data collection (Gay 1991), patients receiving other inhaled bronchodilators that were not under study prior to onset of the investigation (Guerin 1999), and variations in participants and bronchodilator dose (Manthous 1993).

The cross-over design was suitable for all three trials as all participants were deemed clinically stable, with a history of chronic respiratory disease and absence of haemodynamic instability during the study period. The order of receiving treatments was randomized in two studies, using a coin flip (Gay 1991) and a random order table (Guerin 1999). There was insufficient reporting to enable a judgement in the third trial (Manthous 1993). All of the trials were judged to be free from carry over effects with wash out periods ranging from four (Gay 1991; Manthous 1993) to 10 hours (Guerin 1999). We looked for unbiased data to be available with some form of paired analysis, as recommended by Elbourne 2002. No dropouts or systematic differences between the two study periods were present in the trials. Paired analysis (Student's t-test) was available for both interventions in two trials (Gay 1991; Guerin 1999) but only for the nebulizer treatment response in the third (Manthous 1993). The judgement on the classification of risk of bias is shown in Figure 3.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

Reduction in airway resistance

Reduction in airway resistance, measured as a reduction in interrupter resistance (R*int*) and a reduction in additional effective resistance (Δ*R*rs), was reported in one trial (Guerin 1999). Guerin 1999 presented results as mean and standard error of the mean (SEM) at baseline and mean and SEM after cross-over. Manthous 1993 reported resistive pressure drop as a reduction in either total resistance of the respiratory system (*R*rs) or R*int.* Results were presented as mean at baseline and after cross-over, but they did not report whether further reported figures were SEM or standard deviation (SD). See Appendix 6.

The correlation coefficient of the patients' baseline and follow-up measurements, the paired t-test statistics, exact P values or confidence intervals were not available either in the study reports or from the authors direct. Therefore, estimates of the SE of the differences could not be calculated (Elbourne 2002; Higgins 2011) and it was not feasible to combine the study findings.

Results from Guerin 1999 suggest the choice of delivery device affects each component of total respiratory system resistance differently, with the MDI resulting in a significant reduction in R*int* and the nebulizer a significant reduction in Δ*R*rs. Results from Manthous 1993 suggest that a significant reduction in *R*rs or R*int* is achieved when the bronchodilator is administered via the nebulizer.

Manthous 1993 demonstrated methodological adequacy in terms of incomplete outcome data reporting; an unclear randomization process, allocation concealment, blinding and selective outcome reporting alongside a small sample mean it is difficult to place much weight on these results. The authors did not state exactly which measure of respiratory system resistance was being used. From the description, this could be *R*rs or R*int.* Exact figures for post-treatment MDI were not provided, the authors stated that these "had no significant effect" (Manthous 1993, p1568). All results were presented as a figure (Figure 2, p1568) in the published paper. The exact data were not obtainable from the authors direct, and we could not confirm with the authors or publisher if the figure had been altered to fit within the published manuscript. No other reports of this study were available.

Guerin 1999 demonstrated methodological adequacy in terms of randomization, blinding and incomplete outcome data reporting.

An unclear allocation concealment and selective outcome reporting mean results must be interpreted with caution. Additionally, all of the participants had chronic obstructive pulmonary disease (COPD).

We used the approach recommended by Elbourne 2002 to further analyse the study results. Making the assumption that baseline differences in airway resistance prior to administration of either method of delivery were not considered very different, comparisons of post-inhalation measures were carried out. For each study, we estimated the SE for the difference in post-inhalation resistances between MDI and nebulizer using the formula for continuous data provided by Elbourne 2002 and using an arbitrary range of correlation coefficients.

	Post-inhalation resistance				
	MDI mean ± SE	Nebulizer mean ± SE	Difference 95% CI	Adjusted P value	Assumed correlation coefficient
Guerin 1999 (Δ*R*rs)	10.79 ± 0.88	10.79 ± 1.11	0 (-2.99, 2.99)	1.00	0.0
			0 (-2.68, 2.68)	1.00	0.2
			0 (-2.34, 2.34)	1.00	0.4
			0 (-1.93, 1.93)	1.00	0.6
			0 (-1.41, 1.41)	1.00	0.8
Guerin 1999 (R*int*)	4.10 ± 0.60	4.36 ± 0.62	0.26 (-1.56, 2.08)	0.767	0.0
			0.26 (-1.37, 1.89)	0.740	0.2
			0.26 (-1.15, 1.67)	0.702	0.4
			0.26 (-0.89, 1.41)	0.640	0.6
			0.26 (-0.56, 1.08)	0.510	0.8
Manthous 1993 (Δ*R*rs or R*int*)	19.6 ± 4.7	17.6 ± 5.4	-2.00 (-18.19, 14.19)	0.786	0.0
			-2.00 (-16.50, 12.50)	0.762	0.2
			-2.00 (-14.58, 10.58)	0.727	0.4
			-2.00 (-12.32, 8.32)	0.671	0.6
			-2.00 (-9.38, 5.38)	0.555	0.8

There was no observed difference in post-inhalation Δ*R*rs between the two administration methods in the Guerin 1999 study. The assumption that the baseline measures were similar did not hold in this study; the post-inhalation measures were equal hence it was not surprising that there was no statistical evidence of a difference in post-inhalation measures between the two treatments. In terms of R*int*, there was no statistical evidence of a difference in the post-inhalation resistance between the two administration methods, even if the differences were assumed to be highly correlated. The results from Manthous 1993 demonstrated no statistical evidence of a difference in post-inhalation resistance between the two administration methods, even if the correlation coefficient between the differences was assumed to be high.

We also tested the differences in mean reduction between nebulizer and MDI, again using the methods outlined by Elbourne 2002. We estimated the paired SEs using the bounded P value in one arm of the study and assuming the SE of the reductions would be the same in the other arm as each patient acted as their own control.

	Change in resistance

	MDI Mean reduction ± SE	Nebulizer Mean reduction ± SE	Mean difference (Neb - MDI) 95% CI	Adjusted P value	Assumed correlation coefficient
Guerin 1999 (Δ*R*rs)	0.67 ± 0.69	2.01 ± 0.69	1.34 (-0.73, 3.41)	0.190	0.0
			1.34 (-0.51, 3.19)	0.145	0.2
			1.34 (-0.26, 2.94)	0.096	0.4
			1.34 (0.03, 2.65)	0.045	0.6
			1.34 (0.42, 2.27)	0.007	0.8
Guerin 1999 (R*int*)	0.93 ± 0.44	0.87 ± 0.44	-0.06 (-1.38, 1.26)	0.924	0.0
			-0.06 (-1.24, 1.12)	0.916	0.2
			-0.06 (-1.08, 0.96)	0.903	0.4
			-0.06 (-0.89, 0.77)	0.881	0.6
			-0.06 (-0.65, 0.53)	0.832	0.8
Manthous 1993 (Δ*R*rs or R*int*)	-0.7 ± 1.20	3.9 ± 1.20	4.6 (0.76, 8.44)	0.024	0.0
			4.6 (1.17, 8.03)	0.014	0.2
			4.6 (1.63, 7.57)	0.007	0.4
			4.6 (2.17, 7.03)	0.002	0.6
			4.6 (2.88, 6.32)	<0.001	0.8

Assuming a level of significance at P = 0.05, the results from Guerin 1999 suggested that a statistically significant change in resistance was achieved in Δ*R*rs when the correlation coefficient was 0.6 or above. These estimates were based on yet a further assumption and therefore were less likely to be reliable. Further results demonstrated no statistical evidence of a change in R*int* resistance between the two administration methods, even if the correlation coefficient between the differences was assumed to be high.

The Manthous 1993 results suggested that a statistically significant change in resistance was achieved at all levels of correlation. These estimates were based on yet a further assumption and therefore were less likely to be reliable. Additionally, it was not possible to accurately identify the outcome measure used by Manthous 1993 (See Included studies) and therefore these results should be interpreted with extreme caution.

Adverse changes to haemodynamic observations

Adverse changes to haemodynamic observations were measured as a change in heart rate (beats per minute) in two trials (Gay 1991; Guerin 1999). Guerin 1999 presented results as mean and SE at baseline and mean and SE after cross-over. Gay 1991 presented results as the difference in means and SD. The correlation coefficient of the patients' baseline and follow-up measurements, the paired t-test statistics, and the exact P values or confidence intervals were not available in the Guerin 1999 study report or from the authors direct. Therefore, estimates of the SE of the differences could not be calculated (Elbourne 2002; Higgins 2011) and it was not feasible to combine the study findings.

Outcome measure: Heart rate (beats per minute)	
MDI	Nebulizer

	Pre-treatment	Post-treatment	Magnitude of change	Pre-treatment	Post-treatment	Magnitude of change
Guerin 1999	102 ± 4	106 ± 4	2 ± 4	103 ± 5	111 ± 5	8 ± 5
(n = 18)	Not significant			Not significant		
± SEM						

Results suggested that heart rate was not significantly altered with either method of administration.

Guerin 1999 demonstrated methodological adequacy in terms of randomization, blinding and incomplete outcome data reporting. An unclear allocation concealment and selective outcome reporting meant results must be interpreted with caution. Additionally, all of the participants had COPD.

Outcome measure: Change in heart rate (beats per minute)		
	MDI	Nebulizer
Gay 1991	8 ± 8	12 ± 8
(n = 18)	P ≥ 0.15	
± SD		

The increase noted in the heart rate was not statistically different for either method of administration.

Gay 1991 demonstrated methodological adequacy in terms of randomization, blinding, incomplete and selective outcome reporting. Unclear allocation concealment and the endotracheal suctioning of patients "when necessary" (Gay 1991, p68) prior to data collection may have influenced the results as previous studies have demonstrated that a significant rise in heart rate is associated with this procedure (Johnson 1994).

DISCUSSION

Summary of main results

This review included three trials, two addressing the primary outcome measure of a reduction in airway resistance (Guerin 1999; Manthous 1993) (n = 10, n = 18) and two the secondary outcome measure of adverse changes to haemodynamic observations (Gay 1991; Guerin 1999) (n = 18, n = 18). Limitations in data availability and reporting in the included trials precluded meta-analysis and therefore the present review consisted of a descriptive analysis.

Results from Guerin 1999 suggest that a significant reduction in interrupter resistance (R*int*) is achieved when the bronchodilator is administered via a MDI and a significant reduction in additional effective resistance (Δ*R*rs) is achieved when the bronchodilator is administered via a nebulizer. Manthous 1993 suggest that a significant reduction in *R*rs or R*int* is achieved when the bronchodilator is administered via the nebulizer. The exact measure of respiratory system resistance used in this study is unclear. Additionally, post-treatment data for the MDI from Manthous 1993 had to be estimated from a published figure and therefore all results need to be interpreted with caution.

Further analysis of the study results, using the approach recommended by Elbourne 2002 for the estimation of the SEs for the difference of post-inhalation resistances, resulted in no statistical evidence of a difference, even if the correlation coefficient between the differences was assumed to be high. Testing the differences in mean reduction between nebulizer and MDI using the Elbourne 2002 methods, a statistically significant change in resistance is achieved with nebulizer delivery. Results from Guerin 1999 demonstrate this effect only in Δ*R*rs and when the correlation coefficient is 0.6 or above. Results from Manthous 1993 demonstrate this effect across all levels of correlation. However, these results must be interpreted with extreme caution as all further analyses were based on increasing levels of assumption. Additionally, it is not possible to correctly identify the outcome measure used by Manthous 1993 (see Characteristics of included studies). Cautious interpretation of the included study results suggests that nebulizers could be a more effective method of bronchodilator administration than MDIs in terms of a change in resistance.

Heart rate was not significantly altered with either method of administration, however non-standardized respiratory care prior to data collection was present in Gay 1991. Additionally, all participants in Guerin 1999 had chronic obstructive pulmonary disease. No further eligible trials were found that addressed any of the other outcomes of the review.

Due to missing data issues, meta-analysis was not possible. Further analyses of included study results in relation to the primary outcome measure of a reduction in airway resistance had to be based on several levels of assumption about the study design. Additionally, small sample sizes and variability between the studies with regards to patient diagnoses, bronchodilator agent and

administration technique mean that it would be speculative to infer definitive recommendations based on these results at this time. This is insufficient evidence to determine which is the most effective delivery system between nebulizer and MDI for aerosol bronchodilation in adult patients receiving mechanical ventilation.

Overall completeness and applicability of evidence

Three relevant studies were identified for inclusion. The studies identified were not sufficient to address the objectives of the review as variations in the patient diagnoses, bronchodilator agent and administration technique were present. Some primary and secondary objectives were not addressed at all in the evidence.

Quality of the evidence

The body of evidence that has been identified does not allow a robust conclusion regarding the objectives of the review. Three studies were included with a total of 46 participants (n = 10, n = 18, n = 18). Key methodological limitations were small sample sizes and variability between the studies with regards to patient diagnoses, bronchodilator agent and administration technique. The two studies which addressed the primary outcome measure of a reduction in airway resistance were consistent in their finding that nebulizer delivery was associated with the greater, statistically significant reduction. The two studies which addressed the secondary outcome measure of adverse changes to haemodynamic observations were consistent in their finding that no significant rise in heart rate was observed with either mode of delivery. The overall rating of the quality of the body of evidence was moderate. Reasons for downgrading the evidence by one level are the high risk of bias identified in two of the studies (Gay 1991; Manthous 1993) and the potential for imprecision of results due to the small sample sizes and estimation of one study result from a published figure (Manthous 1993).

Potential biases in the review process

Most of the review authors were familiar with the two delivery methods under comparison in this review, from their previous clinical experience. However, this did not influence the assessment of data. To our knowledge, no additional sources of bias were present in the review process.

Agreements and disagreements with other studies or reviews

Duarte 2000 found no difference in either R*int* or Δ*R*rs when comparing the MDI and nebulizer for bronchodilator administration. This study was excluded from this review due to the administration of intravenous steroids, which may in part explain these conflicting results. Previous narrative reviews have had conflicting results. Fink 1999b strongly advocate MDIs, however this recommendation is based on drug deposition and aerosol delivery not on patient response assessed via respiratory variables. Additionally, no nebulizer comparison is considered. Hess 1991 also recommends the use of an MDI but, in agreement with Jantz 1999, highlights the importance of optimal administration techniques to achieve the benefits associated with this delivery route. If an optimal administration technique is used, equal physiological end points may be achieved and either method of administration is purported by Guerin 2008 and Dhand 2007b. Dhand 1997 also advocate MDI based on a cost effectiveness analysis completed by Bowton 1992, which demonstrated potential annual cost savings of $396,000 when MDIs were substituted for nebulizer therapy. Cost effectiveness analysis was not an outcome of this review, therefore these claims cannot be substantiated or refuted. Further narrative reviews (Dolovich 2005; O'Doherty 1997) concluded that no advantage exists with either method of administration and both MDI and nebulizer can be used to achieve successful bronchodilation in patients receiving mechanical ventilation.

AUTHORS' CONCLUSIONS

Implications for practice

Existing randomized controlled trials, including randomized cross-over trials where the order of the intervention was randomized, comparing a nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients do not provide sufficient evidence to support either delivery method at this time.

Implications for research

Further large, randomized cross-over trials are required to assess which is the most effective delivery system for aerosol bronchodilation in adult patients requiring invasive mechanical ventilation. Additionally, there are currently not enough studies that measure the respiratory mechanics of the resistance of the respiratory system to gas flow, despite this appearing to be physiologically the most appropriate measure to assess bronchodilator response to MDIs and nebulizers in this patient group. Future studies should also address patient outcome measures such as mortality during critical care unit admission and duration of mechanical ventilation, the other primary outcomes of this review. In addition, future studies should address the secondary outcome measures of this review.

Any future research evaluating two interventions utilizing a cross-over study design should ensure that findings are reported as a difference in means ± SE or SDM, or provide sufficient data in the study report to enable this to be calculated. This will enable any subsequent meta-analysis of study findings.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gay 1991

Methods	Single-blind, randomized, cross-over study
Participants	13 male, 5 female Age: mean 69 years All patients who were ventilator-dependent and were to receive bronchodilator aerosols for suspected airways obstruction All patients were clinically stable, assessed through an absence of hypotension, tachycardia and/or cardiac arrhythmias 12 patients required ventilation for acute respiratory failure caused by a primary lung disease, 6 had undergone major surgical procedures 11 patients were considered to have asthma or COPD, 15 were smokers
Interventions	Patients received sequentially in a random order albuterol by MDI and NEB administered by the same respiratory therapist MDI: 3 puffs (3 x 90µg albuterol) • 60 seconds between each puff • delivered during a slow manual inflation of the lungs • lungs held at an increased volume for several seconds before mechanical ventilation was again initiated • semi-recumbent patient position • suctioned prior to investigation if required NEB: 2.5mg albuterol in 3ml saline • delivered over 20 minutes • positioned near the Y junction between ventilator tubing and endotracheal tube • semi-recumbent patient position

Gay 1991 *(Continued)*

	• suctioned prior to investigation if required
Outcomes	Respiratory mechanics and vital signs (systemic blood pressure, heart rate) Outcomes were assessed before and 30 minutes after the end of each modality of administration Primary outcomes: • airway resistance: not reported • patient outcome mortality: not reported • patient outcome duration of mechanical ventilation: not reported Secondary outcomes • adverse changes to haemodynamic observations: reported • reduction in wheezing: not reported • freedom from contamination: not reported • quality of life: not reported • practitioner satisfaction including ease of use and convenience: not reported
Notes	2 patients were excluded from the analysis and report as tests did not confirm a diagnosis of airways obstruction Study was funded by United States Government grant HL38107/HL/NHLBI NHHHS/United States

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The same respiratory therapist delivered each aerosol treatment in every patient and determined the sequence of delivery modes with the flip of a coin" (p68)
Allocation concealment (selection bias)	Unclear risk	"The same respiratory therapist delivered each aerosol treatment in every patient and determined the sequence of delivery modes with the flip of a coin" (p68)
Blinding (performance bias and detection bias) All outcomes	Low risk	"Investigators responsible for data acquisition and post sampling analysis were blinded to the treatment sequence" (p68)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Twenty adult ventilator-dependent patients...consented to be studied...Two patients were excluded from this report, because our tests did not confirm a diagnosis of airway obstruction" (p66) Study findings appear to report on all 18 participants (p69) "Two patients in who VPmean was greater than 0.8L/s had been excluded from this study." (p69) Results presented for 18 patients in Figure 3 and Figure 4
Selective reporting (reporting bias)	High risk	3 hypotheses were to be examined: 1. albuterol delivered as either nebulized solution in an updraft inhaler or via metered dose inhaler results in equivalent degrees of bronchodilation 2. there is no difference in the incidence of adverse cardiovascular side effects directly attributed to the delivery system 3. in our practice setting the cost per treatment is lower when using MDI

Gay 1991 *(Continued)*

		Results are presented for bronchodilator responsiveness and cost comparison. Data collected for cardiovascular side effects included systemic blood pressure, but only heart rate reported
Other bias	Unclear risk	"When necessary, excess secretions were removed by endotracheal suctioning before baseline Pao/V curves, systemic blood pressure, and heart rate were acquired" (p68) No further information as to how the need for suctioning was assessed or decided, or how many of the patients received this prior to commencing data collection
Appropriate design?	Low risk	"All patients were clinically stable, as indicated by the absence of hypotension, tachycardia, and/or cardiac arrhythmias" (p66)
Order of treatments randomized?	Low risk	"The same respiratory therapist delivered each aerosol treatment in every patient and determined the sequence of delivery modes with the flip of a coin" (p68)
Free from carry-over effects?	Low risk	"Baseline and posttreatment measurements were repeated 4 h later after crossover to the alternate delivery mode" (p68)
Unbiased data available?	Low risk	“using paired Student’s *t*-test statistics” (p68) No dropouts or systematic differences between two study periods

Guerin 1999

Methods	Single blind randomized cross-over study
Participants	13 male, 5 female Age: 67 years ± 3 All patients were orotracheally intubated and were mechanically ventilated and all patients had COPD 10 patients had acute exacerbation of COPD, 8 patients had pneumonia 6 patients had received other bronchodilator agents but these were withheld for at least 4 hours before the onset of investigation
Interventions	Patients received sequentially in a random order fenoterol-ipratroprium bromide by MDI and NEB administered by the same respiratory therapist MDI: 4 puffs (4 x 50µg fenoterol/20µg ipratropium bromide) • 60 seconds between each puff • actuation just before onset on mechanical breath, with a 4 second inflation hold with each puff • positioned in inspiratory limb of ventilator circuit, 15/20cm from the Y-piece • semi-recumbent patient position • suctioned prior to investigation NEB: 1.25mg fenoterol/500µg ipratropium bromide in 5ml saline • device was run on gas flow of 5l/min • device was run until almost dry on visual inspection, average 30 minutes per dose • positioned in inspiratory limb of ventilator circuit, 15/20cm from the Y-piece • semi-recumbent patient position

Guerin 1999 *(Continued)*

	• suctioned prior to investigation
Outcomes	Respiratory mechanics and vital signs (heart rate, oxygen saturations and systemic blood pressure) Outcomes were assessed before and 30 minutes after the end of each modality of administration Primary outcomes: • airway resistance: reported • patient outcome mortality: not reported • patient outcome duration of mechanical ventilation: not reported Secondary outcomes • adverse changes to haemodynamic observations: reported • reduction in wheezing: not reported • freedom from contamination: not reported • quality of life: not reported • practitioner satisfaction including ease of use and convenience: not reported
Notes	Research funded from a grant from Baxter who manufactured the MDI and nebulizer used in the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Patients received sequentially in a random order (random order table)” (p1037)
Allocation concealment (selection bias)	Unclear risk	Random order table was used (p1037), but no information provided as to how this was used/interpreted or any indication if there was blinding or concealment used at this stage
Blinding (performance bias and detection bias) All outcomes	Low risk	“The investigators who performed the post sampling analysis of the respiratory signals were blinded to the treatment modality” (p1038)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data presented as n=18. No missing data apparent
Selective reporting (reporting bias)	Unclear risk	“We aimed at studying in detail the respiratory mechanics, and specifically the flow resistive properties of the respiratory system” (p1036) No pre-set outcomes stated
Other bias	Unclear risk	6 patients received other inhaled bronchodilators (other than the fenoterol-ipratropium bromide under study) before entry into the study. In these patients, treatment was withheld for at least 4 hours before the onset of investigation
Appropriate design?	Low risk	"They all had COPD which was diagnosed by clinical history, chest radiographs and pulmonary function tests." (p1037) "Acute respiratory failure had been triggered by acute exacerbation in 10 patients and pneumonia in eight patients. They were investigated 1 to 10 d after the onset of tracheal intubation and ventilation" (p1037)

Guerin 1999 *(Continued)*

Order of treatments randomized?	Low risk	“patients received sequentially in a random order (random order table) fenoterol-ipratropium bromide by MDI and NEB” (p1037)
Free from carry-over effects?	Low risk	“A period of at least 10 h was allowed between the administration of the bronchodilator with the two modalities” (p1037)
Unbiased data available?	Low risk	"The comparison of the values of respiratory mechanics and vital signs before and after inhalation were made within and between delivery modalities by using Student's paired *t* tests" (p1038) No dropouts or systematic differences between two study periods

Manthous 1993

Methods	Prospective randomized cross-over study
Participants	6 males, 4 females Age range 44-78 years (mean 66 years) All patients admitted to the ICU who required mechanical ventilation and had a difference of more than 15cm H_2O between their peak and pause airway pressures on tidal volume inflation and who gave informed consent 3 patients had pneumonia, 2 patients had COPD, 1 patient had lung cancer
Interventions	Patients were prospectively randomized to receive albuterol therapy by MDI or nebulizer; 4 hours were allowed for wash out of the first course of albuterol. The patient was then crossed over to receive albuterol by the alternative method of administration MDI: doses of 10, 20, 30 and 40 puffs at 30 minute intervals • each puff had 90 µg albuterol • adapter attached directly to ET tube and each puff delivered at end expiration or early inspiration • canister shaken every 10 breaths NEB: successively increasing doses 2.5, 5, and 7.5 mg in 3 ml of saline at 30 minute intervals • position 10-20cm from ET tube • gas flow from an independent oxygen source at 6l/min
Outcomes	Respiratory mechanics and dose-response relationship including the development of toxicity. Toxicity was defined by heart rate increment of 20 per minute, more than 4 premature ventricular or atrial contractions per minute, tremulousness or nausea Primary outcomes: • airway resistance: reported • patient outcome mortality: not reported • patient outcome duration of mechanical ventilation: not reported Secondary outcomes • adverse changes to haemodynamic observations: reported • reduction in wheezing: not reported • freedom from contamination: not reported • quality of life: not reported

Manthous 1993 *(Continued)*

- practitioner satisfaction including ease of use and convenience: not reported

Notes	Grant from National Institute of Health (US Government Grant)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided but p1567 patients were described as: "prospectively randomized"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	"prospectively randomized 10 mechanically ventilated patients" (abstract p1567) Results presented for 10 patients (figure 1 p1568 / figure 2 p1569). No missing data apparent
Selective reporting (reporting bias)	Unclear risk	"compared the efficacy and dose-response relationship of albuterol delivered by MDI and NEB in a prospective randomized cross over study" *(*p1567) No further outcomes given
Other bias	High risk	"a wide variety of diseases requiring mechanical ventilation for reasons other than primary airflow obstruction" (p1568) Table 1: 2 different types of ventilator (p1568). All patients on different ventilator settings "meticulous attention was paid to counting only puffs that were entrained with inspiration and fewer than 10 puffs/100 needed to be repeated in any patient" (p1567) therefore dose with MDI was potentially different for these patients
Appropriate design?	Low risk	"All patients admitted to the University of Chicago Medical Center intensive care units in August and September of 1992, who required mechanical ventilation and had a difference of more than 15cm H_2O between their peak (P_{peak}) and pause (P_{pause}) airway pressures on tidal - volume inflation" (p1597) "Patients were excluded if they had a history of symptomatic coronary artery disease in the 6 months prior to admission, or a history of haemodynamically significant arrhythmias" (p1597)
Order of treatments randomized?	Unclear risk	"patients who were randomized to receive albuterol by NEB first....patients who received albuterol by MDI first" (figure 2, p1569)
Free from carry-over effects?	Low risk	"four hours were allowed for washout of the first course of albuterol. The patient was then crossed over to receive albuterol by alternative method" (p1567-8)
Unbiased data available?	Unclear risk	"Individual responses of resistive pressure (ordinate) to cumulative doses of nebulized albuterol" (Figure 3, p1569) No paired analyses provided of nebulizer treatment response

Manthous 1993 *(Continued)*	
	No dropouts or systematic differences between the two study periods

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Duarte 2000	"All patients received intravenous steroids as part of their medical regime, and one patient received an Aminophylline infusion" (p818). Author contacted and confirmed the inclusion of this patient in the overall data analysis. No further study reports or raw data were available which exclude this patient, or would allow for re-analysis of the study data.
Fernandez 1990	The study compared 2 different types of MDI to an intravenous bronchodilator (aminophylline), with no nebulizer comparison.
Fuller 1990	Study primarily recorded percentage of deposition of drug given via MDI or nebulizer to the lung. Peak inspiratory pressure was measured at baseline, 5, 10, 15 and 30 minutes after administration of the bronchodilator (fenoterol) and the results presented as a percentage change from baseline over time. No further measurements were carried out which could enable calculation of the respiratory mechanics that are the primary outcomes of this review.
Fuller 1994	Participants were randomized to receive bronchodilator aerosol from MDI, from one of four devices. No nebulizer comparison group.
Gervais 1987	Patients were breathing spontaneously, not mechanically ventilated.
Gutierrez 1988	Only limited data available from study abstract. Author contacted and responded with no further study reports or data available.
Marik 1999	Airway responses were not assessed or recorded. Efficacy of two different delivery methods evaluated through the measurement of total urinary excretion of albuterol.
Waugh 1998	The study compared 2 different types of MDI and spacer, with no nebulizer comparison.

APPENDICES

Appendix 1. Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Metered Dose Inhalers explode all trees
#2 MeSH descriptor Nebulizers and Vaporizers explode all trees
#3 MeSH descriptor Bronchodilator Agents explode all trees
#4 MeSH descriptor Administration, Inhalation explode all trees
#5 MeSH descriptor Drug Delivery Systems explode all trees
#6 MeSH descriptor Nitric Oxide explode all trees
#7 metered-dose inhaler*
#8 MDI:ti,ab
#9 Nebuliser
#10 (bronchodilat* near (therap* or strateg*))
#11 (heated near humidific*)
#12 (spacer near devic*)
#13 (helium near oxygen)
#14 ((nitric oxide or NO) near mixture*)

#15 (bronchodilator* near delivery)
#16 (aerosol near bronchodilat*)
#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 MeSH descriptor Respiration, Artificial explode all trees
#19 mechanical near ventilat*
#20 (#18 OR #19)
#21 (#17 AND #20)

Appendix 2. Search strategy for MEDLINE (OvidSP)

1. exp Metered Dose Inhalers/

2. exp "Nebulizers and Vaporizers"/ or Bronchodilator Agents/

3. Administration, Inhalation/

4. Drug Delivery Systems/

5. Nitric Oxide/ad, tu, sd [Administration & Dosage, Therapeutic Use, Supply & Distribution]

6. metered-dose inhaler*.mp.

7. MDI.ti,ab.

8. Nebuliser.mp.

9. (bronchodilat* adj6 (therap* or strateg*)).mp.

10. (heated adj3 humidific*).mp.

11. (spacer adj3 devic*).mp.

12. (helium adj3 oxygen).mp.

13. ((nitric oxide or NO) adj3 mixture*).ti,ab.

14. (bronchodilator* adj3 delivery).mp.

15. (aerosol adj6 bronchodilat*).mp.

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. exp Respiration, Artificial/

18. (mechanical adj3 ventilat*).mp.

19. 18 or 17

20. 19 and 16

21 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) and humans.sh.

22. 21 and 20

Appendix 3. Search strategy for EMBASE (OvidSP)

1 exp Metered Dose Inhaler/
2 exp Nebulizer/ or exp Medical Nebulizer/
3 exp Vaporizer/
4 exp Bronchodilating Agent/
5 exp Inhalational Drug Administration/
6 exp Drug Delivery System/
7 exp Nitric Oxide/dt, ad, do, ih [Drug Therapy, Drug Administration, Drug Dose, Inhalational Drug Administration]
8 metered-dose inhaler*.mp.
9 MDI.ti,ab.
10 Nebuliser.mp.

11 (bronchodilat* adj6 (therap* or strateg*)).mp.
12 (heated adj3 humidific*).mp.
13 (spacer adj3 devic*).mp.
14 (helium adj3 oxygen).mp.
15 ((nitric oxide or NO) adj3 mixture*).ti,ab.
16 (bronchodilator* adj3 delivery).mp.
17 (aerosol adj6 bronchodilat*).mp.
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 exp Artificial Ventilation/
20 (mechanical adj3 ventilat*).mp.
21 19 or 20
22 21 and 18

Appendix 4. Search strategy for CINAHL (EBSCOhost)

S26 S19 and S25
S25 S20 or S21 or S22 or S23 or S24
S24 AB trial* or random*
S23 (MM "Multicenter Studies")
S22 (MM "Placebos")
S21 (MM "Double-Blind Studies") or (MM "Single-Blind Studies") or (MM "Triple-Blind Studies")
S20 (MM "Random Assignment") or (MH "Clinical Trials+")
S19 S15 and S18
S18 S16 or S17
S17 TX mechanical and ventilat*
S16 (MH "Respiration, Artificial+")
S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14 TX aerosol and bronchodilat*
S13 TX bronchodilator* and delivery
S12 AB nitric oxide or NO
S11 TX helium and oxygen*
S10 AB spacer*
S9 TX heated and humidific*
S8 AB bronchodilat* and therap*
S7 TX Nebuliser
S6 TX metered-dose inhaler*
S5 (MH "Nitric Oxide")
S4 (MH "Drug Delivery Systems+")
S3 (MM "Administration, Inhalation")
S2 (MH "Bronchodilator Agents+")
S1 (MM "Nebulizers and Vaporizers")

Appendix 5. Study quality assessment and data extraction form

Study ID	Report ID	Review author name

First author	Full reference

Study eligibility

Type of study Is the study described as randomized?	Yes	Unclear	No
	Next question	*Next question*	**Exclude**
Participants Were the participants mechanically ventilated and: - defined as adult by trialists OR - NOT identified as paediatric	Yes	Unclear	No
	Next question	*Next question*	**Exclude**
Interventions Did the study contain at least two interventions, comparing any model of nebulizer to MDI for aerosol bronchodilation?	Yes	Unclear	No
	Next question	*Next question*	**Exclude**
Was the difference in bronchodilator delivery device the only planned difference between the comparison interventions?	Yes	Unclear	No
	Next question	*Next question*	**Exclude**
Were the same bronchodilatory agents used in all comparison groups?	Yes	Unclear	No
	Next question	*Next question*	**Exclude**
Were only bronchodilators delivered during the trial? (i.e. no other drug groups/agents mixed in with bronchodilator agent/s)	Yes	Unclear	No
	Next question	*Next question*	**Exclude**
Was there any combination administration of bronchodilators of differing drug groups?	Yes	Unclear	No
	Exclude	*Next question*	*Next question*
Outcomes Did the study **record** airway `responses*?`	Yes	Unclear	No
	Include	Include	**Exclude**

(Continued)

		(subject to clarification of "unclear" points)	
Final decision	**Include**	**Unclear**	**Exclude**

If the study is to be excluded, record the reason and details to add to "Table of excluded studies":

General information

Authors
Contact address
Country of study
Language of publication

Any other published versions/reports of this trial?

All references to a trial need to be linked under one Study ID both on this form (p1) and in RevMan.

Code	Authors	Full reference	Linked Study ID on p1? (tick)	Linked Study ID in RevMan? (tick)
A				
B				
C				

Add other additional lines/codes as required

Trial characteristics – Risk of bias assessment

Sequence generation
Was the allocation sequence adequately generated?
Give text which enabled your decision, including page no:
"YES" if used: · Random number table · Computer random number generator · Coin tossing · Shuffling cards/envelopes · Throwing dice · Minimization
"No" if used non-random method such as: · Odd / even D.O.B · Date of admission · Hospital/clinic number · Clinician judgement · Participant preference · Lab test results · Availability of intervention
"Unclear" if there is insufficient information to permit "Yes" or "No" judgement.

Allocation concealment
Was the allocation adequately concealed?(i.e. participants/investigators enrolling participants could not foresee assignment)
Give text which enabled your decision, including page no:
"YES" if used: · Central allocation · Sequentially numbered containers of identical appearance · Sequentially numbered opaque, sealed envelopes

(Continued)

· Or equivalent method

"No" if investigators could potentially foresee allocation such as:

· Open random allocation scheme e.g. random list

· Envelopes without safeguards e.g. unsealed, non opaque

· Alteration / rotation

· Date of birth

· Case record number

· Other unconcealed procedure

"Unclear" if there is insufficient information to permit "Yes" or "No" judgement.

Blinding of participants, personnel and outcome assessors

Was knowledge of allocated intervention adequately prevented during study?

Note: Blinding of personnel not possible with current review, but consider if a lack of blinding has potentially influenced results

Give text which enabled your decision, including page no:

"YES" if:

· No blinding, but unlikely to influence results

· Outcome assessment blinded

"No" if:

· No blinding and is likely to influence result

· Non-blinding is likely to have introduced bias

"Unclear" if there is insufficient information to permit "Yes" or "No" judgement, OR study did not address this outcome

Incomplete outcome data

Were incomplete outcome data adequately addressed?

Give text which enabled your decision, including page no:

"YES" if missing data:

· Complete - none missing

· Unlikely to be related to true outcome

· Is balances across groups

· Effect size not enough to have clinical relevance impact on observed effect size

(Continued)

· Have been imputed appropriately

"No" if missing data:

· Likely to be related to true outcome

· Effect size enough to have clinical relevance impact on observed effect size

· "as treated" analysis done with very different numbers than at outset

· potentially inappropriate data imputation

"Unclear" if there is insufficient information to permit "Yes" or "No" judgement OR study did not address this outcome

Selective outcome reporting

Are study reports free of selective outcome reporting?

Give text which enabled your decision, including page no:

"YES" if:

· Protocol available and pre-set outcomes are reported in pre-set way

· No protocol, but clear published reports of all expected outcomes, including pre-set ones

"No" if:

· Not all pre-set outcomes reported

· 1/1+ of primary outcomes reported in different methods, units, subsets of participants to protocol

· 1/1+ primary outcomes not pre-set

· 1/1+ outcomes reported incompletely

· Report does not include key outcome which would be expected

"Unclear" if there is insufficient information to permit "Yes" or "No" judgement.

Other potential threats to validity

Was the study free of anything else which may put it at risk of bias?

Give text which enabled your decision, including page no:

"YES" if:

· Appears free from other sources

"No" if other potential source of bias e.g.:

(Continued)

- Study design
- Stopped early
- Extreme baseline imbalance
- Claims to be fraudulent
- Other problem

"Unclear" if there is insufficient information to permit "Yes" or "No" judgement.

Cross – over trials

Consider these potential sources of bias if the study is a cross-over design

	Give text which enabled your decision, including page no:
Was the design appropriate?	
Order of receiving treatments randomized?	
Not biased from carry-over effects?	
Unbiased data available?	

Trial characteristics

Participants

Age (mean, median, range)

Sex (numbers/%)

Any other ventilation/bronchodilation strategies? e.g.:

- Heated humidification
- Use of spacer devices
- Helium oxygen mixtures
- Nitric oxide mixtures

Pre-existing lung pathology? e.g.:

- COPD

(Continued)

· Asthma

Other Include sources of funding, conflicts of interest and any unexpected findings

Data extraction

Outcomes	
	Reported in study?
Airway response:	
Airway resistance (*R*rs min, *R*rs max, Δ*R*rs)	Yes / No
Patient outcome:	
Mortality	Yes / No
Duration of mechanical ventilation	Yes / No
Adverse changes to haemodynamic observations	Yes / No
Reduction in wheezing	Yes / No
Freedom from contamination	Yes / No
Practitioner satisfaction	*Yes / No*
Associated cost	*Yes / No*
Quality of life measures	*Yes / No*

Continuous Outcomes - RCTs						
	Unit of measurement	Intervention		Control		Details if outcomes are only described
		n	Mean (SD)	*n*	Mean (SD)	

(Continued)

Airway resistance	Δ*R*rs
	*R*rs max
	*R*rs min
Duration of mechanical ventilation	
Practitioner satisfaction	

Continuous Outcomes – Cross over trials										
	Unit of measurement	Intervention		Control		Cross over trial data Record all that is available in the paper Note – it is the *within patient differences* that you need the SD, standard error and CI for				
		n	Mean (SD)	*n*	Mean (SD)	SD	Standard error	CI	*t*	*P value*
Airway resistance	Δ*R*rs									
	R*int*									
	*R*rs max									
	*R*rs min									
Duration of mechanical ventilation										
Practitioner satisfaction										

Dichotomous Outcomes		
	Intervention (n) Note: n = number of participants, **NOT** number of events	Control (n) Note: n = number of participants, **NOT** number of events
Mortality – during critical care unit admission		
Adverse changes to haemodynamic observations		
Reduction in wheezing		
Freedom from contamination		

Any other relevant information about results

e.g. if data was obtained from the trialists, if results were estimated from graphs or are calculated by you (if so, state formula and calculations)

Freehand space for actions

Please document any contact with study authors and changes here

Trial characteristics
Single/multicentre?
Country/countries
Definition used of participant eligibility
How many people randomized?
Number of participants in each intervention group
Make and model of ventilator used
Ventilator settings used
Number of participants who received intended treatment
Number of participants who were analysed

(Continued)

Bronchodilator and make and model of each device used
Dose and frequency of administration
Detail administration process e.g. use of spacer device, position of nebulizer/MDI in circuit, patient positioning etc for each intervention
Duration of treatment
How was the decision to withdraw mechanical ventilation made? (i.e. protocol, clinical judgement or a combination)
Length of follow up reported for patient outcome
Time points when measurements were taken during the study
Time points reported
Time points you are using in RevMan
Any additional information

⋆ measures to include airway resistance (Rrs min, Rrs max, Δ*R*rs, Rint) Remember – we are looking for *recording* of these outcomes; not reporting.

Appendix 6. Summary of primary outcome measures

Outcome measure: Reduction in Δ*R*rs (H_2O $l^{-1}s$)				
	MDI		Nebulizer	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Guerin 1999 (n = 18) ± SEM	11.46 ± 1.04	10.79 ± 0.88	12.80 ± 1.59	10.79 ± 1.11
	Not significant		P <0.01	

Outcome measure: Reduction in R*int* (H_20 l^{-1} s)				
	MDI		Nebulizer	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Guerin 1999 (n = 18)	5.03 ± 0.81	4.10 ± 0.60	5.23 ± 0.82	4.36 ± 0.62

(Continued)

± SEM		
	P <0.05	Not significant

Outcome measure: Reduction in *R*rs or R*int* (cm H_20)				
	MDI		Nebulizer	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Manthous 1993	18.9 ± 2.6	19.6 ± 4.7	21.5 ± 5.7	17.6 ± 5.4
(n = 10)		(estimate from a published figure)		
± SEM				
	Not significant		P <0.01	

WHAT'S NEW

Date	Event	Description
21 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Agi Holland (AH)

Co-ordinating the review: AH

Undertaking manual searches: AH and Gill McCrossan (GM)

Screening search results: AH and Linda Veitch (LV)

Organizing retrieval of papers: GM and LV

Screening retrieved papers against inclusion criteria: AH and LV

Appraising quality of papers: AH and Fiona Smith (FS)

Abstracting data from papers: AH and FS

Writing to authors of papers for additional information: GM and LV

Providing additional data about papers: GM and LV

Obtaining and screening data on unpublished studies: Not required

Data management for the review: AH and FS

Entering data into Review Manager (RevMan 5.1): AH and FS

RevMan statistical data: Not required

Other statistical analysis not using RevMan: Kay Penny (KP)

Double entry of data: (data entered by person one: AH; data entered by person two: FS)

Interpretation of data: AH, LV, FS, GM, KP

Statistical inferences: KP

Writing the review: AH, FS, KP, GM

Securing funding for the review: AH

Performing previous work that was the foundation of the present study: AH

Guarantor for the review (one author): AH

Person responsible for reading and checking review before submission: AH

DECLARATIONS OF INTEREST

Agi Holland: see Sources of support

Fiona Smith: see Sources of support

Kay Penny: none known

Gill McCrossan: see Sources of support

Linda Veitch: none known

Caroline Nicholson: none known

SOURCES OF SUPPORT

Internal sources

- Edinburgh Napier University, UK.

External sources

- Karen Hovhannisyan, Denmark.

  Help with search strategies
- The Chief Scientist Office of The Scottish Government, UK.

  Financial support for Agi Holland, Gill McCrossan and Fiona Smith to undertake the Review through Grant number CZG/2/417

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Dr Kay Penny joined the review team for statistical advice and support following Dr Sandra Bonnellie's retirement from Edinburgh Napier University.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; *Metered Dose Inhalers; *Nebulizers and Vaporizers; *Respiration, Artificial; Aerosols; Airway Resistance [*drug effects] [physiology]; Bronchodilator Agents [*administration & dosage]; Heart Rate [drug effects] [physiology]; Intensive Care Units; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans