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[Intervention Protocol]

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

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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 are planned according to other ventilation and bronchodilation strategies, ventilator settings and administration variables.

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, a significant proportion of patients still require invasive ventilation to treat their acute exacerbation (Brochard 1995; Plant 2000). 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 2008).

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 through 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; nebulizer and 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 2008). 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 to 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 2006a; Dhand 2007a; Dhand 1996; 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 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 dependant 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 nebulizer (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 using older ventilator models (Beaty 1989).

Multi-center survey data on bronchodilator administration practices in mechanically ventilated neonates highlights 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 therefore will 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 are 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 will include randomized controlled trials (RCTs), including randomized cross-over trials where the order of the intervention is randomized, comparing nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients.

Types of participants

We will include adult patients (as defined by the trialists) receiving invasive mechanical ventilation in critical care units. If no definition is available, we will assume the participants as being adult unless identified as paediatric in the studies.

Types of interventions

We will exclude studies in which aerosol bronchodilation agents are 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) will be allowed. We will exclude any studies in which bronchodilator agents are 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 will be allowed if equally distributed between the intervention and control groups. We will also exclude studies where different bronchodilation agents are used between the intervention and control groups.

Types of outcome measures

Primary outcomes

1. Reduction in airway resistance - measured as a reduction in 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 will search the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) ([Appendix 2](#)); OVID MEDLINE (1950 to date) ([Appendix 3](#)); OVID EMBASE (1980 to present) ([Appendix 4](#)); and CINAHL via EBSCOhost (1982 to date) ([Appendix 5](#)).

Searching other resources

We will not limit the search by language or publication status. We will contact 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 meet the inclusion criteria.

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

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

Data collection and analysis

Selection of studies

We will undertake the systematic review using the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Two authors (AH and LV) will independently examine the titles and abstracts identified by the search strategy to remove any duplicate records and obviously irrelevant reports. We will retrieve and evaluate the full text versions of potentially relevant studies identified by at least one author. Two authors (AH and LV) will independently assess each study to determine if they meet the eligibility criteria outlined above in the section [Criteria for considering studies for this review](#). We will resolve any disagreements by discussion between the authors (AH and LV), with a further author (FS) acting as arbiter. We will provide details of both included and excluded studies in the respective tables of the review.

Data extraction and management

AH and FS will extract data independently utilising a standardized data extraction form based on Cochrane Anaesthesia Review Group recommendations (see [Appendix 1](#)). We will resolve any disagreements by discussion between the authors (AH and FS), with a further author (LV) acting as arbiter. The data extraction form will include 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 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 will use the statistical package Review Manager software [RevMan 5.0](#), 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 will assess the risk of bias of included studies using The Cochrane Collaboration's tool for assessing risk of bias as outlined by [Higgins 2008](#). 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. Each component will be judged 'Yes' for low risk of bias, 'No' for high risk of bias or 'Unclear'. We will include a 'Risk of bias' table as part of the 'Table of characteristics of included studies' and a 'Risk of bias summary' figure which will detail all of the judgements made for all included studies in the review.

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

Measures of treatment effect

We will use the statistical package Review Manager software [RevMan 5.0](#). For dichotomous outcomes, we will calculate the risk ratio (RR). For continuous outcomes, we will calculate a mean difference (MD) or the standardized mean difference (SMD) with a 95% confidence interval (CI) as appropriate.

Unit of analysis issues

Cross-over trials

Where suitable data are available from cross-over trials, we will adopt the approach recommended by [Elbourne 2002](#). We will include data using results from paired analyses, where estimates of within patient differences, means and standard errors are either available, can be obtained from the trialists or can be calculated.

Dealing with missing data

Where data are missing, we will contact the original investigators to request the missing data. We intend to perform intention-to-treat (ITT) analysis for dichotomous data. For continuous data we will perform ITT analyses if sufficient results are available from included studies. If data are insufficient, we will undertake an available case analysis and consider the potential impact of the missing data in the interpretation of the results of the review ([Higgins 2008](#)).

Assessment of heterogeneity

We will assess clinical heterogeneity using a three step approach. We will initially assess graphical depictions of confidence intervals generated by Review Manager software [RevMan 5.0](#) for the amount of overlap present. Statistical heterogeneity is indicated if there is poor overlap of confidence intervals ([Higgins 2008](#)). We

will explore the presence of heterogeneity formally using the Chi^2 statistic and quantify it using the I^2 statistic (Higgins 2008). We will consider meta-analysis if studies are suitably homogenous, in terms of clinical diversity, to provide a meaningful summary.

Assessment of reporting biases

We will generate funnel plots 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 are to be included in a meta-analysis, we will also use the regression asymmetry test to test for funnel plot asymmetry as described by Egger 1997. Where the intervention effect is measured in terms of odds ratios for binary data, we will test funnel plot asymmetry using the arcsine test proposed by Rücker 2008.

Data synthesis

We will 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 will incorporate data from the first time period only if the necessary information is available. For cross-over trials when both time periods are used and no standard deviation of the mean difference is available, we will impute this using the correlation coefficient from other studies. We will calculate this from as many other studies as possible. We will analyse the results using inverse variance meta-analysis.

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

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

Subgroup analysis and investigation of heterogeneity

If adequate data are available relating to other ventilation and bronchodilation strategies such as heated humidification, use of spacer devices, helium oxygen mixtures and nitric oxide mixtures for ventilation, we will conduct subgroup analyses on these groups.

We will also conduct subgroup analyses on groups in which similar ventilation settings were used, in which an inhalation chamber was utilized in the administration process or not, and in which it is possible to group these according to their location in the ventilator circuit.

To estimate the impact of differing doses of bronchodilator agents, we will perform a subgroup analysis comparing the intervention effect in trials in which higher doses of bronchodilator were used to trials in which lower doses were administered, if the data available enable such groupings to be made.

Sensitivity analysis

We will 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 will perform a sensitivity analysis comparing the intervention effect in trials that based the decision to discontinue mechanical ventilation upon pre-specified standardized criteria within the study compared to studies that based this decision on clinicians' judgements alone. This will be done to estimate the potential for a biased effect when the duration of mechanical ventilation is determined by a subjective judgement.

We will 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 will provide an estimate of the potential for a biased treatment effect when combination bronchodilator therapy is utilized.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

APPENDICES

Appendix I. 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
	<i>Next question</i>	<i>Next question</i>	Exclude
Participants Were the participants mechanically ventilated and: - defined as adult by trialists OR - NOT identified as paediatric	Yes	Unclear	No
	<i>Next question</i>	<i>Next question</i>	Exclude
Interventions Did the study contain at least two interventions, comparing any model of nebuliser to MDI for aerosol bronchodilation?	Yes	Unclear	No
	<i>Next question</i>	<i>Next question</i>	Exclude
Was the difference in bronchodilator delivery device the only planned difference between the comparison interventions?	Yes	Unclear	No
	<i>Next question</i>	<i>Next question</i>	Exclude
Were the same bronchodilatory agents used in all comparison groups?	Yes	Unclear	No

(Continued)

	<i>Next question</i>	<i>Next question</i>	Exclude
Were only bronchodilators delivered during the trial? (i.e. no other drug groups/agents mixed in with bronchodilator agent/s)	Yes	Unclear	No
	<i>Next question</i>	<i>Next question</i>	Exclude
Was there any combination administration of bronchodilators of differing drug groups?	Yes	Unclear	No
	Exclude	<i>Next question</i>	<i>Next question</i>
Outcomes Did the study record airway responses?	Yes	Unclear	No
	Include	Include (subject to clarification of “unclear” points)	Exclude
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

<u>Sequence generation</u>	
Was the allocation sequence adequately generated?	
	Give text which enabled your decision, including page no:
“YES” if used: <ul style="list-style-type: none"> · Random number table · Computer random number generator · Coin tossing · Shuffling cards/envelopes · Throwing dice · Minimization 	
“No” if used non-random method such as: <ul style="list-style-type: none"> · 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	

(Continued)

<u>Allocation concealment</u> 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: <ul style="list-style-type: none">· Central allocation· Sequentially numbered containers of identical appearance· Sequentially numbered opaque, sealed envelopes· Or equivalent method	
“No” if investigators could potentially foresee allocation such as: <ul style="list-style-type: none">· 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	

<u>Blinding of participants, personnel and outcome assessors</u> Was knowledge of allocated intervention adequately prevented during study? <i>Note: Blinding of personnel not possible with current review, but consider if a lack of blinding has potentially influenced results</i>	
	Give text which enabled your decision, including page no:
“YES” if: <ul style="list-style-type: none">· No blinding, but unlikely to influence results· Outcome assessment blinded	
“No” if: <ul style="list-style-type: none">· 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	

<u>Incomplete outcome data</u> Were incomplete outcome data adequately addressed?	
	Give text which enabled your decision, including page no:

(Continued)

<p>“YES” if missing data:</p> <ul style="list-style-type: none"> · Complete - none missing · Unlikely to be related to true outcome · Is balanced across groups · Effect size not enough to have clinical relevance impact on observed effect size · Have been imputed appropriately 	
<p>“No” if missing data:</p> <ul style="list-style-type: none"> · 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 	
<p>“Unclear” if there is insufficient information to permit “Yes” or “No” judgement OR study did not address this outcome</p>	

<p><u>Selective outcome reporting</u> Are study reports free of selective outcome reporting?</p>	
	Give text which enabled your decision, including page no:
<p>“YES” if:</p> <ul style="list-style-type: none"> · 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 	
<p>“No” if:</p> <ul style="list-style-type: none"> · 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 	
<p>“Unclear” if there is insufficient information to permit “Yes” or “No” judgement</p>	

(Continued)

<u>Other potential threats to validity</u>	
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.: · 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	
<u>Cross - over trials</u>	
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/%)	

(Continued)

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

Data extraction

Outcomes	
	Reported in study?
Airway response:	
Airway resistance (<i>Rrs</i> min, <i>Rrs</i> max, ΔRrs)	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
<i>Practitioner satisfaction</i>	<i>Yes / No</i>
<i>Associated cost</i>	<i>Yes / No</i>
<i>Quality of life measures</i>	<i>Yes / No</i>

Continuous Outcomes - RCTs						
	Unit of measurement	Intervention		Control		Details if outcomes are only described
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
Airway resistance	ΔRrs					
	<i>Rrs</i> max					
	<i>Rrs</i> 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 <i>within patient differences</i> that you need the SD, standard error and CI for				
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	SD	Standard error	CI	<i>t</i>	<i>P value</i>
Airway resistance	ΔRrs									
	<i>Rrs</i> max									
	<i>Rrs</i> min									
Duration of mechanical ventilation										

(Continued)

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	
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 nebuliser/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	
<i>Any additional information</i>	

measures to include airway resistance (Rrs min, Rrs max, ΔRrs) Remember - we are looking for *recording* of these outcomes; not reporting.

Appendix 2. 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 3. Search strategy for MEDLINE (Ovid SP)

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 4. Search strategy for EMBASE (Ovid SP)

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 5. 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")

HISTORY

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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: AH, GM and LV

Data management for the review: AH and FS

Entering data into Review Manager ([RevMan 5.0](#)): AH and FS

RevMan statistical data: AH and FS

Other statistical analysis not using RevMan: Sandra Bonellie (SB)

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

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

Statistical inferences: SB

Writing the review: AH, LV, FS, 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

None known.

SOURCES OF SUPPORT

Internal sources

- Edinburgh Napier University, UK.

External sources

- Karen Hovhannisyanyan, Denmark.

Help with search strategies

- The Chief Scientist Office of The Scottish Government, UK.

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