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[Intervention Review]

Inhaled bronchodilators for acute chest syndrome in people with sickle cell disease

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ABSTRACT

Background

Bronchodilators are used to treat bronchial hyper-responsiveness in asthma. Bronchial hyper-responsiveness may be a component of acute chest syndrome in people with sickle cell disease. Therefore, bronchodilators may be useful in the treatment of acute chest syndrome. This is an update of a previously published Cochrane Review.

Objectives

To assess the benefits and risks associated with the use of bronchodilators in people with acute chest syndrome.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings. Additional searches were carried out on MEDLINE (1966 to 2002) and Embase (1981 to 2002).

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 11 July 2016.

Selection criteria

Randomised or quasi-randomised controlled trials. Trials using quasi-randomisation methods will be included in future updates of this review if there is sufficient evidence that the treatment and control groups are similar at baseline.

Data collection and analysis

We found no trials investigating the use of bronchodilators for acute chest syndrome in people with sickle cell disease.

Main results

We found no trials investigating the use of bronchodilators for acute chest syndrome in people with sickle cell disease.

Authors' conclusions

If bronchial hyper-responsiveness is an important component of some episodes of acute chest syndrome in people with sickle cell disease, the use of inhaled bronchodilators may be indicated. There is need for a well-designed, adequately-powered randomised controlled trial to assess the benefits and risks of the addition of inhaled bronchodilators to established therapies for acute chest syndrome in people with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Inhaled drugs for opening up the airways in cases of acute chest syndrome in people with sickle cell disease

Review question

We reviewed the evidence about whether using inhaled, short-acting bronchodilators for acute chest syndrome reduces illness and mortality in people with sickle cell disease and to assess whether this treatment causes adverse effects. This is an update of a previously published Cochrane Review.

Background

Sickle cell disease is an inherited blood disorder. People with sickle cell disease often suffer from acute chest syndrome, although it is not known why. Acute chest syndrome can cause fever, coughing, chest pain and shortness of breath and can be life-threatening. Often, people with sickle cell disease and acute chest syndrome also wheeze. This suggests that airways are narrowed, as with asthma. Bronchodilators are drugs which relax the muscles in the airways, thus opening them up to make breathing easier. They are used in this way for asthma, so may be of similar use in acute chest syndrome.

Search date

The evidence is current to: 11 July 2016.

Study characteristics

We found no trials to show the effects of these drugs for this condition.

Key results

Research needs to assess the benefits and risks of using inhaled bronchodilators for acute chest syndrome in people with sickle cell disease.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a group of genetic haemoglobin disorders with multicentric origins in sub-Saharan Africa and the Indian sub-continent. Population mobility has spread the disorders through Europe, Asia and the Americas. Homozygous sickle cell (SS) disease is the most common of all haemoglobin disorders, with 230,000 new cases per year in sub-Saharan Africa, a region that accounts for 70% of the worldwide prevalence (Weatherall 2001; WHO 1994). Significant morbidity and premature death may result from SS disease with average life expectancy estimated at between 42 years and 53 years for men and between 48 and 58 years for women (Platt 1994; Wierenga 2001).

Acute chest syndrome is defined as the onset of pulmonary symptoms accompanied by a new infiltrate on chest radiograph in a person with SCD. Fever is the most frequent symptom, with cough, chest pain, shortness of breath and pain also being common. In the North American National Acute Chest Syndrome Study, wheezing was documented in a quarter of all episodes, and pulmonary function testing during some episodes suggested airways narrowing (Vichinsky 2000).

Acute chest syndrome is one of the most common causes of illness and death in people with SCD. North American data suggest that 50% of children with SS disease have at least one episode of acute chest syndrome (ACS) by 10 years of age (Gill 1995). As a cause of hospital admission in people with SCD, ACS is second only to painful crisis and is the most common cause of premature death (Castro 1994; Gray 1991; Thomas 1982). The aetiology of ACS is diverse including infection, pulmonary fat embolism, infarction, sequestration and pulmonary embolism (Vichinsky 2000). Although asthma has been shown to be associated with recurrent ACS, the role played by bronchial hyper-responsiveness (BHR) is currently unclear (Knight-Madden 2005).

Description of the intervention

Bronchial hyper-responsiveness may be more common in people with SCD than in the general population. In one study, cold air or bronchodilator challenge showed a positive response in 83% of people with SS disease known to have asthma and 64% of those with no history of asthma (Leong 1997). However, other studies suggest that asthma prevalence may be unaffected by coincidental SCD (Bayoumi 1997; Savoy 1988; Sofowora 1970). A case report suggests that ACS may be more difficult to manage in those with severe asthma (Perin 1983) and a clinical response to albuterol inhalations may assist in the treatment of ACS (Handelman 1991).

Bronchodilators are used to bring prompt symptomatic relief in the treatment of BHR (Barnes 2000). This class of drugs includes beta-adrenergic receptor agonists such as albuterol and terbutaline and anti-cholinergic agents such as ipratropium bromide. Albuterol acts within minutes and its effect lasts a maximum of six to eight hours. The most commonly used anti-cholinergic agent, ipratropium bromide, acts within 15 minutes and its effect lasts from four to six hours. These drugs are effectively administered by metered dose inhaler or nebulizer. The usefulness of bronchodilators in ACS in SCD has not been reviewed before.

While nitric oxide may cause bronchodilation, this is not the primary effect that is sought when it is used, which are the

intravascular effects. Therefore, this intervention is not eligible for this review and is considered in another Cochrane Review (Al Hajeri 2008).

Current treatment modalities

It is often impossible to rule out infection thus making antibiotic use important. Due to the frequent involvement of atypical bacteria, appropriate coverage is suggested, but studies have not been conducted to determine the relative efficacies of different antibiotic regimens (Knight 1999; Vichinsky 2000).

How the intervention might work

In the North American Acute Chest Syndrome Study, bronchodilators were used in 61% of the participants, and in 20% of these participants, bronchodilators had a positive effect (defined as an increase of 15% in forced expiratory volume in one second) (Vichinsky 2000). During episodes of ACS characterised by wheezing or chest tightness, or both, and have evidence of BHR, bronchodilators may improve pulmonary function and bring symptomatic relief.

Why it is important to do this review

The routine use of bronchodilators in ACS will add to the cost of care. Also, commonly used bronchodilators can have side effects such as tachycardia, nervousness and hyperactivity and, in one reported case, myocardial infarction (Corso 2005). For these reasons, it is important to have evidence of the beneficial effects of bronchodilators in ACS before recommendations for use are applied uniformly.

Methylxanthines, for example theophylline, are not used primarily as bronchodilators. Long-acting beta-agonists are used as prophylaxis rather than in acute management and have long half-lives. These are beyond the scope of this review. In this review we will examine the usefulness of inhaled bronchodilators in ACS.

This review is an update of a previously published Cochrane Review (Knight-Madden 2003; Knight-Madden 2012; Knight-Madden 2014).

OBJECTIVES

The aim of the review is to determine whether the use of inhaled, short-acting bronchodilators for ACS reduces morbidity and mortality in people with SCD and to assess whether this treatment causes adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials. Trials in which quasi-randomised methods, such as alternation, are used will be included if there is sufficient evidence that the treatment and control groups were similar at baseline.

Types of participants

People with one of four SCD genotypes (SS, SC, S-β⁺-thalassaemia and S-β⁰-thalassaemia) of all ages and both sexes, who have had an episode of ACS defined as the onset of pulmonary symptoms and/or signs accompanied by a new infiltrate on chest radiograph. SCD

must be proven by electrophoresis and sickle solubility test, with family studies or DNA (deoxyribonucleic acid) tests as appropriate.

Types of interventions

Acute use of inhaled short-acting bronchodilators during an episode of ACS compared to an alternative treatment or no treatment.

Types of outcome measures

It was planned that outcome data would be grouped into those measured during an episode, within one month, between one and six months, and between six months and one year. If outcome data were reported at other time periods, consideration would be given to examining these as well.

Primary outcomes

1. All causes of mortality
2. Mortality with confirmed ACS
3. Pulmonary function as measured by peak flow, forced vital capacity and forced expiratory flow in one-minute
4. Adverse events

Secondary outcomes

1. Need for blood transfusion
2. Duration of oxygen supplementation
3. Duration of hospital admission
4. Dyspnoea scores
5. High dependency and intensive care unit admissions
6. Occurrence of stroke
7. Changes in measures of oxygenation (saturation, blood gases)

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND acute chest syndrome.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

We performed an additional search using MEDLINE (1966 to February 2004) and Embase (1981 to February 2004). For the full search strategy, please see the appendix attached to this review ([Appendix 1](#)).

Date of the most recent search of the Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 11 July 2016.

Searching other resources

The electronic searches found no eligible trials, but we had planned to search the bibliographic references of all retrieved literature for additional reports of trials. We would then contact lead authors of published work for their knowledge of other trials. We also planned to obtain full reports from authors where trials have been published in abstract form or presented at meetings.

Data collection and analysis

Selection of studies

We planned to screen the trials found by the initial search of all the databases and reference lists to identify papers with potential relevance to the review. However, no trials were found. If we find trials for future updates of this review, we will seek the full text of selected articles (translated into English where required), and select trials for inclusion using our defined eligibility criteria. We will not be blinded to authors and journal. We plan that discussion and if necessary the involvement of a third party will resolve disagreements, should they occur. We will assess our level of agreement on inclusion of selected articles using the kappa measure of agreement ([Armitage 1994](#)).

Data extraction and management

For future updates of this review, and if we are able to include trials, we plan to independently extract the data from the selected trials using a standard form. We would plan to verify numeric calculations when possible, and confirm data when necessary.

Assessment of risk of bias in included studies

We will independently assess the risk of bias of the trials and resolve any disagreements by discussion. For each included trial we will assess six specific features: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and 'other issues'. We will use the Cochrane 'risk of bias' assessment tool to summarise and judge each feature as low risk, high risk, or unclear risk of bias ([Higgins 2011a](#)).

For each included trial, we will report the numbers of participants with missing data and any reasons given for these missing data. We will also report on whether the investigators had performed and adequately reported a sample-size calculation, and whether they used and fully described an intention-to-treat (ITT) analysis.

Measures of treatment effect

For the dichotomous outcome variables of each individual trial, we will calculate the summary weighted odds ratios and 95% confidence intervals (CIs) (fixed-effect model). For continuous outcome variables we will calculate weighted mean difference when outcomes are measured in a standard way across trials, or standard mean difference when outcomes are conceptually the same but measured in different ways, along with 95% confidence intervals (95% CI). We will assess the potential impact of missing outcome data as we interpret our results. For all analyses we will use Cochrane's statistical package ([RevMan 2014](#)).

Unit of analysis issues

For cross-over trials, we will calculate the mean treatment differences where possible and enter these using the fixed-effect generic inverse variance (GIV) analysis in RevMan, to provide summary weighted differences and 95% CIs (RevMan 2014). In cross-over trials, if we believe there is a carryover effect which will outlast any washout period included in the trial, we will include only data from the first arm in the meta-analysis (Elbourne 2002).

Dealing with missing data

Our primary endpoints are dichotomous (mortality, adverse events) and continuous (pulmonary function). For all endpoints with missing data, we will use available-case analysis. The effect of this analysis choice will be assessed by sensitivity analysis, and we will also assess the risk of bias resulting from incomplete outcome data as part of our general assessment of bias. For missing summary measures, we will request further information from the primary investigators where possible.

Assessment of heterogeneity

We will describe any heterogeneity between the trial results and test this to see if it reached statistical significance using the χ^2 test. We will consider heterogeneity to be significant when the P value is less than 0.10 (Higgins 2011b). We also plan to use the I^2 statistic, where heterogeneity is categorised such that a value of under 25% is considered low, around 50% is considered moderate and over 75% is considered a high degree of heterogeneity (Higgins 2003).

Assessment of reporting biases

We plan to construct a funnel display of effect size to test for the possible presence of publication bias in our population of trials.

Data synthesis

We will include the 95% CI, estimated using a fixed-effect model. However, we will use the random-effects model if there are concerns about statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity

We plan to conduct limited a priori subgroup analyses for the known baseline heterogeneity between genotypical clinical courses. We will examine outcome measures in two genotype groups: 'severe genotypes' (SS and S- β 0) and 'mild genotypes' (SC and S- β +). If we find heterogeneity we will use limited *post hoc* subgroup analyses in an attempt to identify reasons for this variation.

Sensitivity analysis

If trial heterogeneity is found, we will perform sensitivity analyses based on risk of bias, and publication status of the trials. For our dichotomous endpoints, we will investigate our choice of available-case analysis by re-analysing using intention-to-treat (ITT) with a selected number of outcome data imputation methods:

1. assuming that all missing participants experienced the event;
2. assuming that all missing participants did not experience the event;
3. imputing outcome data according to the event rate observed in the control group.

RESULTS

Description of studies

We found no trials that were eligible for inclusion in this review.

Risk of bias in included studies

We found no trials that were eligible for inclusion in this review.

Effects of interventions

We found no trials that were eligible for inclusion in this review.

DISCUSSION

Inhaled bronchodilators have few significant side effects and are useful in asthma and chronic obstructive airways disease because bronchoconstriction and bronchial hyper-responsiveness (BHR) play an important role in the pathophysiology of these diseases (Murray 2000).

We have found no appropriate trials to clarify the role of bronchoconstriction and BHR in acute chest syndrome (ACS), and there are conflicting observational reports on the possibly increased prevalence of baseline BHR in people with sickle cell disease (SCD) (Koumbourlis 2001; Leong 1997). Some episodes of ACS are characterised by BHR (Vichinsky 2000). Inhaled bronchodilators predominately work by modulating activity of receptors of the autonomic nervous system leading to airway smooth muscle relaxation, which relieves bronchospasm. The need for a therapeutic trial of inhaled bronchodilator use in people with ACS has been suggested (Vichinsky 2000).

The additional cost of care that will result from routine use of inhaled bronchodilators cannot be ignored in low and lower-middle income countries, which carry most of the worldwide SCD burden.

Until adequate data become available, clinicians should be guided by the history, clinical examination and investigations. It is likely that bronchodilators will be helpful in those with ACS who have a history of asthma and in those who demonstrate wheezing or reversible obstructive airways disease during the episode of ACS (Vichinsky 2000).

Clinicians in centres which do not have pulmonary function equipment available, will need to balance the undefined possible benefits against the possible risks of treatment and the additional costs incurred.

AUTHORS' CONCLUSIONS

Implications for practice

No randomised controlled trials on the use of inhaled bronchodilators in ACS were identified for inclusion in this review. The research evidence on which to base clinical decisions is therefore limited to case reports, and other less robust evidence.

Implications for research

There is need for a well-designed, adequately-powered randomised controlled trial to assess the benefits and risks of the addition of inhaled bronchodilators to established therapies for ACS in people with SCD.

ACKNOWLEDGEMENTS

Ms Tracy Elliot participated as a review author while this review was in the protocol stage. We thank all our referees for their constructive suggestions and criticism.

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APPENDICES

Appendix 1. Search Strategy Using OVID interface

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1 exp hemoglobinopathies/
2 sickle.tw.
3 (hemoglobin ss or hemoglobin sc or hemoglobin c).ti,ab.
4 (haemoglobin ss or haemoglobin sc or haemoglobin c).ti,ab.
5 meniscocytosis.tw.
6 hemoglobinopath$.tw.
7 haemoglobinopath$.tw.
8 drepanocyt$.tw.
9 thalassemia.tw.
10 thalassaemia.tw.
11 "acute chest".ti,ab.
12 asthma.ti,ab.
13 'chronic obstructive airways disease'.ti,ab.
14 bronchodilator$.ti,ab.
15 ALBUTEROL/
16 salbutamol.mp.
17 TERBUTALINE/
18 Ipratropium/
19 or/ 1-10
20 or/ 11-18
21 19 and 20
22 limit 21 to human

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WHAT'S NEW

Date	Event	Description
20 September 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis Haemoglobinopathies Trials Register identified 10 potentially eligible references, none of which were eligible for any section of the review.
20 September 2016	New citation required but conclusions have not changed	The update contains minor changes throughout the text.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 3, 2003

Date	Event	Description
1 August 2014	New citation required but conclusions have not changed	Minor changes have been made throughout the review.
1 August 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Haemoglobinopathies Trials Register identified 18 potentially relevant references, none of which were eligible for inclusion in the review.
25 May 2012	New citation required but conclusions have not changed	Minor changes have been made throughout the review.
25 May 2012	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Haemoglobinopathies Trials Register identified two potentially eligible trials, neither of which were eligible for inclusion within the review.
20 September 2010	Amended	Contact details updated.
16 April 2010	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials potentially eligible for inclusion in the review.
31 July 2008	Amended	<p>Converted to new review format.</p> <p>A new plain language summary has been written in line with latest guidance from The Cochrane Collaboration.</p> <p>Parts of the methods section has been re-worded. The methods sections on 'Assessment of risk of bias in included studies', 'Assessment of heterogeneity', and 'Sensitivity analysis' have been updated. The methods sections on 'Unit of analysis issues' and 'Dealing with missing data' have been added. Four additions have been made to 'Other references'.</p>
31 July 2008	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials potentially eligible for inclusion in the review.
1 November 2006	New search has been performed	Review update: November 2006

Date	Event	Description
		The search of the Haemoglobinopathies Trials Register found no potentially eligible trials for inclusion in the review. The 'Methods of review' section has been updated.
1 April 2005	New search has been performed	Review update: April 2005 The search of the Haemoglobinopathies Trials Register found no potentially eligible trials for inclusion within the review. The 'Background' section was updated with additional references added to the review.
1 April 2004	New search has been performed	The search of the Haemoglobinopathies Trials Register found no potentially eligible trials for inclusion in the review.

CONTRIBUTIONS OF AUTHORS

This review was conceived by Dr Jennifer Knight-Madden.

Dr Knight-Madden, Professor Hambleton and the Cochrane Cystic Fibrosis and Genetics Disorders Group conducted searches for relevant trials.

Dr Knight-Madden and Professor Hambleton planned to screen, appraise and abstract data for the review.

For future updates, Dr Knight-Madden and Professor Hambleton will perform data entry and data interpretation, with advice from the Cochrane Cystic Fibrosis and Genetics Disorders Group.

Dr Knight-Madden and Professor Hambleton have jointly contributed to review writing and subsequent updates.

Dr Knight-Madden acts as the guarantor of the review.

DECLARATIONS OF INTEREST

Both authors: none known.

SOURCES OF SUPPORT

Internal sources

- Sickle Cell Unit, Tropical Medicine Research Institute, Jamaica.
- Chronic Disease Research Centre, Tropical Medicine Research Institute, Barbados.

External sources

- Medical Research Council, UK.
- National Institute for Health Research, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

Acute Chest Syndrome [*drug therapy]; Anemia, Sickle Cell [*complications]; Bronchodilator Agents [administration & dosage] [*therapeutic use]; Nebulizers and Vaporizers

MeSH check words

Humans