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Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease (Review)

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[Intervention Review]

Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease

Amani Al Hajeri[1], Graham R Serjeant[2], Zbys Fedorowicz[3]

[1]Department of Genetics, Ministry of Health, Awali, Bahrain. [2]Sickle Cell Trust (Jamaica), Kingston 6, Jamaica. [3]UKCC (Bahrain Branch), The Cochrane Collaboration, Awali, Bahrain

Contact: Amani Al Hajeri, Department of Genetics, Ministry of Health, Box 25438, Awali, Bahrain. alhajeriamani@gmail.com.

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ABSTRACT

Background

Acute chest syndrome has been defined as a new infiltrate visible on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnoea, dyspnoea, or new-onset hypoxia. Symptoms and complications of this syndrome, whether of infectious or non-infectious origin, vary quite widely in people with sickle cell disease. Lung infection tends to predominate in children, whilst infarction appears more common in adults. However, these are often interrelated and may occur concurrently. The differences in clinical course and severity are suggestive of multiple causes for acute chest syndrome. Successful treatment depends principally on high-quality supportive care. The syndrome and its treatment have been extensively studied, but the response to antibiotics, anticoagulants, and other conventional therapies remains disappointing. The potential of inhaled nitric oxide as a treatment option has more recently provoked considerable interest. Nitric oxide appears to play a major role in both the regulation of vascular muscle tone at the cellular level and in platelet aggregation (clumping). Much of the pathophysiology of sickle cell disease is consistent with a mechanism of nitric oxide depletion and although there has been extensive research on the pathophysiology of acute chest syndrome, the possible therapeutic role of inhaled nitric oxide for acute chest syndrome in sickle cell disease is still to be determined.

Objectives

To assess the effectiveness of inhaled nitric oxide for treating acute chest syndrome by comparing improvement in symptoms and clinical outcomes against standard care.

Search methods

We searched The Group's Haemoglobinopathies Trials Register, which comprises references identified from comprehensive electronic database searches and handsearching of relevant journals and abstract books of conference proceedings. In July 2007 the following clinical trials registers were searched: ClinicalTrials.gov; the WHO International Clinical Trials Registry Platform; Current Controlled Trials; and Clinicaltrials.com.

Most recent search of the Haemoglobinopathies Trials Register: 10 September 2010.

Selection criteria

All randomised or quasi-randomised controlled trials of people with sickle cell disease suffering from acute chest syndrome, comparing the use of inhaled nitric oxide to placebo or standard care for any single or multiple treatment and over any time period.

Data collection and analysis

No studies identified were eligible for inclusion.

Main results

No studies identified were eligible for inclusion.

Authors' conclusions

There is a need for well-designed, adequately-powered randomised controlled trial to assess the benefits and risks of this form of treatment as an adjunct to established therapies.

PLAIN LANGUAGE SUMMARY

Inhaled nitric oxide for acute chest syndrome in people with sickle cell disease

Sickle cell disease is an inherited blood disorder affecting approximately 250 million people worldwide. Sickle-shaped red blood cells which are characteristic of sickle cell disease may block blood vessels causing pain, tissue death and even severe damage in the major organs. Similar blockages in the blood vessels of the lungs can lead to lung injury and a complication known as acute chest syndrome which occurs in approximately 30% of people with sickle cell disease. Common symptoms include fever, coughing, chest pain and shortness of breath; some of which can be life-threatening. Treatment is mainly supportive and given when an individual experiences symptoms and may include antibiotics, drugs to help prevent the clotting of blood and other conventional treatments. Interest has been shown recently in inhaling nitric oxide, a soluble gas. This gas is known to play a role in expanding blood vessels and clumping platelets, to relieve some of the symptoms of acute chest syndrome. It is also used for treatment in similar conditions, namely pulmonary hypertension (high blood pressure in the blood vessels of the lungs) in babies up to four weeks old. The authors of the review did not find any trials showing how effective inhaled nitric oxide is for acute chest syndrome in people with sickle cell disease. The authors concluded that future research should provide evidence for people to make informed decisions about whether nitric oxide is effective.

BACKGROUND

Aetiology and prevalence

Sickle cell disease (SCD) is an inherited blood condition and one of the most prevalent genetic diseases worldwide. It is particularly common in Sub-Saharan Africa, South and Central America, Saudi Arabia, India and a number of Mediterranean countries (Alvim 2005; El-Hazmi 1998; Fleming 1989; Loureiro 2005). In the USA the disease affects around 72,000 people and occurs at a rate of 1 in every 500 African-American and 1 in every 1000 to 1400 Hispanic-American births (WHO 2005).

Abnormal haemoglobin genes are responsible for the different forms of the disease. These include homozygous sickle cell (SS) disease in which the sickle haemoglobin (HbS) gene is inherited from both parents; sickle cell-haemoglobin C (SC) disease in which the genes for HbS and HbC are inherited; and two further types resulting from the interaction of HbS genes with those for beta thalassaemia; sickle cell/ß^{o} -thalassaemia and sickle cell/ß$^{+}$ thalassaemia (Sß0 and Sß$^{+}$). Homozygous sickle cell (SS) disease and sickle cell/ß^{o} -thalassaemia are generally considered the more severe forms of the disease whilst (SC) disease and sickle cell/ß+ thalassaemia tend to be milder.

The main clinical features result from the tendency of HbS molecules to polymerise, leading to a reduced pliability of the red blood cells which are then prematurely broken down and eventually cause blockages and reduced flow in some of the blood vessels (vaso-occlusion). Some of the potentially serious complications in SCD are: chronic haemolytic anaemia; increased susceptibility to infections; recurrent episodes of pain; an increased risk of stroke; and multiple organ dysfunction. Acute chest syndrome (ACS) is a frequent complication of sickle cell anaemia, as well as a major cause of morbidity and the greatest single cause of mortality in SCD from the age of two years (Vichinsky 2000). Data from the 'Clinical Course of Sickle Cell Disease Cooperative Study' indicate that this complication occurs with an incidence of 10,500 per 100,000 patients per year (Castro 1994). Acute chest syndrome has been defined as a new infiltrate visible on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnoea, dyspnoea, or new-onset hypoxia (Vichinsky 2000). Complications occurring in the lungs include infection, infarction (death of tissue due to blockage of the blood vessels by blood clots or bone marrow fat) and acute pulmonary sequestration. Recurrent attacks of ACS may also result in pulmonary fibrosis, pulmonary hypertension, and right-sided heart failure.

Clinical features and symptoms

Symptoms and complications of ACS may vary quite widely between individuals with SCD. Clinical features may include: new infiltrate visible on chest X-ray; fever; cough; sputum production; chest pain and respiratory symptoms e.g. dyspnoea (breathing difficulties) or hypoxia (poor oxygenation). Infection in the lungs tends to predominate in children whilst infarction appears to be more common in adults, but these two are often interrelated and may occur concurrently (Taylor 2004). Rates of infection have been reported as: chlamydia 7.2%; mycoplasma 6.6%; viruses 6.4% and *Streptococcus pneumoniae*, 4.3% (Vichinsky 2000). Bacterial pneumonia has also been reported in up to 40% of cases with ACS (Davies 1984).

Treatment options

The syndrome has been extensively studied but the responses to: antibiotics, as found in a recent Cochrane Review (Martí-Carvajal 2008); anticoagulants; and other conventional therapies remain disappointing. Against this background, the advent of inhaled nitric oxide (inhNO) as a potential treatment option has gained considerable interest. The effect of nitric oxide on red blood cells in vitro and inhNO in a number of volunteers with sickle cell anemia has previously been investigated (Head 1997).

Nitric oxide has several mechanisms of action, but it appears to play a major role in both the regulation of vascular muscle tone at the cellular level as well as in platelet aggregation (clumping) (Gladwin 1999). In SCD, especially SS disease, the rapid release of cell-free haemoglobin may exceed the normal clearance mechanisms such as by binding to haptoglobin, and thus the excess free haemoglobin consumes nitric oxide and impairs its regulatory role (Rother 2005). It is perceived that the restoration of nitric oxide levels, which may be most readily achieved by inhalation, may return abnormal vascular tone towards normal. Preliminary studies have shown that inhNO can be effective in reducing pulmonary hypertension in neonates by improving oxygenation and reducing inflammation and pulmonary oedema (Atz 1997). It has been suggested that its use in acute respiratory distress syndrome (ARDS) may lend support to its use in ACS (Gerlach 1993).

Much of the pathophysiology of SCD is consistent with a mechanism of nitric oxide depletion. Although there has been extensive research on the pathophysiology of ACS (Rossaint 1993), the role of inhNO in ACS (one of the most serious complications of SCD) raises the possibility of new therapies for sickle cell anaemia based on nitric oxide.

OBJECTIVES

To assess the effectiveness of inhaled nitric oxide for treating ACS by comparing improvement in symptoms and clinical outcomes against standard care.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials.

Types of participants

People with sickle cell disease of any age, of either gender and in any setting, and diagnosed with ACS.

The definition of ACS was according to the clinical signs, symptoms and criteria described by Vichinsky as, a new infiltrate visible on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnoea, dyspnoea, or new-onset hypoxia (Vichinsky 2000).

Types of interventions

Inhaled nitric oxide compared to placebo or standard care for any single or multiple treatment and over any time period.

Types of outcome measures

Primary outcomes

1. Chest pain
   a. intensity (expressed as scores obtained through any validated patient reported outcomes instrument either generic or sickle cell disease specific)
   b. duration
2. Fever
3. Laboratory Investigations
   a. arterial blood gases
   b. pulse oximetry

Secondary outcomes

1. Duration of any assisted ventilation
2. Duration of hospitalisation in the intensive care unit (ICU): the number of inpatient days
3. Quality of life (e.g. absence from school, lost time at work, mobility) as assessed by any validated questionnaire either generic or SCD specific
4. Participant satisfaction with the intervention assessed by any appropriate and validated questionnaire (either generic or SCD specific)

Adverse effects

We intended reporting on any specific adverse effects, systemic or local, toxicity, any clinically diagnosed hypersensitivity or other unacceptable or adverse events associated with this treatment.

Search methods for identification of studies

There were no language restrictions on included studies and if necessary the authors would have arranged to translate and report any relevant non-English papers.

Electronic searches

We identified relevant trials from the Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND acute chest syndrome.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*) and quarterly 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 Cystic Fibrosis and Genetic Disorders Group Module.

The reference lists of any clinical trials identified were to be cross checked and the review authors' personal databases of trial reports were examined in an attempt to identify any other relevant studies. In an attempt to find additional published and unpublished studies and to obtain information about ongoing trials we contacted a number of experts by electronic mail and searched several clinical trials registers: ClinicalTrials.gov ; the WHO INTERNATIONAL Clinical Trials Registry Platform; Current Controlled Trials; and Clinicaltrials.com in July 2007.

Date of most recent search of the Haemoglobinopathies Trials Register: 10 September 2010.

Searching other resources

The reference lists of any clinical trials identified were to be cross checked and the review authors' personal databases of trial reports were examined in an attempt to identify any other relevant studies. In an attempt to find additional published and unpublished studies and to obtain information about ongoing trials we examined the bibliographical references of the background papers to this review.

We planned to contact investigators of included studies by either conventional or electronic mail to ask for details of additional published and unpublished trials.

Data collection and analysis

Selection of studies

Two authors Amani Al Hajeri (AAH) and Zbys Fedorowicz (ZF) independently assessed the abstracts of studies resulting from the searches. On first inspection, none of the identified studies were found to be eligible for inclusion in the review. For future updates, full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision will be obtained. The full text papers will be assessed independently by two authors and any disagreement on the eligibility of potentially included studies will be resolved through discussion and consensus with a third author. After assessment by the authors remaining studies that do not match the inclusion criteria will be excluded from further review and the reasons for their exclusion will be noted in the Characteristics of excluded studies table.

For future updates, when studies are identified for inclusion in the review, the following methods will be applied.

Data extraction and management

We will collect study details and outcome data using a predetermined form designed for this purpose. We will independently enter the study details into the Characteristics of included studies table and the extracted data into the 'Comparisons and data' table in RevMan 5.0 and automatically check for differences (RevMan 2008). AAH will hold the master copy. We will only include data if there is an independently reached consensus. We will discuss any disagreements and if required consult a third review author.

We will extract the following details.

1. Study methods: method of allocation; masking of participants; exclusion of participants after randomisation; and proportion of and reasons for follow-up losses.
2. Participants: country of origin; sample size; age; sex; inclusion and exclusion criteria as described in the Criteria for considering studies for this review section.
3. Intervention: frequency; and duration of usage.
4. Control: type; dose; and frequency of any comparison or placebo.

5. Outcomes: primary and secondary outcomes as described in the outcome measures section of this protocol.

If stated, we will record the sources of funding of any of the included studies.

We will use this information to assess the clinical homogeneity and the external validity of the trials.

Assessment of risk of bias in included studies

Every study reporting a randomized clinical trial will be assessed according to the criterion grading system described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0 (Higgins 2008). Assessment will be made of the following domains of risk of bias:

Randomisation

This criterion will be graded as 'Yes' (low risk of bias), 'Unclear', and 'No' (high risk of bias). Examples of methods that will be graded as 'Yes' will include: computer generated or table of random numbers; drawing of lots; coin-toss; shuffling cards; or throw of a dice. Methods graded as inadequate are, for example, those were the method of randomisation is not described. We will judge as 'No' (inadequate), methods of randomisation such as: case record number; date of birth; or alternate numbers.

Concealment of allocation

We will grade this criterion as 'Yes' (low risk of bias), 'Unclear', and 'No' (high risk of bias). Examples of methods of allocation concealment that will be graded as 'Yes' are central randomisation or sequentially numbered sealed opaque envelopes. Methods graded as 'No' (inadequate) are, for example, use of open allocation sequence where the participants or trialists, or both, could foresee the upcoming assignment.

Blinding (of participants, researchers and outcome assessment)

Blinding will be assessed using the following criteria:

1. blinding of participants (yes/unclear/no);
2. blinding of caregiver (yes/unclear/no);
3. blinding of outcome assessment (yes/unclear/no).

Handling of withdrawals and losses

This criterion will be graded as 'Yes' (low risk of bias), 'Unclear', and 'No' (high risk of bias) according to whether there was a clear description given of the difference between the two groups of losses to follow up.

Risk of bias in the included studies will be categorised according to the following:

1. low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
2. moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partly met;
3. high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.0 (Higgins 2008).

Measures of treatment effect

We will calculate the mean difference and 95% confidence intervals for continuous data obtained from visual analogue scales. We will calculate the risk ratios and their 95% confidence intervals for all dichotomous data.

We will pool results of clinically and statistically homogeneous trials to provide estimates of the efficacy of the interventions, only if the included studies have similar interventions received by similar participants. We will calculate the number needed to treat to benefit (NNTB) and number needed to treat to harm (NNTH) for the whole pooled estimates with 95% confidence intervals.

Assessment of heterogeneity

We will assess the statistical homogeneity using a chi-squared test and the I^2 statistic, where I^2 values over 50% indicate moderate to high heterogeneity (Higgins 2003).

Assessment of reporting biases

If we identify a sufficient number of RCTs, we will attempt to assess publication bias using a funnel plot (Egger 1997). If we detect asymmetry in the funnel plot, then we will investigate other possible causes.

Data synthesis

For meta-analysis of any quantitative data we intend to use the fixed-effect and random-effects models as appropriate. If we establish that there is significant statistical heterogeneity between the studies, we will use the random-effects model.

In the event that there are insufficient clinically homogeneous trials for this intervention or insufficient study data that could be pooled, we will present a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

We plan to assess clinical heterogeneity by examining the characteristics of the studies; the similarity between the types of participants; the interventions; and the outcomes as specified in the criteria for included studies.

Sensitivity analysis

If there are sufficient included studies, we intend conducting sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment; exclusion of studies with no or unclear blinding of outcomes assessment; and unclear or inadequate completeness of follow up.

RESULTS

Description of studies

Nine references to studies were initially identified, but on inspection of the title and abstract none met our inclusion criteria. All were subsequently excluded from further analysis.

Our searches of several clinical trials registers did reveal two ongoing multicenter trials investigating the effectiveness of inhaled nitric oxide in SCD, but both focused on vaso-occlusive pain crises. No studies can be included in this review at this time.

Risk of bias in included studies

No studies were included in the review.

Effects of interventions

No studies were included in the review.

DISCUSSION

Whilst preliminary studies have shown that inhNO can be effective in reducing pulmonary hypertension in neonates (Atz 1997), and its use in acute respiratory distress syndrome (ARDS) (Gerlach 1993) may be supportive of its use in ACS, we were unsuccessful in finding relevant trials to clarify the role of inhNO in ACS. The need for a therapeutic trial to evaluate the clinical effectiveness of inhNO in people with ACS was suggested several years ago (Gladwin 1999). The absence of this form of high level evidence may in part reflect some of the complexities associated with conducting a trial, where the aetiology of the condition (ACS) is not clearly understood. In addition there are significant ethical issues to be faced in withholding life-saving treatment or offering a placebo in such a trial.

This review illustrates that there is currently insufficient evidence to support the use of inhNO in the management of ACS in people with SCD.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current information we cannot recommend in favour of, or against the use of inhNO for treating ACS in people with SCD.

Implications for research

The absence of evidence exemplified by the lack of studies in this systematic review highlights the importance of further high quality research to provide reliable evidence for the effectiveness of this intervention for the relief of at least some of the symptoms, e.g. pain in ACS. Therefore, well-designed, randomised controlled trials are needed to assess the effectiveness of inhNO in people with SCD.

ACKNOWLEDGEMENTS

The authors would like to thank Tracey Remmington and Nikki Jahnke of the Cochrane Cystic Fibrosis & Genetic Disorders Group and the referees for their help and support in conducting this review.

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WHAT'S NEW

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Date	Event	Description
24 January 2013	Amended	Contact details updated.

HISTORY

Review first published: Issue 1, 2008

Date	Event	Description
3 November 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.
28 August 2008	New search has been performed	A search of the Group's Heamoglobinopathies Trials Register did not identify any potentially eligible trials.
1 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Amani Al Hajeri (AAH) and Zbys Fedorowicz (ZF) were responsible for:
Designing the review
Co-ordinating the review and subsequent updates

ZF and AAH were responsible for:
Organising retrieval of papers
Writing to authors of papers for additional information
Providing additional data about papers.

AAH, ZF were responsible for:
Data collection for the review
Screening search results
Screening retrieved papers against inclusion criteria
Appraising quality of papers
Extracting data from papers
Obtaining and screening data on unpublished studies
Entering data into RevMan
Analysis of data

AAH, ZF, and Graham Serjeant (GS) were responsible for writing the review.

AAH conceived the idea for the review and will also be the guarantor for the review.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

NOTES

The protocol was peer reviewed in June 2007, but the completed protocol was never published prior to the publication of the full review.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Anemia, Sickle Cell [*complications]; Bronchodilator Agents [*administration & dosage]; Nitric Oxide [*administration & dosage]; Respiration Disorders [*drug therapy] [etiology]; Syndrome

MeSH check words

Humans