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Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease (Review)

Radunovic A, Annane D, Rafiq MK, Mustfa N

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TABLE OF CONTENTS

[Intervention Review]

Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease

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ABSTRACT

Background

Amyotrophic lateral sclerosis, also known as motor neuron disease, is a fatal neurodegenerative disease. Neuromuscular respiratory failure is the commonest cause of death, usually within two to five years of the disease onset. Supporting respiratory function with mechanical ventilation may improve survival and quality of life. This is the first update of a review first published in 2009.

Objectives

The primary objective of the review is to examine the efficacy of mechanical ventilation (tracheostomy and non-invasive ventilation) in improving survival in ALS. The secondary objectives are to examine the effect of mechanical ventilation on functional measures of disease progression and quality of life in people with ALS; and assess adverse events related to the intervention.

Search methods

We searched The Cochrane Neuromuscular Disease Group Specialized Register (1 May 2012), CENTRAL (2012, Issue 4), MEDLINE (January 1966 to April 2012), EMBASE (January 1980 to April 2012), CINAHL Plus (January 1937 to April 2012), and AMED (January 1985 to April 2012). We also searched for ongoing studies on ClinicalTrials.gov.

Selection criteria

Randomised and quasi-randomised controlled trials involving non-invasive or tracheostomy assisted ventilation in participants with a clinical diagnosis of amyotrophic lateral sclerosis, independent of the reported outcomes. We planned to include comparisons with no intervention or the best standard care.

Data collection and analysis

For the original review, four authors independently selected studies for assessment and two authors reviewed searches for this update. All authors extracted data independently from the full text of selected studies and assessed the risk of bias in studies that met the inclusion criteria. We attempted to obtain missing data where possible. We planned to collect adverse event data from included studies.

Main results

For the original Cochrane review, the review authors identified and included two randomised controlled trials involving 54 participants with ALS receiving non-invasive ventilation. There were no new randomised or quasi-randomised controlled trials at this first update.

Incomplete data were published for one study and we contacted the trial authors who were not able to provide the missing data. Therefore, the results of the review were based on a single study of 41 participants that compared non-invasive ventilation with standard care. It was a well conducted study with low risk of bias.

The study showed that the overall median survival was significantly different between the group treated with non-invasive ventilation and the standard care group. The median survival in the non-invasive ventilation group was 48 days longer (219 days compared to 171 days for the standard care group (estimated 95% CI 12 to 91 days, P = 0.0062)). This survival benefit was accompanied by an enhanced quality of life. On subgroup analysis, the survival and quality of life benefit was much more in the subgroup with normal to moderately impaired bulbar function (20 participants); median survival was 205 days longer (216 days in NIV group versus 11 days in the standard care group, P = 0.0059). Non-invasive ventilation did not prolong survival in participants with poor bulbar function (21 participants), although it showed significant improvement in the mean symptoms domain of the Sleep Apnoea Quality of Life Index but not in the Short Form-36 Health Survey Mental Component Summary score. Neither trial reported clinical data on intervention related adverse effects.

Authors' conclusions

Evidence from a single randomised trial of non-invasive ventilation in 41 participants suggests that it significantly prolongs survival and improves or maintains quality of life in people with ALS. Survival and some measures of quality of life were significantly improved in the subgroup of people with better bulbar function, but not in those with severe bulbar impairment. Future studies should examine the health economics of NIV and factors influencing access to NIV. We need to understand the factors, personal and socioeconomic, that determine access to NIV.

PLAIN LANGUAGE SUMMARY

Non-invasive ventilation for people with amyotrophic lateral sclerosis or motor neuron disease

Management of amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), has evolved rapidly in the last ten years and although still incurable, ALS is not untreatable. In this updated review we examined the evidence from two randomised trials, involving 54 participants in total, of non-invasive ventilation (using a face or nasal mask and a small portable ventilator) in people with ALS. Complete data were only available from a single trial of 41 participants. The results of this trial indicate that non-invasive ventilation significantly prolongs survival and improves or maintains quality of life compared to standard care. Average survival was increased by 48 days from 171 to 219 days (estimated 95% CI 12 to 91 days). The survival benefit from non-invasive ventilation was shown to be much greater in those people with ALS who had normal or only moderately impaired bulbar function (impairments to the muscles used for speaking, chewing and swallowing). Among these 20 participants, the average survival for those treated with non-invasive ventilation was increased by 205 days (survival was 216 days with non-invasive ventilation, compared to 11 days with standard care). The quality of life was also maintained in participants with mild to moderate bulbar impairment. In the 21 participants with severe bulbar impairment, non-invasive ventilation significantly improved sleep-related symptoms compared to standard care but did not prolong survival. Neither trial reported on adverse effects due to the intervention. Future studies should examine the health economics of non-invasive ventilation and factors that influence access to non-invasive ventilation.

BACKGROUND

Amyotrophic lateral sclerosis, also known as motor neuron disease (MND), is a fatal neurodegenerative disease characterised by loss of upper and lower motor neurons in the brain and spinal cord (Brooks 1994; Brooks 2000). The incidence of ALS is 1 to 2 per 100,000 of the population and the age specific incidence and mortality rates peak at 55 to 75 years (Worms 2001).The average life

expectancy is two to three years from the onset of symptoms, although 10% of people with ALS may survive for 10 years or more (Haverkamp 1995; Turner 2003). Death usually results from respiratory failure, due to denervation weakness in respiratory muscles. As such, respiratory muscle function at any time point during the disease trajectory is the most important predictor of survival and an important predictor of quality of life (QoL) (Bach 1995; Haverkamp 1995; Vitacca 1997; Stambler 1998; Fitting 1999; Chaudri 2000; Bourke 2001; Lyall 2001a; Varrato 2001; Lechtzin 2002). Measures of respiratory muscle strength (for example, forced vital capacity, sniff nasal inspiratory pressure) are useful in monitoring the progression of respiratory muscle weakness, but no single test of respiratory function can be used to reliably predict the onset of respiratory failure. Furthermore, respiratory function tests have limitations in people with bulbar weakness who cannot blow effectively (Lyall 2001a).

Assisted ventilation has long been used to support ventilation in respiratory failure (Annane 2007). Assisted ventilation can be provided with invasive (tracheostomy ventilation, TV) and non-invasive (NIV) means. TV can prolong survival for many years (Bach 1993; Cazzoli 1996) but is resource intensive and risks ventilator entrapment which exacts a significant emotional toll on people with ALS and their carers (Moss 1993; Cazzoli 1996; Moss 1996). It may prolong life in the face of increasing disability and dependency and hence quality of life may not be sustained. Nevertheless, people affected by ALS are increasingly aware of this option. TV in ALS is not encouraged in Europe and North America (Hayashi 1997; Borasio 1998; Yamaguchi 2001). In Japan, however, the predominant form of ventilation offered to people with ALS is TV and the cost is fully covered by the government and medical insurance (Kawata 2008).

NIV is another option for treating respiratory failure in people with ALS. NIV utilises a face or nasal mask and a volume cycled or bilevel pressure limited ventilator to provide an intermittent positive pressure to support ventilation. Until the turn of the century, the use of NIV varied greatly across North America and Europe (Melo 1999; Borasio 2001; Bradley 2001; Cedarbaum 2001; Chio 2001; Bourke 2002). Evidence from several retrospective and some prospective studies indicated that NIV may be associated with gain in survival (Pinto 1995; Aboussouan 1997; Kleopa 1999; Bach 2002), improved quality of life (QoL) (Hein 1997; Hein 1999; Aboussouan 2001; Bourke 2001; Jackson 2001; Lyall 2001b) and improved cognitive function (Newsom-Davis 2001). People with ALS who have little or no bulbar muscle weakness may tolerate NIV better than those with significant bulbar involvement (Cazzoli 1996; Aboussouan 1997). In the absence of a randomised controlled clinical trial, uncertainties remained over the benefits and unwanted effects of TV and NIV.

A Cochrane review of nocturnal mechanical ventilation for people with chronic hypoventilation (Annane 2007) identified eight randomised trials, two of which involved people with ALS. This review concluded that nocturnal ventilation may relieve chronic hypoventilation related symptoms and prolong survival, but that the quality of the studies was poor and the benefit of long-term mechanical ventilation should be confirmed in further trials.

Over the past few years, the use of NIV in ALS has been greatly increased (O'Neill 2012). A randomised controlled trial evaluated the effects of NIV on survival and quality of life in people with ALS (Bourke 2006). The National Institute for Health and Clinical Excellence UK (NICE) has published guidelines on the use of NIV in people with ALS (NICE 2010). The aim of this review is to assimilate the evidence for mechanical ventilation in ALS and inform the benefits and unwanted effects of TV and NIV. The original version of this review (Radunovic 2009) was based on this single study of 41 participants. For this first update, no new randomised or quasi-randomised controlled trials have been identified.

OBJECTIVES

The primary objective of the review is to examine the efficacy of mechanical ventilation (tracheostomy and NIV) in improving survival in ALS. The secondary objectives are to examine the effect of mechanical ventilation on functional measures of disease progression and quality of life in people with ALS; and assess adverse events related to the intervention..

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials, involving NIV or tracheostomy assisted ventilation. Quasi-randomised trials are those where treatment allocation was intended to be random but may have been biased (for example alternate allocation or allocation according to the day of the week). Studies were selected independently of reported outcomes.

Types of participants

All those with a clinical diagnosis of ALS/MND (pure mixed upper motor neuron and lower motor neuron degeneration with supportive electromyogram) according to the El Escorial criteria (Brooks 1994; Brooks 2000), at any stage of disease and with any clinical pattern of the condition (e.g. bulbar and limb onset). Subgroups of interest were participants with or without significant bulbar symptoms as categorised by the authors of the papers reviewed.

Types of interventions

All forms of NIV (using a nasal or facial mask or mouth piece) and tracheostomy assisted ventilation. The effects of these interventions are compared against no intervention or the best standard care.

Types of outcome measures

Primary outcomes

The primary outcome was overall survival after initiation of assisted ventilation as assessed by a pooled hazards ratio using life table/Cox regression methods to combine disparate periods of observation from all studies. This would have been supplemented where possible by pooled estimates of the 75%, 50% (median) survival times and confidence intervals (CIs) if available as appropriate. This is to allow for the situation where the proportional hazards assumption, necessary for Cox regression, has not been met.

Secondary outcomes

The secondary outcome measures were:

1. survival at one month and six months or longer;
2. quality of life assessed using validated health status questionnaires (for example Short Form Health Survey-36 (SF-36) (Lyall 2001b)) at one month and six months or longer;
3. any validated functional rating scale such as the ALS Functional Rating Scale (ALSFRS 1996) or the ALSFRS-Revised (Cedarbaum 1999), Norris (Norris 1974) or Appel (Haverkamp 1995) scales at one month and six months or longer;
4. the proportion of people experiencing adverse events related to mechanical ventilation. Adverse events would have been considered in two categories. The first category would have included the proportion of participants experiencing any adverse event attributed to ventilation (for example: fistulae, pneumothorax, bleeding, local infection, hospitalisation or death) and the second category would have included participants experiencing severe complications of mechanical ventilation, including life-threatening episodes, prolonged hospitalisation, and death.

Search methods for identification of studies

We searched The Cochrane Neuromuscular Disease Specialized Register (1 May 2012) using 'amyotrophic lateral sclerosis' or 'motor neuron disease' or 'motor neurone disease' 'motorneurone disease' or 'motorneuron disease' or 'motoneuron disease' or 'motoneurone disease' combined using AND with 'mechanical ventilation' or 'artificial ventilation' or 'assisted ventilation' or 'artificial respiration' or 'respiratory failure' or 'intubation, intracheal' or 'tracheotomy' or 'tracheostomy' or 'BiPAP' or 'positive pressure ventilation' or 'positivepressure ventilation' or 'non invasive ventilation' or 'noninvasive ventilation'.

We also searched CENTRAL (2012, Issue 4 in the Cochrane Library), MEDLINE (January 1966 to April 2012), EMBASE (January 1980 to April 2012), CINAHL Plus (January 1937 to April 2012) and AMED (January 1985 to April 2012). The detailed search strategies are in the appendices: Appendix 1 (MEDLINE), Appendix 2 (EMBASE), Appendix 3 (CENTRAL), Appendix 4 (CINAHLPlus) and Appendix 5 (AMED). We also searched for ongoing or unpublished trials on the U.S. National Institutes of Health trials registry ClinicalTrials.gov.

Data collection and analysis

Selection of studies

For the original review, all four review authors (AR, DA, KJ, NM) checked titles and abstracts identified by the searches for randomised or quasi-randomised trials and two review authors (MKR, DA) reviewed the searches for the update. We obtained the full text of all potentially relevant studies and assessed them independently.

Data extraction and management

All review authors extracted data independently onto a specially designed form. We tried to obtain missing or additional data from the study authors wherever possible. For our primary outcome, overall survival of assisted ventilation, we planned to extract hazard ratios with standard errors or CIs, or median survival times with 95% CIs or the numbers required to construct a life table, for example the numbers surviving/failing to survive after initiation of assisted ventilation for each of a sequence of specified time intervals.

Assessment of risk of bias in included studies

All review authors decided which trials fitted the inclusion criteria for the review and assessed the risk of bias in the included studies. We resolved disagreement about inclusion by discussion and reaching consensus between the review authors. We completed an assessment of risk of bias on all included studies according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 (Higgins 2008, updated Higgins 2011). We looked at randomisation sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. We then made a judgement on each of these criteria relating to the risk of bias of 'High risk', 'Low risk' or 'Unclear

risk', where 'Unclear risk' indicates an unclear or unknown risk of bias.

We planned to undertake sensitivity analyses to demonstrate the effect of downweighting or ignoring those studies that received low scores in the individual aspects of quality criteria on the meta-analyses, had sufficient numbers of trials and relevant data been available.

Measures of treatment effect

For the primary outcome measure we were planning to calculate an overall measure of treatment efficacy combining survival results at different time points. This measure is based on estimating a pooled hazard ratio (i.e. at any given time point the risk of death for the survivors in the treated group divided by risk of death for the survivors in the control group) as described by Parmar 1998. We wanted to use this measure rather than the summary risk ratio (RR) calculated by the Cochrane statistical software, Review Manager (RevMan) (current version RevMan 5.2 (RevMan 2012), because the Parmar method uses all the data on survival from the whole observation period and the RevMan program needs the survival rates at a fixed point in time since the start of observation to be the same for all the studies if they are to be combined.

For the secondary outcome measures to combine trial results for appropriate pairings of treatments, we were planning to calculate a mean of the difference between their effects using RevMan. If we had found trials using dichotomous outcome measures such as death rates after a fixed time, for example three months, we planned to obtain RR with 95% CI and we would have expressed results as mean differences (MDs) with 95% CI for continuous outcomes.

If we had found trials where the studies measure continuous outcomes that are conceptually the same but are measured in different ways (such as different assessment scales), we planned to combine the results and express them as standardised mean differences (SMD using standard deviation units) with 95% CI.

Assessment of heterogeneity

We planned to test for heterogeneity across trials and if found to undertake sensitivity analyses by repeating the calculation omitting the trials which had low scores on individual quality items. If variations in trial quality did not explain heterogeneity, we planned to use a random-effect approach to obtain the pooled estimates from the group of trials.

RESULTS

Description of studies

Results of the search

The updated database searches for this update produced the following results: MEDLINE 153 (101 new references), EMBASE 89 (37 new), AMED 5 (1 new), CINAHL 62 (27 new), Cochrane Neuromuscular Disease Group Specialized Register 27 (8 new), CENTRAL (30 references), ClinicalTrials.gov 39 (3 new references).

After removal of duplicates, we obtained and evaluated the full text studies of 23 potentially relevant studies. We excluded 21 studies (see Characteristics of excluded studies) after independent assessment as they were non-randomised (Aboussouan 1997; Bach 1993; Buhr-Schinner 1999; Cazzoli 1996; Cedarbaum 2001; David 1997; Goulon 1989; Kamimoto 1989; Kleopa 1999; Lo Coco 2007; Lo Coco 2006; Lyall 2001b; Newsom-Davis 2001; Perez 2003; Pinto 1995; Pinto 1999; Pinto 2003; Saito 1999; Shoesmith 2007; Sivak 1982; Winterholler 2001).

We categorised seven of the trial registry entries as ongoing studies (see Characteristics of ongoing studies).

Included studies

All review authors agreed on the inclusion of two studies (Jackson 2001; Bourke 2006).

The first study (Jackson 2001) was a prospective randomised three-month study in three ALS centres in the US. The study included 20 people with ALS (no age or sex provided) of whom 13 were randomised when overnight oximetry studies documented oxygen saturation below 90% for at least one cumulative minute throughout the duration of the study (a minimum of six hours) and the individual had at least two significant symptoms of nocturnal hypoventilation. There were two groups: an early group where the participants were started immediately on NIV (seven participants) and a second (late) group (six participants) in which NIV was initiated when FVC was less than 50% predicted. No demographic characteristics for the participants were provided. The effect of NIV on ALSFRS respiratory version, Pulmonary Symptom Scale, and SF-36 was estimated. No survival data are available from this study.

The second study (Bourke 2006) was a RCT in a single ALS centre in the UK and included 92 participants of whom 41 met the criteria for randomisation (orthopnoea and/or maximum inspiratory pressures less than 60% or symptomatic hypercapnia) and were followed up for at least 12 months or until death. Random allocation was computer generated by the process of minimisation, the process which allows all significant prognostic factors to be included in the model. Twenty-two participants were assigned to the NIV group and 19 participants to the standard care group. Demographic and functional characteristics of the participants in the two groups were similar at randomisation (Characteristics of included studies). The effect of NIV on survival, and quality of life outcome domains, eg. SF-36 and the Sleep Apnea Quality ofLife Index (SAQLI) was estimated in the whole cohort but also in the

subgroups of participants with and without severe impairment of the bulbar function.

Excluded studies

One study (Perez 2003) was excluded as it was terminated early due to the problems recruiting participants into the trial. We excluded a study (Pinto 2003) as it used historical controls. One study (Pinto 1999) was a controlled study of exercise in ALS patients with respiratory insufficiency. One study (Sivak 1982) was an anecdotal study. Twelve studies (Bach 1993; Buhr-Schinner 1999; Cazzoli 1996; Cedarbaum 2001; David 1997; Goulon 1989; Kamimoto 1989; Kleopa 1999; Lo Coco 2007; Saito 1999; Shoesmith 2007; Winterholler 2001) were retrospective studies of which only Kleopa 1999 study had a control group. Five studies (Aboussouan 1997; Lyall 2001b; Newsom-Davis 2001; Lo Coco 2006; Pinto 1995) were non-randomised prospective observational studies.

Pinto 1995 was a single centre study in Portugal which included 20 consecutive participants with bulbar features and probable or definite ALS according to El Escorial criteria. The first 10 participants were treated with oxygen, bronchodilators and physiotherapy. The following 10 participants were submitted to bilevel positive airway pressure. Two participants were excluded, one in the first group because the participant had tracheostomy and the other in the second group for refusing the treatment. Although it was a controlled trial, participants were not randomised and hence risk of bias cannot be excluded.

Ongoing studies

We identified the following ongoing studies (NCT00386464; NCT00537446; NCT00560287; NCT00580593; NCT01363882; NCT01641965). See Characteristics of ongoing studies for details and the Discussion.

Risk of bias in included studies

For summary see Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study. A green plus sign indicates low risk of bias, a red minus sign indicates high risk of bias and a yellow question mark indicates unclear risk of bias.

Allocation

Allocation was adequately concealed in both included studies. Random allocation was computer generated by the process of minimisation, thus allowing centralised randomisation in the Bourke 2006 study. Although no data for allocation concealment are given in the Jackson 2001 paper we were informed by the study authors that the randomisation was undertaken by an independent statistician who prepared two sets of random assignment in blocks of four which were then allocated to each centre.

Blinding

Blinding of the participants was not possible in either study as it was not possible to blind delivery of the NIV. Outcome assessors were blinded in Jackson 2001 study but no information is given in Bourke 2006 on whether outcome asessors were blind to knowledge of allocation intervention when assessing the data.

Incomplete outcome data

In the Jackson 2001 study, data were provided on only six participants from the early intervention group. The outcome of one randomised participant was not clear and no data were given for the late intervention group. No obvious attrition bias was noted in the Bourke 2006 study. Thirteen participants withdrew during surveillance but none withdrew after randomisation and all participants were followed up until the end of the study or death in the Bourke 2006 study.

Selective reporting

The Bourke 2006 study is free of a suggestion of selective outcome reporting as the study protocol is available and all primary and secondary outcomes set in the study have been reported in the prespecified way. No study protocol is available for Jackson 2001 study. The results of the Jackson 2001 study were intended to be used as preliminary data but unfortunately no funding was secured for a future study.

Other potential sources of bias

In the Jackson 2001 study, nocturnal hypoventilation is not defined as per the universally accepted criteria; oxygen desaturation below 90% for at least one cumulative minute was accepted as evidence for nocturnal hypoventilation. Whereas, nocturnal oximetry showing oxygen desaturation below 88% for at least five consecutive minutes or oxygen saturation below 90% for more than 5% of sleep time are considered sufficient to initiate NIV (Mehta 2001).

Effects of interventions

Both included studies used NIV.
Unfortunately, there were insufficient data from Jackson 2001 to be included and this made overall analysis for either primary or secondary outcome measures not possible. Therefore our review is based on the results of one study, Bourke 2006. Neither were we able to obtain individual patient data or life tables from the Bourke 2006 trialists.

Primary outcome

The Bourke 2006 study showed that the overall median survival after initiation of assisted ventilation was significantly different between the NIV and standard care groups (P = 0.0062). The median survival for the NIV group participants was 48 days longer than the standard care group participants (219 days compared to 171 days). The published information did not provide a 95% CI for the median survival difference (48 days) or for our secondary outcomes. Approximate CIs could be derived from P values and median survival estimates under an assumption that median survival follows a lognormal distribution. A statistical method based on a lognormal survival model gave the following estimates for the 95% CI: 12 to 91 days for the estimated 48 day survival difference (private communication from statistical referee Dan Moore).
The overall median survival of the subgroup with good or moderately impaired bulbar function was also significantly different in the NIV group (P = 0.0059), with NIV group participants surviving 205 days longer than the standard care group participants (median 216 days in NIV group versus 11 days in the standard care group).
In participants with poor bulbar function, NIV did not confer survival advantage (P = 0.92), with an overall median survival for NIV group participants of 39 days less than the standard care group (222 versus 261 days).

Secondary outcomes

1. Survival at 1 or 6 months or longer

No data were available for survival at 1 and 6 months. For overall survival in the Bourke 2006 study see Primary outcome.

2. Quality of life assessed using validated health status questionnaires at 1 and 6 months or longer

No data were available for 1 and 6 months for either study.
There was an increase in the vitality subscale of SF-36 at 3 months (P = 0.071) in the early NIV group in the Jackson 2001 study. The mean vitality sub scale was 10.7 at baseline and 13.0 at 3 months but no data are given for the late NIV group.
The Bourke 2006 study showed that the median time maintained above 75% of the baseline of the SF-36 mental component summary (T_iMCS) and the SAQLI symptoms domain ($T_i$sym) after initiation of assisted ventilation were significantly different between the NIV and standard care groups (P = 0.0017 and 0.0013 for T_iMCS and $T_i$sym respectively). T_iMCS and $T_i$sym above 75% of the baseline in the subgroup with normal and moderately impaired bulbar function were significantly different between NIV and standard care groups (P = 0.001 and 0.0004 for T_iMCS and $T_i$sym respectively). In participants with poor bulbar function NIV conferred no benefit in maintaining T_iMCS and $T_i$sym above 75% of baseline (P = 0.64 and 0.26 for T_iMCS and $T_i$sym respectively). Some quality indices in SAQLI were improved by NIV in the subgroup with poor bulbar function as shown by significant difference in mean improvement of SAQLI (μsym) between NIV and standard care group (P = 0.018).

2a. Quality of life median values at 1 and 6 months

No data were available.

3. Functional rating scale at 1 or 6 months or longer

No data were available for the ALSFRS to be analysed.

3a. Functional rating scales median values

No data were available.

4. Proportion experiencing adverse events related to mechanical ventilation

Neither Jackson 2001 nor Bourke 2006 reported adverse events related to mechanical ventilation.

DISCUSSION

Two reports of randomised trials of nocturnal mechanical ventilation in ALS were available for this review. Both trials employed NIV. Since only one of the reports (Bourke 2006) was judged to be of adequate methodological quality, no meta-analysis was possible.

The Bourke 2006 study was designed to assess the effect of NIV on survival and quality of life of people with ALS. The study showed that NIV prolongs median survival and maintains the quality of life in ALS patients overall. The benefit of NIV was striking in the subgroup of participants with normal or moderately impaired bulbar function but it is, however, important to note that six of nine participants in the standard group died within two weeks of randomisation thus probably overestimating the effect of NIV in this subgroup of people with ALS. NIV does not prolong survival in people with ALS who have severe bulbar dysfunction but improves sleep-related symptoms in this subgroup.

Despite the above shortcomings, the Bourke 2006 study has shown that NIV significantly improves quality of life and prolongs life for longer than riluzole and has confirmed previous observations from non-randomised trials of survival advantage and improved quality of life in people with ALS who start and can tolerate NIV at the onset of respiratory impairment (Pinto 1995; Aboussouan 1997; Kleopa 1999; Bach 1993; Lyall 2001b). It is unlikely that there will be further randomised controlled trials of NIV in unselected cohorts of people with ALS. In the view of the authors, the Bourke 2006 study demonstrates that NIV is a major advance in the management of ALS and it will be unethical not to offer NIV to people with ALS who have symptoms of nocturnal hypoventilation. The evidence is in favour of offering NIV to all people with ALS, including those with poor bulbar function. The National Institute for Health and Clinical Excellence carried out a cost-effectiveness analysis using the Markov model and concluded that the use of NIV in the management of people with ALS represents a cost-effective use of resources.

Conclusions from the Bourke 2006 study cannot be extended to people with ALS who do not have respiratory symptoms. It has been suggested that early treatment with NIV may offer a survival benefit above that demonstrated in the Bourke 2006 study. There is some evidence from non-controlled studies (Carratu 2009) that early NIV improves survival and reduces decline of FVC in ALS. There are currently two ongoing RCTs (NCT01641965; NCT00386464), evaluating the impact of early NIV in ALS participants with mild respiratory involvement. A pilot study (NCT00580593) aiming to determine the feasibility of conducting a randomised, double-blind, placebo controlled trial of nocturnal NIV in people with ALS has completed data collection and likely to publish in the year 2013.

NIV settings may require titration with the disease progression. A randomised trial (NCT01363882) is evaluating the use of polysomnography in guiding the initiation and further titration of NIV therapy during the course of the disease. Different ventilator modes and settings are to be assessed in two NIV trials in people with ALS. The Italian multicentre randomised NIV study (NCT00560287) was designed to evaluate clinical efficacy, the participants' tolerance and quality of life and the frequency of changing settings in people with ALS who are undergoing NIV with pressure support ventilation or volume assisted ventilation. However, this trial is compromised with incomplete outcome data. The Columbia University study (NCT00537446) is designed to measure difference in pulmonary function and respiratory muscle pressure testing, difference in gas exchange, and difference in subjective dyspnoea between baseline and two different ventilator modes (high and low level non-invasive positive pressure ventilation). See Characteristics of ongoing studies for details.

A limitation of this review is being based on a single randomised controlled trial. Findings of this trial are consistent with the findings of several other studies which together offer strong support towards the benefit of NIV for people with ALS in respiratory failure. No study was identified that addressed the adverse effects of NIV. New ongoing studies are addressing further issues about the timing of NIV initiation and further titration with the disease progression. It is hoped that the next update will incorporate more information about the effects of NIV in ALS.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from a single randomised trial of NIV involving 41 participants suggest that it significantly improves and maintains quality of life and prolongs survival in people with ALS. Survival and some measures of quality of life were significantly improved in the subgroup of people with better bulbar function, but not in those with severe bulbar impairment. We believe adverse effects related to NIV should be systematically reported as at present there is little information on this subject.

Implications for research

Future studies should examine the health economics of NIV and factors influencing access to NIV. Access to NIV remains restricted in many parts of the world, including Europe and North America. We need to understand the factors, personal and socioeconomic, that decide access to NIV.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bourke 2006

Methods	Randomised controlled trial
Participants	41 participants with ALS (22 assigned NIV and 19 assigned standard care). Age: 63.7 ± 10.3 and 63.0 ± 8.1 years, male sex 64% and 53%, disease duration 1.9 ± 1.3 and 2. 0 ± 1.1 years, vital capacity (% predicted) 55.6 ± 18.7% and 48.8 ± 20.7%, maximum inspiratory pressure - $P_i$max (% predicted) 31.1 ± 11.0% and 31.0 ± 10.6%, SNIP (% predicted) 22.6 ± 11.4% and 24.4 ± 10.8%, $PaCO_2$ (mmHg) 6.1 ± 1.1 and 6.4 ± 1.2 in NIV and standard care group respectively at randomisation (mean ± SD)
Interventions	Intervention: NIV Control: standard care
Outcomes	Primary outcome: overall survival after initiation of assisted ventilation Secondary outcomes: survival at 1 and 6 months, SF-36 and SAQLI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Immediate allocation following randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible to blind delivery of the non-invasive ventilation. No information given on whether outcome assessors were blind to knowledge of allocation intervention when assessing the data
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 withdrawals during surveillance, but no participant withdrew after randomisation. One participant remains alive 45 months after randomisation; all others were followed up to death All outcome measures were measured by intention to treat.
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way
Other bias	Low risk	No other bias identified.

Jackson 2001

Methods	Prospective randomised study
Participants	7 participants with ALS in early NIPPV group and 6 participants in late NIPPV group. No age or sex provided. FVC = 77 ± 13% (mean ± SD) in early NIPPV group at baseline and time of randomisation. FVC = 77 ± 6% (mean ± SD) in late NIPPV at baseline. The time to randomisation (FVC < 50% predicted) for the late NIPPV group = 59 ± 38 days (mean ± SD)
Interventions	Early NIPPV (FVC 70 to 100%) and late NIPPV (FVC < 50%) - "standard of care"
Outcomes	Primary outcome: not available Secondary outcome: survival at 3 months, short form SF-36, ALSFRS-R and SAQLI
Notes	Pilot study which failed to develop further, due to lack of funding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no method of randomisation stated
Allocation concealment (selection bias)	Low risk	Two sets of random assignments in blocks of four for each centre were prepared by a statistician. Randomisation was carried out separately for bulbar and limb onset participants
Blinding (performance bias and detection bias) All outcomes	High risk	Trial described as a single-blind study, with pulmonary assessments, ALSFRS-R, SAQLI and SF-36 repeated every 3 months by a blinded clinical evaluator. Participants were not blinded to their treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only early NIPPV group analysed, outcome of 1 participant not clear
Selective reporting (reporting bias)	High risk	Pilot study, the expected sample size not clear. Study protocol not available
Other bias	High risk	Nocturnal hypoventilation not defined as per the universally accepted criteria

ALFFRS-R: revised Amyotrophic Lateral Sclerosis Functional Rating Scale
FVC: forced vital capacity
NIPPV: non-invasive positive pressure ventilation
NIV: non-invasive ventilation
SAQLI: sleep apnoea quality-of-life index
SD: standard deviation

SF-36: Short Form-36 Health Survey
SNIP: sniff nasal inspiratory pressure

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

Study	Reason for exclusion
Aboussouan 1997	Not a randomised trial. Observational cohort study of 18 NIV tolerant and 21 NIV non-tolerant participants with ALS
Bach 1993	Not a randomised trial. Retrospective study of 89 people with ALS. No control group
Buhr-Schinner 1999	Not a randomised trial. Retrospective study without control group. 38 people with ALS received intermittent nasal mechanical ventilation, using pressure- and volume-cycled respirators
Cazzoli 1996	Not a randomised trial. Retrospective study. 29 people with ALS used nasal intermittent positive pressure ventilation and 50 used tracheostomy intermittent positive pressure ventilation
Cedarbaum 2001	Not a randomised trial. No control group. 28 participants received BPAP and 7 received mechanical ventilation via tracheostomy
David 1997	Not a randomised trial. Retrospective study without control group. 13 people with ALS received BPAP
Goulon 1989	Not a randomised trial. Retrospective study of 16 people with ALS receiving assisted ventilation
Kamimoto 1989	Not a randomised trial. Retrospective study of 13 people with ALS receiving mechanical ventilation
Kleopa 1999	Not a randomised trial. Retrospective study of 122 people with ALS. 38 participants used BPAP for more than 4 hours day, 32 participants used BPAP for less than 4 hours a day and 52 participants refused to try BPAP
Lo Coco 2006	Not a randomised trial. Prospective study of 44 NIV tolerant ALS participants and 27 NIV non-tolerant participants
Lo Coco 2007	Not a randomised trial. Retrospective study of 33 consecutive ALS patients in acute respiratory failure receiving tracheostomy intermittent positive pressure ventilation
Lyall 2001b	Not a randomised trial. Prospective cohort study of 16 people with ALS on NIV and 11 normal age matched controls
Newsom-Davis 2001	Not a randomised trial. Prospective study of 9 ALS patients with hypoventilation given NIPPV, compared with 10 normal age matched controls without ventilation problems
Perez 2003	Randomised trial terminated early due to problems recruiting participants into the trial
Pinto 1995	Not a randomised trial. Prospective controlled study of 20 consecutive patients, first 10 received standard care and following 10 received NIV

(*Continued*)

Pinto 1999	Not a randomised trial. Controlled study of exercise in ALS patients with respiratory insufficiency. 8 participants on NIV and 12 ALS controls
Pinto 2003	Not a randomised trial. Historical controls.
Saito 1999	Not a randomised trial. Retrospective review of 25 cases using positive pressure ventilation with tracheostomy
Shoesmith 2007	Not a randomised trial. Retrospective review of 13 cases.
Sivak 1982	Not a randomised trial. Anecdotal study.
Winterholler 2001	Not a randomised trial. Retrospective study without control group. 20 ALS participants received NIPPV

ALS: amyotrophic lateral sclerosis
BPAP: bilevel positive airway pressure
NIPPV: non-invasive positive pressure ventilation
NIV: non-invasive ventilation

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

NCT00386464

Trial name or title	Noninvasive ventilation in ALS patients with mild respiratory involvement
Methods	Cross-over assignment, open label, randomised study
Participants	People with ALS and mild respiratory involvement
Interventions	NIV at night or usual care
Outcomes	Decline in FVC, quality of life, respiratory quality of life
Starting date	April 2002, completed September 2007
Contact information	John Hopkins University School of Medicine, Noah Lechtzin, MD
Notes	Data still awaiting analysis.

NCT00537446

Trial name or title	Effect of noninvasive positive pressure ventilation on pulmonary function testing in amyotrophic lateral sclerosis
Methods	Randomised, single-blind, cross-over trial
Participants	People with ALS and FVC <50% predicted or signs/symptoms of respiratory insufficiency
Interventions	NIPPV
Outcomes	Difference in pulmonary function and respiratory muscle pressure testing, difference in gas exchange, and difference in subjective dyspnoea between baseline and the two different ventilator modes. One arm of the trial to undergo 2 hours of high-level NIPPV, with an inspiratory positive airway pressure of 12 cm H_2O and an expiratory positive airway pressure of 3 cm H_2O. The other arm to undergo 2 hours of low-level NIPPV, with an inspiratory positive airway pressure of 6 cm H_2O and an expiratory positive airway pressure of 3 cm H_2O.
Starting date	September 2007
Contact information	Amy Atkeson, Columbia University, ad720@columbia.edu
Notes	

NCT00560287

Trial name or title	Non-invasive ventilation in amyotrophic lateral sclerosis: Volume versus pressure mode
Methods	Randomised, double-blind, parallel assignment trial
Participants	People with ALS and initial chronic respiratory failure
Interventions	NIV delivered with one of the ventilators specifically designed for NIV and given to the participant by the home care providers
Outcomes	Quality of life, tolerance to NIV, number of hours of NIV, frequency of hospital admission, frequency of changing the ventilator settings by the operator Survival, pulmonary function tests, diurnal and nocturnal gas exchange
Starting date	January 2008
Contact information	Fondazione Salvatore Maugeri, Stefano Nava MD snava@fsm.it
Notes	

NCT00580593

Trial name or title	Pilot placebo-controlled trial of early noninvasive ventilation for ALS
Methods	Double-blind, randomised, parallel assignment trial
Participants	People with ALS who have a FVC greater than 50%
Interventions	BPAP versus sham-NIPPV
Outcomes	NIPPV adherence, SF-36, pulmonary function tests, dyspnoea indexes
Starting date	April 2007
Contact information	Kirsten Gruis, University of Michigan, kgruis@umich.edu
Notes	

NCT01363882

Trial name or title	Progression of respiratory dysfunction in amyotrophic lateral sclerosis (ALS) patients: a comparison of standard of practice vs polysomnography-directed nocturnal non-invasive positive pressure ventilation
Methods	Double-blind, randomised, parallel assignment trial
Participants	People with ALS initiated on NIV as per current standard practice
Interventions	Polysomnography guided adjustment of NIV
Outcomes	Measures of respiratory function
Starting date	February 2008
Contact information	Robert C Basner, Columbia University
Notes	

NCT01641965

Trial name or title	Impact of early non-invasive ventilation in amyotrophic lateral sclerosis patients: a randomized controlled trial
Methods	Open label, randomised study
Participants	People with ALS and FVC $\leq$ 75%
Interventions	Home pressure ventilator model Vivo 40 (BREAS Medical AB)
Outcomes	Survival until death or tracheostomy, rate of decline in FVC

NCT01641965 (*Continued*)

Starting date	April 2012
Contact information	Eva Farrero, Hospital Universitari Bellvitge, Spain, efarrero@bellvitgehospital.cat
Notes	

ALS: amyotrophic lateral sclerosis
ALFFRS-R: revised Amyotrophic Lateral Sclerosis Functional Rating Scale
BPAP: bilevel positive airway pressure
FVC: forced vital capacity
NIPPV: non-invasive positive pressure ventilation
NIV: non-invasive ventilation
SF-36: Short Form-36 Health Survey

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to April Week 3 2012>
Search Strategy:
---
1 randomized controlled trial.pt. (324772)
2 controlled clinical trial.pt. (83939)
3 randomized.ab. (229093)
4 placebo.ab. (130412)
5 drug therapy.fs. (1523445)
6 randomly.ab. (165539)
7 trial.ab. (236973)
8 groups.ab. (1089746)
9 or/1-8 (2827168)
10 exp animals/ not humans.sh. (3702877)
11 9 not 10 (2400315)
12 exp Motor Neuron Disease/ (17091)
13 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp. (5683)
14 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (63)
15 charcot disease.tw. (10)
16 Amyotrophic Lateral Sclerosis.mp. (13741)
17 or/12-16 (20549)
18 Respiration, Artificial/ (35148)
19 exp Ventilators, Mechanical/ (7835)
20 exp Respiratory Insufficiency/ (48002)
21 Positive-Pressure respiration/ (14097)
22 tracheotomy/ or tracheostomy/ (11773)
23 exp Intubation, Intratracheal/ (29511)
24 ((artificial adj1 respiration) or (mechanical adj1 ventilator$) or respiratory insufficiency or positive pressure$ or positivepressure$ or bipap or tracheotomy or tracheostomy or intubation).mp. (133592)
25 ((non invasive or noninvasive) adj5 ventilation).mp. (3028)
26 or/18-25 (153594)
27 11 and 17 and 26 (157)
28 remove duplicates from 27 (153)

Appendix 2. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2012 Week 17>
Search Strategy:
---
1 crossover-procedure.sh. (33662)
2 double-blind procedure.sh. (108422)
3 single-blind procedure.sh. (15770)
4 randomized controlled trial.sh. (320525)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (860435)
6 trial.ti. (129160)
7 or/1-6 (985906)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1172868)
9 animal/ or nonanimal/ or animal experiment/ (3259461)
10 9 not 8 (2702307)
11 7 not 10 (903458)
12 limit 11 to embase (699211)
13 Motor Neuron Disease/ or amyotrophic lateral sclerosis/ (22477)
14 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease$1).mp. (8385)
15 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (105)
16 charcot disease.tw. (16)
17 amyotrophic lateral sclerosis.tw. (13788)
18 or/13-17 (25015)
19 exp Artificial Ventilation/ (100238)
20 Ventilator/ (12524)
21 exp Respiratory Failure/ (50500)
22 exp Assisted Ventilation/ (88946)
23 Tracheotomy.mp. or TRACHEOTOMY/ (10728)
24 tracheostomy.mp. or TRACHEOSTOMY/ (14318)
25 RESPIRATORY TRACT INTUBATION/ (1461)
26 ((non invasive or noninvasive) adj5 ventilation).mp. (5117)
27 (artificial ventilat$ or artificial respiration or (mechanical adj1 ventilator$) or respiratory failure or respiratory insufficiency or positive pressure$ or positivepressure$ or bipap or assisted ventilation or intubation).mp. (176881)
28 or/19-27 (232957)
29 12 and 18 and 28 (89)
30 remove duplicates from 29 (89)

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor Motor Neuron Disease explode all trees
#2 “motor neuron disease” OR “motor neurone disease” OR “motoneuron disease” OR “motorneuron disease” OR “amyotrophic lateral sclerosis”
#3 (Gehrig* NEAR syndrome*)
#4 (Gehrig* NEAR disease*)
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Ventilators, Mechanical explode all trees
#7 MeSH descriptor Respiratory Insufficiency explode all trees
#8 MeSH descriptor Intubation explode all trees
#9 artificial NEAR/1 respiration
#10 mechanical NEAR/1 ventilat*
#11 positive NEXT pressure next respiration
#12 tracheostomy or tracheotome or intubation
#13 respiratory NEXT insufficiency

#14 (positive NEXT pressure) or positivepressure or bipap
#15 non NEXT invasive NEAR ventilation
#16 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#5 AND #16)

Appendix 4. CINAHLPlus (EBSCOhost) search strategy

Tuesday, May 01, 2012 1:52:16 PM

S32 S30 and S31 27
S31 EM 20081115- 1206764
S30 S18 and S23 and S29 62
S29 S24 or S25 or S26 or S27 or S28 31641
S28 (non invasive or noninvasive) and ventilation 1366
S27 (MH "Intubation, Intratracheal+") 8969
S26 respiratory failure or Tracheotomy or Tracheostomy or intratracheal intubation 15463
S25 mechanical ventilat* or positive pressure* or positivepressure* or bipap 12629
S24 (MH "Mechanical Ventilation (Iowa NIC)") OR (MH "Ventilators, Mechanical") OR (MH "Respiration, Artificial") 11383
S23 S19 or S20 or S21 or S22 4690
S22 ("Amyotrophic Lateral Sclerosis") 1911
S21 Lou Gehrig* and (disease* or syndrome*) 31
S20 (moto* neuron* disease* or moto?neuron* disease) 829
S19 (MH "Motor Neuron Diseases+") 4425
S18 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 or S15 or S16 or S17 533543
S17 ABAB design* 74
S16 TI random* or AB random* 108880
S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy)) 225044
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 75851
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 21873
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*)) 17807
S11 PT ("clinical trial" or "systematic review") 101048
S10 (MH "Factorial Design") 814
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 175955
S8 (MH "Meta Analysis") 13922
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 30
S6 (MH "Quasi-Experimental Studies") 5373
S5 (MH "Placebos") 7478
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 23982
S3 (MH "Clinical Trials+") 140526
S2 (MH "Crossover Design") 9169
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 56172

Appendix 5. AMED (OvidSP) search strategy

Database: AMED (Allied and Complementary Medicine) <1985 to April 2012>
Search Strategy:
---
1 Randomized controlled trials/ (1520)
2 Random allocation/ (302)
3 Double blind method/ (432)
4 Single-Blind Method/ (25)
5 exp Clinical Trials/ (3179)
6 (clin$ adj25 trial$).tw. (5402)
7 ((singl$ or doubl$ or treb$ or trip$) adj25 (blind$ or mask$ or dummy)).tw. (2213)
8 placebos/ (518)
9 placebo$.tw. (2489)
10 random$.tw. (12632)
11 research design/ (1670)
12 Prospective Studies/ (441)
13 meta analysis/ (108)
14 (meta?analys$ or systematic review$).tw. (1809)
15 control$.tw. (27285)
16 (multicenter or multicentre).tw. (719)
17 ((study or studies or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).tw. (9622)
18 or/1-17 (42059)
19 Motor neuron disease/ (89)
20 (moto$1 neuron$1 disease$1 or moto?neuron$1 disease).mp. (162)
21 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease)).mp. (2)
22 charcot disease.tw. (1)
23 Amyotrophic Lateral Sclerosis/ (171)
24 amyotrophic lateral sclerosis.tw. (244)
25 or/19-24 (382)
26 exp Respiration artificial/ or artificial respiration.mp. (413)
27 Ventilators mechanical/ or mechanical ventilat$.mp. (375)
28 exp respiratory insufficiency/ (145)
29 respiratory insufficiency.mp. (132)
30 (positive pressure$ or positivepressure$).mp. (174)
31 bipap.mp. (4)
32 Tracheotomy/ or tracheotomy.mp. (26)
33 tracheostomy.mp. (73)
34 Intubation/ or intubation.mp. (116)
35 ((non invasive or noninvasive) adj5 ventilation).mp. (103)
36 or/26-35 (980)
37 18 and 25 and 36 (5)

Appendix 6. ClinicalTrials.gov search strategy

1 Ventilation in ALS
2 Non-invasive ventilation in ALS
3 Tracheostomy ventilation in ALS
4 Mechanical ventilation in ALS

WHAT'S NEW

Last assessed as up-to-date: 1 May 2012.

Date	Event	Description
24 August 2012	New citation required but conclusions have not changed	Searches updated to May 2012, no new trials included. The background of the review has been updated and the review edited. Muhammad K Rafiq is a new author, Kate Jewitt withdrew
6 August 2012	New search has been performed	This is an update of a review first published in 2009.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 4, 2009

Date	Event	Description
23 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Aleksandar Radunovic drafted the review, with Naveed Mustfa and Djillali Annane. Kate Jewitt edited the protocol and original version of the review. Muhammad K Rafiq with Djillali Annane selected studies for the update; the other authors approved the text.

DECLARATIONS OF INTEREST

Djillali Annane: no conflicts of interest. Naveed Mustfa: no conflicts of interest. Aleksandar Radunovic: no conflict of interest. Muhammad K Rafiq: no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Institute of Psychiatry, UK.
- Guy's, King's & St. Thomas' School of Medicine, King's College London, UK.
- Hopital Raymond Poincaré, Garches, France.

External sources

- Motor Neurone Disease Association, UK.
- Muscular Dystrophy Association, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

P Nigel Leigh withdrew from authorship after protocol publication. Kate Jewitt withdrew following publication of the full review. Muhammad K Rafiq became an author for this update.

The authors assessed 'Risk of bias' expressed as 'Low risk', 'High risk' or 'Unclear risk' of bias in accordance with Higgins 2011.

We have included a statement that we will include comparisons with no intervention or the best standard care, under "Types of interventions" and clarified that adverse events will be collected from included trials. We reworded the review objective in accordance with current guidance.

INDEX TERMS

Medical Subject Headings (MeSH)

Amyotrophic Lateral Sclerosis [complications; *mortality]; Disease Progression; Motor Neuron Disease [mortality]; Quality of Life; Randomized Controlled Trials as Topic; Respiration, Artificial [*mortality]; Respiratory Insufficiency [etiology; *mortality; therapy]

MeSH check words

Humans