Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma (Review)

Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, Rowe BH, Smith BJ

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[Intervention Review]

Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

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ABSTRACT

Background

Asthma is a chronic respiratory condition causing inflammation and changes to the airways. Care of people with asthma includes routine and urgent management across primary and tertiary care; however, due to sub-optimal long-term care and delays in obtaining help during acute exacerbations, the mortality and morbidity related to asthma is still a major health concern. There is reason to believe that non-invasive positive pressure ventilation (NPPV) could be beneficial to patients with severe acute asthma; however, the evidence surrounding the efficacy of NPPV is unclear, despite its common use in clinical practice.

Objectives

To determine the efficacy of NPPV in adults with severe acute asthma in comparison to usual medical care with respect to mortality, tracheal intubation, changes in blood gases and hospital length of stay.

Search methods

We carried out a search in the Cochrane Airways Group Specialised Register of trials (July 2012). Following this, the bibliographies of included studies and review articles were searched for additional studies (July 2012).

Selection criteria

We included randomised controlled trials of adults with severe acute asthma as the primary reason for presentation to the emergency department or for admission to hospital. Asthma diagnosis was defined by internationally accepted criteria. Studies were included if the intervention was usual medical care for the management of severe acute asthma plus NPPV applied through a nasal or facemask compared to usual medical care alone. Studies including patients with features of chronic obstructive pulmonary disease (COPD) were excluded unless data were provided separately for patients with asthma in studies recruiting both COPD and asthmatic patients.

Data collection and analysis

A combination of two review authors independently assessed trial quality and extracted data. Study authors were contacted for additional information where required. All data were analysed using RevMan 5.1. For continuous variables, a mean difference and 95% confidence interval were used and for dichotomous variables, risk ratio with 95% confidence interval were calculated.

Main results

We identified six trials for inclusion. Five studies on 206 participants contributed data, while one study was available in abstract form only and was not fully incorporated into this review. For the primary outcome of endotracheal intubation there were two studies that contributed data: two intubations were needed in 45 participants on NPPV and no intubations in 41 control patients (risk ratio 4.48; 95% CI 0.23 to 89.13). There were no deaths in either of these studies. Length of hospital stay was reported in two studies, though meta-analysis was not possible. Hospitalisation was reported in one small study, in which there were three admissions out of 17 on NPPV and 10 admissions out of 16 in control patients (RR 0.28, 95% CI 0.09, 0.84).

Authors' conclusions

This review of studies has highlighted the paucity of data that exist to support the use of NPPV in patients in status asthmaticus. As such this course of treatment remains controversial despite its continued use in current clinical practice. Larger, prospective randomised controlled trials of rigorous methodological design are needed to determine the role of NPPV in patients with asthma.

PLAIN LANGUAGE SUMMARY

Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Non-invasive positive pressure ventilation (NPPV) enhances breathing in acute respiratory conditions by resting tired breathing muscles. It has the advantage that it can be used intermittently for short periods, which may be sufficient to reverse the breathing problems experienced by patients during severe acute asthma. We undertook this review to determine the effectiveness of NPPV in patients with severe acute asthma. Six randomised controlled trials were included in the review. Compared to usual medical care alone, NPPV reduced hospitalisations, increased the number of patients discharged from the emergency department, and improved respiratory rate and lung function measurements. The application of NPPV in patients with asthma, despite some promising preliminary results, still remains controversial. Further studies are needed to determine the role of NPPV in the management of severe acute asthma and especially in status asthmaticus.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Patient or population: patients with asthma
Settings:
Intervention: non-invasive positive pressure ventilation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Non-invasive positive pressure ventilation				
Mortality Follow-up: 30 days	See comment	See comment	Not estimable	86 (2 studies)	⊕◯◯◯ **very low**[1,2,3]	Not estimable
Endotracheal intubation Follow-up: 30 days	See comment	See comment	**RR 4.48** (0.23 to 89.13)	86 (2 studies)	⊕⊕◯◯ **low**[1,2]	No events in control group
Length of hospital stay Follow-up: 30 days	See comment	See comment	See comment	86 (2 studies)	⊕◯◯◯ **very low**[1,2,3]	Unable to pool data
Number of hospital admissions Follow-up: 30 days	**625 per 1000**	**175 per 1000** (56 to 525)	**RR 0.28** (0.09 to 0.84)	33 (1 study)	⊕◯◯◯ **very low**[2,3,4]	
FEV1 (% predicted) Percentage scale from: 1% to 150%. Follow-up: 1 to 30 days	Mean FEV1 (% predicted) ranged across control groups from **35.51 L to 43.9 %**	The mean FEV1 (% predicted) in the intervention groups was **14.02 % higher** (7.73 to 20.32 higher)	**MD 14.02** (7.73 to 20.32)	66 (2 studies)	⊕⊕◯◯ **low**[2,5]	

FVC (% predicted) Percentage scale from: 1% to 150%. Follow-up: 1 to 30 days	Mean FVC (% predicted) ranged across control groups from **41.26 L to 58.1 %**	The mean FVC (% predicted) in the intervention groups was **12.27 % higher** (4.38 to 20.16 higher)	**MD 12.27** (4.38 to 20.16)	66 (2 studies)	⊕⊕◯◯ **low**[2,5]
Respiratory rate (breaths per minute). Scale from: 12 to 40. Follow-up: 1 to 30 days	Mean respiratory rate ranged across control groups from **17.8 per minute to 23.3 per minute**	Mean respiratory rate in the intervention groups was **1.42 breaths per minute higher** (2.77 to 0.07 higher)	**MD -1.42** (-2.77 to -0.07)	146 (3 studies)	⊕⊕◯◯ **low**[2,5]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; OR: odds ratio

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

[1] Soroksky 2003 had three areas of unclear risk whereas Gupta 2010 had a high risk for selective reporting
[2] Small sample size
[3] Comparison of intervention not available
[4] Unclear risk of bias for allocation sequence generation, allocation concealment and reporting of incomplete outcome data
[5] Some studies had areas of unclear risk, being sequence generation, allocation concealment and selective reporting

BACKGROUND

Description of the condition

Asthma is a chronic respiratory condition causing inflammation, as well as structural and related functional changes of the airways. It is characterised by recurrent attacks on breathlessness and wheezing, which vary in severity and frequency from person to person. During acute exacerbations of asthma the lining of the bronchial tube swells, and the smooth muscle around the airway contracts, causing a narrowing of the airway that reduces the flow of air into and out of the lungs, which is known as bronchoconstriction (WHO 2011). This narrowing of the airways may be in response to exposure to a variety of stimuli including allergens (i.e. immunoglobulin E (IgE)-dependent release of mediators from mast cells) or other factors such as exercise, cold air or irritants (NHLBI 2007). Current evidence suggests asthma affects 300 million people globally (Masoli 2004) and is estimated to account for one in every 250 deaths worldwide, many of which are preventable (Masoli 2004). In 2009, the Global Initiative for Asthma reported that asthma prevalence ranges from 1% to 18% in different populations around the world (GINA 2010). In 2009, the prevalence of asthma in the US was 8.2% of the population, that is 24.6 million people (Akinbami 2011). Asthma is the tenth leading contributor to the overall burden of disease in Australia (AIHW 2010) affecting 14.7% of all Australians (Braman 2006; AIHW 2008). As such, asthma has been an Australian national health priority since 1996, with one in five Australians diagnosed with asthma at some point in their lives (AIHW 2008). One study suggests a cumulative incidence of asthma to middle age of 37% (Burgess 2008). In one calendar year, asthma is reported to account for 2.4 million general practice encounters, 105,000 emergency department visits and 40,000 hospital admissions (0.5% of all admissions) in Australia (AIHW 2005). The asthma healthcare burden is significant and increasing (Bahadori 2009), with costs in the developed world estimated at USD300 to USD1300 per patient (Braman 2006). The effects of asthma on quality of life are also significant. In one survey, 25% of adults with asthma rated their health as only 'fair to poor' compared with 14% of adults without asthma (AIHW 2010).

The causes of asthma are not completely understood, although known risk factors for developing asthma include inhaling asthma triggers, such as allergens, tobacco smoke and chemical irritants. Asthma is incurable; however, appropriate management can control the disorder and enable people to enjoy a high quality of life (WHO 2011). Care of people with asthma includes routine and urgent management across primary and tertiary care. However, due to sub-optimal long-term care and delays in obtaining help during acute exacerbations, the mortality and morbidity related to asthma is still a major health concern (Braman 2006). A 2010 publication on asthma control across five European countries reported that the proportion of asthmatics with 'not well-controlled' asthma had not improved since 2006, with a patient-reported 'physician diagnosis' of asthma of 6.1% of the study population (15 million people) (Demoly 2010). The subsequent burden of disease is steadily increasing resulting in confounding pressures on the healthcare system as well as families and patients themselves (Masoli 2004). This morbidity has been attributed to sub-optimal delivery of care, including under-treatment with corticosteroids, limited knowledge and poor asthma self-management skills among patients with severe asthma (Gibson 1993; Kandane-Rathayake 2009).

Description of the intervention

While non-invasive positive pressure ventilation (NPPV) is not commonly used in asthma, it has been established as an alternative treatment option for patients admitted to hospital with hypercapnic respiratory failure secondary to acute exacerbation of chronic obstructive pulmonary disease (COPD) (Meduri 1989; Foglio 1992; Bott 1993; Kramer 1995). Traditionally, patients who do not respond to conventional treatment are invasively mechanically ventilated. This involves sedation, intubation, attachment to a ventilator and transfer to the intensive care unit (ICU). Most patients do recover with tracheal intubation and assisted ventilation. However, these treatments are associated with high morbidity and there may be considerable difficulties weaning this patient group from ventilation (Brochard 1994; Esteban 1995). In addition, although intubation and mechanical ventilation are common practice, complications can result from the intubation process (damage to local tissue, drug interactions, side effects to procedures) and during the course of ventilation (ventilator-associated pneumonia, pneumothorax and sinusitis) (Fagon 1993). Prolonged stays in ICU are therefore common.

NPPV employs a full facial or nasal mask that administers ventilatory support from a flow generator. NPPV may include bi-level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). In BiPAP, a different pressure is used during the inspiratory and expiratory phases of the respiratory cycle, while in CPAP, only one constant positive airway pressure is maintained throughout the respiratory cycle (Gupta 2010). NPPV enhances ventilation by unloading fatigued ventilatory muscles and its use has been established in the treatment of patients with a variety of chronic hypo-ventilatory syndromes (Moloney 1999). NPPV has the advantage that it can be applied intermittently for short periods, which may be sufficient to reverse the ventilatory failure. Moreover, sedation is not required allowing patients to eat, drink and talk, and also permitting participation in decisions about their own care. Finally, the incidence of nosocomial pneumonia with NPPV use is lower than in intubated patients (Guerin 1997; Kramer 1999; Nourdine 1999). Since the 2000s NPPV has been increasingly used as an adjunct therapy in the management of acute exacerbations of COPD, congestive heart failure and other conditions. NPPV has been successfully used to treat patients with COPD who are prone to exacerbations of res-

piratory failure. One systematic review of trials in patients with respiratory failure has shown significant reductions in mortality, need for intubation, complications, treatment failure and length of hospital stay with rapid improvements in blood gases and respiratory rate among patients with COPD (Ram 2003). A trend favouring NPPV for other causes of respiratory failure, including acute respiratory distress syndrome and asthma has also been observed (Brochard 2002; Ram 2003; Keenan 2009). For these reasons it is believed that NPPV may be an effective and worthwhile intervention for use in people with a severe acute exacerbation of asthma.

How the intervention might work

NPPV has been postulated to have a direct bronchodilating effect (Buda 1979) and improve alveolar recruitment. The bronchodilatory effect has been found to be independent of drug dispersion (Soroksky 2003). This is thought to be due to the effect of external positive end-expiratory pressure (PEEP) offsetting intrinsic PEEP that builds up during an asthma attack (Broux 1991; Aldrich 1993). The improved flow through collateral lung channels to atelectatic lung segments then re-expands atelectatic lung regions (Anderson 1979) and improves ventilation-perfusion mismatch, subsequently reducing the work of breathing (Soroksky 2003). As such, NPPV has been thought to assist inspiratory muscles (Shivaram 1987). CPAP has also been shown in two small studies to improve respiratory mechanics in histamine-induced asthma (Martin 1982) and reduced bronchial hypersensitivity in methacholine-induced asthma (Lin 1995).

Why it is important to do this review

Evidence has shown that NPPV is effective in COPD patients with acute respiratory failure (Jasmer 2000; Liesching 2003; Ferrer 2009; Schmidbauer 2011); however, the role of NPPV in patients with acute respiratory failure following an exacerbation of asthma is not clear. In some ways the pathophysiological condition of acute respiratory failure in asthma is similar to that of acute respiratory failure in COPD. As such, patients with respiratory failure due to acute exacerbations of asthma that are not responding to conventional therapy and require mechanical ventilation could also improve with the administration of NPPV. Few reports have described the use of NPPV in patients with respiratory failure due to exacerbations of asthma (Meduri 1991; Benhamou 1992; Thys 1999; Soma 2002; Soma 2008) with conflicting results. To consolidate the available evidence into a usable summary, this review is necessary to provide a systematic overview of the evidence to support the use of NPPV in respiratory failure due to severe acute exacerbations of asthma.

OBJECTIVES

To determine the efficacy of NPPV in adults with severe acute asthma in comparison to usual medical care, with respect to mortality, tracheal intubation, changes in blood gases and hospital length of stay.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled clinical trials (RCTs) that compared the treatment of asthma with usual medical care plus NPPV versus usual medical care alone.

Types of participants

We included studies of adults with severe acute asthma as the primary reason for presentation to the emergency department or for admission to hospital. We accepted diagnoses of asthma as defined by internationally accepted criteria (e.g. British Thoracic Society, American Thoracic Society). Studies including patients with features of COPD were excluded unless data were provided separately for patients with asthma in studies recruiting both COPD and asthma patients. We excluded patients with a primary diagnosis of pneumonia.

Types of interventions

Eligible interventions were usual medical care plus NPPV applied through a nasal or facemask compared to usual medical care alone. Treatment in the usual medical care control group could include any form of standard therapy for the management of severe acute asthma, providing it did not involve NPPV. Usual medical care included but was not limited to therapies such as supplemental oxygen, antibiotics, bronchodilators and systemic corticosteroids. We excluded weaning studies and studies where CPAP or endotracheal intubation preceded enrolment of patients into the trial.

Types of outcome measures

Primary outcomes

- Endotracheal intubation
- Mortality during the hospital admission

Secondary outcomes

- Respiratory rate
- Arterial blood gases (ABGs) and pH
- Lung function measurements
- Length of hospital stay
- Length of intensive treatment unit (ITU)/ICU stay
- Treatment failure (the combination of mortality, endotracheal intubation and intolerance to the allocated treatment)
- Symptom score (e.g. Borg scores)
- Complications

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). All records in the CAGR coded as 'asthma' were searched using the following terms:

((nasal* OR mechanical*) AND ventilat*) OR non-invasive or "non invasive" or "positive pressure" or positive-pressure OR "pressure support" OR "positive airway" or "intermittent positive pressure" OR "airway* pressure" OR pressure-control* OR volume-control* OR bi-level OR "ventilat* support" OR NIPPV OR NPPV OR NIV

The most recent search was conducted in July 2012. There were no limits on the language of publication.

We also searched online clinical trial registers for ongoing and recently completed studies including, Controlled Clinical Trials (www.controlled-trials.com), government registries (www.clinicaltrials.gov), and WHO registries (www.who.int/trialsearch/).

Searching other resources

We contacted companies that manufacture ventilators for potential studies as well as researchers working in the area. We also searched the bibliographies of each RCT obtained (and any review articles) for additional RCTs. We contacted authors of identified RCTs for other published, unpublished or ongoing studies.

Data collection and analysis

Selection of studies

Three review authors independently reviewed the literature searches from the title, abstract or descriptors and excluded all studies that clearly did not meet the inclusion criteria and reviewed the full text of retrieved articles to assess eligibility for inclusion. There was complete agreement (after discussion) between review authors regarding inclusion and exclusion criteria for all full-text studies obtained for closer examination.

Data extraction and management

Data for each study were extracted independently by a combination of two review authors onto standardised data collection forms. We requested unpublished data from the primary authors where necessary. This data was then entered into Review Manager 5.1 software for analysis (RevMan 2011). We performed retrospective data extraction for the one original study included in this review, using the updated standardised data collection form.

Assessment of risk of bias in included studies

Two review authors independantly assessed each study for risk of bias in relation to allocation sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting and other threats to validity, in line with recommendations made in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). A retrospective risk of bias assessment using the above method was also applied to the original study included in the review.

Measures of treatment effect

We analysed outcomes as continuous or dichotomous data using standard statistical techniques with a fixed-effect model or random-effects model for all studies deemed similar enough to be pooled.

For continuous outcomes, we calculated mean difference (MD) with 95% confidence intervals (CI) and pooled as a MD or standardised mean difference (SMD). For dichotomous outcomes, we calculated risk ratios (RR) with 95% CIs. A narrative synthesis was also performed for each of the included studies.

Unit of analysis issues

We did not have any unit of analysis issues as we did not include any cross-over studies, cluster randomised studies or multiple observational studies in the review. Had a cluster randomised study been identified for inclusion the analysis would have occurred on the level of the individual while accounting for clustering within the data, as per recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 16.3.4 (Higgins 2009).

Dealing with missing data

Missing information regarding participants was evaluated on an available case analysis basis as described in Chapter 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). Where statistics essential for analysis were missing (e.g. group means and standard deviations for both groups were not reported) and could not be calculated from other data, we attempted to contact the study authors to obtain data. Loss of participants that occurred prior to performance of baseline measurements was assumed to have no effect on the eventual outcome data of the study. Any losses after the baseline measurement were taken were assessed and discussed on an intention-to-treat analysis basis. A narrative synthesis was also performed for each of the included studies.

Assessment of heterogeneity

In meta-analyses of outcomes pooling two or more studies, we tested heterogeneity estimates using the Der Simonian and Laird method, with $P < 0.05$ and an I^2 statistic $\geq 50\%$ considered to be statistically significant together with visual inspection of the data. We reported results using the fixed-effect model; however, in the presence of significant heterogeneity, we planned to investigate possible sources of heterogeneity using the following pre-planned sensitivity analyses: study quality, duration of NPPV, time to initiation of NPPV, type of NPPV and type of mask used to administer NPPV.

Assessment of reporting biases

Providing the minimum inclusion of 10 studies, we planned to explore potential reporting biases using a funnel plot. Asymmetry in the plot could have been attributed to publication bias though it could also have been due to true heterogeneity, poor methodological design, quality or artefact. In instances of less than 10 studies, potential reporting biases were extrapolated within the other bias section in the risk of bias tables, as occurred in this review.

Data synthesis

We analysed data from all trials using Review Manager 5.1 (RevMan 2011). For continuous variables, an MD and 95% CI were calculated for each study outcome. For dichotomous variables RR with 95% CI were calculated.

Subgroup analysis and investigation of heterogeneity

Had there been more than one included study, we planned to perform the following subgroup analyses:

- study quality;
- duration of NPPV;
- time to initiation of NPPV;
- type of NPPV;
- type of mask used to administer NPPV;
- baseline or admission $PaCO_2$ (< 45 mmHg or $\geq$ 45 mmHg or 6 kPa);
- pH (< 7.30 or $\geq$ 7.35 to 7.30);
- location of the study within the hospital (ICU vs. respiratory ward).

Sensitivity analysis

We conducted sensitivity analyses on studies with a high risk of selection bias for sequence generation or allocation concealment, or both, and studies with significant differences following visual inspection of the data.

RESULTS

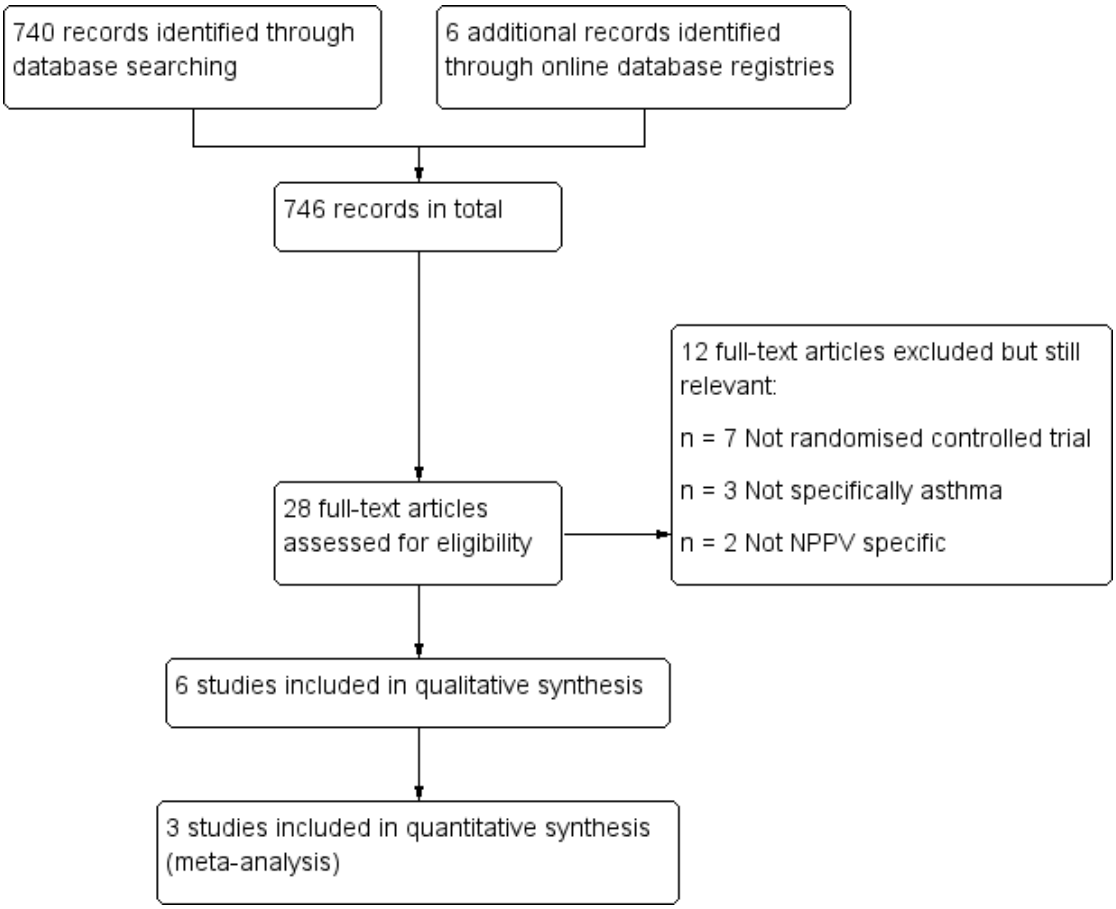
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

From an initial search of 746 abstracts, 28 studies were obtained in full-text for further examination (see Figure 1). Of these, 12 were excluded but still considered relevant (Pollack 1995; Meduri 1996; Clark 1997; Thys 1999; Compagnoni 2000; Archis 2001; Fernandez 2001; Akingbola 2002; Ergun 2002; Soma 2002; Thill 2004; Soma 2008). Reasons for exclusions are provided in the 'Characteristics of excluded studies' table. Five completed studies (Soroksky 2003; De Miranda 2004; Brandao 2009; Filho 2009; Gupta 2010) met all of the inclusion criteria with a detailed description of each available in the 'Characteristics of included studies' table, while one additional study identified through online database searches for protocols was awaiting publication at conclusion of this review (Characteristics of studies awaiting classification).

Figure 1. Study flow diagram.



Included studies

Five studies (Soroksky 2003; De Miranda 2004; Brandao 2009; Filho 2009; Gupta 2010) met the inclusion criteria for the review (see Characteristics of included studies table). Four of these studies (De Miranda 2004; Brandao 2009; Filho 2009; Gupta 2010) were added following the update of the review in June 2011. A detailed manuscript was not available for one study; therefore, data extraction and analyses could only be performed based on the published abstract (Filho 2009). Another study was published in Portuguese hence data extraction and analyses were performed with the aid of both the published English abstract and a translated data extraction of key items (De Miranda 2004).

Design

All included studies were RCTs with pre- and post-test control groups. Participants were randomised into either intervention or control group. No studies were able to perform blinding of treatment assignment and only one reported using sham NPPV for the control group (Soroksky 2003).

Population

The included studies were based in different countries and geographic regions. Soroksky 2003 was conducted in Israel while Gupta 2010 was performed in India. The three other studies were all conducted in Brazil (De Miranda 2004; Brandao 2009; Filho 2009). All trials were single-centre trials. Brandao 2009, De Miranda 2004, Filho 2009 and Soroksky 2003 were conducted in a hospital emergency department setting while Gupta 2010 was done in the respiratory ICU of a hospital. A total of 206 patients were included in this review, an aggregate sum across all five included trials. All patients had acute severe asthma as diagnosed using criteria set in an internationally accepted guideline. The number of patients recruited in each trial varied from 21 to 63.

Three trials had similar numbers of patients for the intervention and control groups (Soroksky 2003; Filho 2009; Gupta 2010), whereas Brandao 2009 and De Miranda 2004 each had two intervention groups, resulting in the intervention group having twice the amount of patients compared to the control group. All participants were at least 18 years old, with ranges in Gupta 2010, Soroksky 2003 and Brandao 2009 from 18 to 62 years, having a mean age of 38.6 years. However, it was not possible to ascertain the age range or mean age for the De Miranda 2004 or Filho 2009 studies. There were 56 male and 126 female participants, giving a reported male to female ratio of 1:2.25. The genders of patients in Filho 2009 and of three patients who dropped out of the Soroksky 2003 trial were not reported.

Interventions

Treatment type

In four of the five included studies, BiPAP (also known as BPPV) was used for the intervention (Soroksky 2003; Brandao 2009; Filho 2009; Gupta 2010), while CPAP was used for intervention participants in the De Miranda 2004 study.

Treatment intensity

Two studies titrated the respiratory pressure settings according to participants' clinical parameters up to a maximal pre-determined level (Soroksky 2003; Gupta 2010) whereas two other studies allocated patients to standardised respiratory pressures specified at the onset of the study (Brandao 2009; Filho 2009). The respiratory pressures used for the participants in De Miranda 2004 could not be determined. The inspiratory pressures ranged from 8 mmHg (Soroksky 2003; Gupta 2010) to 20 mmHg (Gupta 2010) and the expiratory pressures ranged from 3 mmHg (Soroksky 2003) to 10 mmHg (Brandao 2009; Gupta 2010).

The duration of intervention ranged from nine minutes (De Miranda 2004) to more than 14 hours (Gupta 2010). Two studies delivered the intervention to participants for less than one hour (De Miranda 2004; Brandao 2009), two studies delivered the intervention for more than one hour (Soroksky 2003; Gupta 2010) and the duration of intervention could not be determined in one study (Filho 2009).

Length of follow-up

Follow-up ranged widely from 15 minutes (De Miranda 2004) to one month (Soroksky 2003) after intervention. Two studies followed up participants for less than one hour after intervention (De Miranda 2004; Brandao 2009) while two other studies reported follow-up periods of more than four hours (Soroksky 2003; Gupta 2010). The follow-up duration was not reported for the Filho 2009 study.

Outcome measures

No included studies reported mortality as an outcome measure. Two studies reported treatment failure or the need for invasive mechanical ventilation as one of the outcomes (Soroksky 2003; Gupta 2010). The length or need for hospitalisation was reported in two studies (Soroksky 2003; Gupta 2010). All five included studies reported on one or more parameters of lung function test. None of the studies reported on symptom scores; however, all five included studies reported changes in respiratory rate and four studies reported changes in heart rate (Soroksky 2003; De Miranda 2004; Brandao 2009; Filho 2009). Three studies (De Miranda 2004; Brandao 2009; Filho 2009) reported on peripheral oxygen saturation (SpO_2) and one study (Gupta 2010) reported various measured parameters for ABG. None of the studies formally assessed complications arising from the intervention.

Excluded studies

Twelve studies were assessed as being excluded but still relevant to the review. Seven were not RCTs, three were not specific to asthma and two were not specific to NPPV. For a more detailed description of the reason for each excluded study see the Characteristics of excluded studies table.

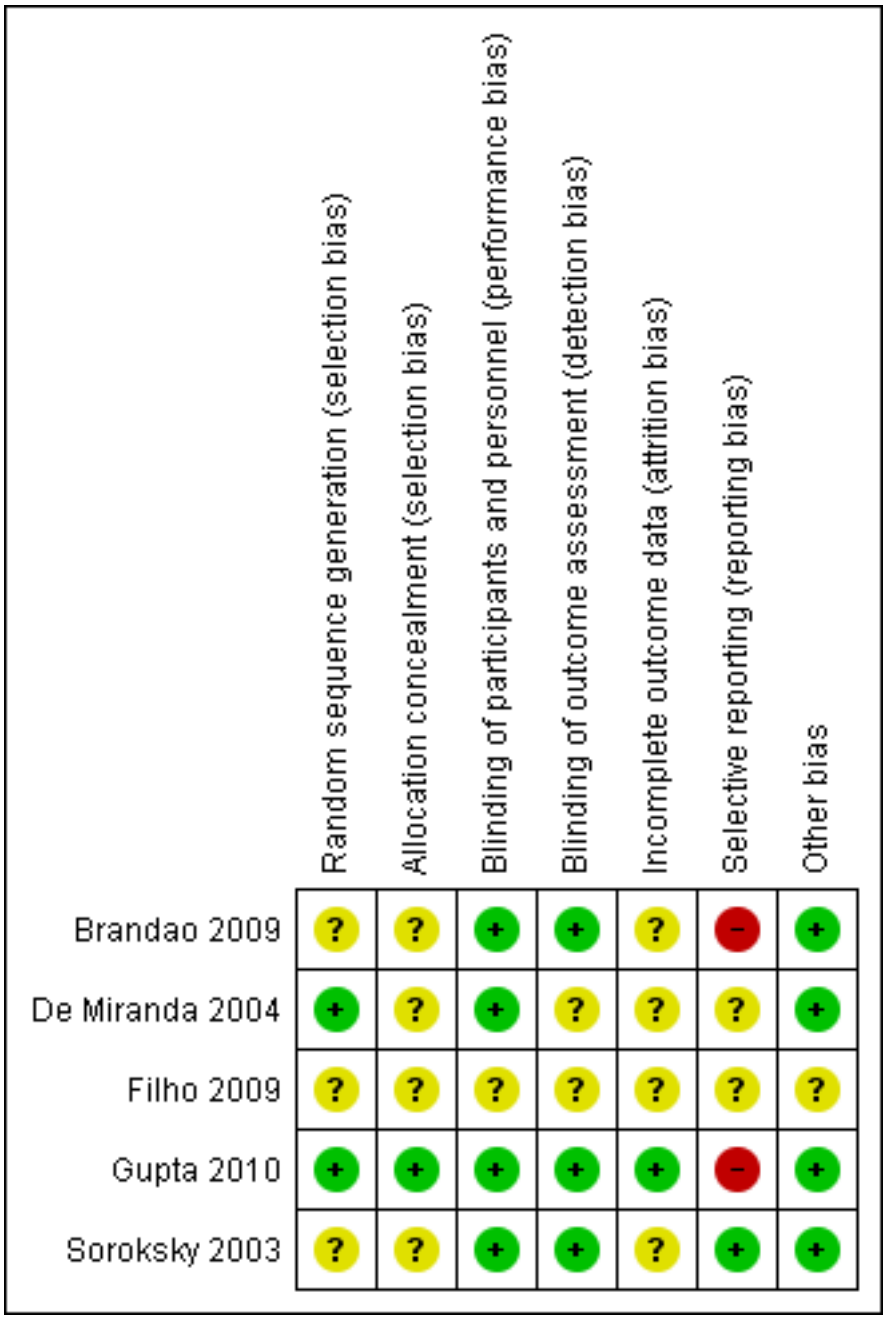
Studies awaiting classification

One study with 50 participants was identified to be included; however, due to a lack of fully published data, a complete assessment was unable to be performed (Chaudhry 2010). The RCT examined the role of NPPV in the management of severe acute asthma. NPPV was reported to produce a statistically significant reduction in accessory muscles of aspiration and improvement in Borg dyspnoea score but it had no effect on respiratory rate and forced expiratory volume in one second (FEV). Although the study fulfilled most of the inclusion criteria, the review authors were unable to determine whether the study included participants under the age of 18 years. Attempts to contact study authors were unsuccessful.

Risk of bias in included studies

Methodological details for the five included studies are provided in the 'risk of bias table' at the end of the 'Characteristics of included studies' tables. Key methodological features are summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Two studies reported adequate methods of sequence generation (De Miranda 2004; Gupta 2010) while the remaining three studies were unclear. Adequate methods included random draw or the use of randomisation sequence generated with statistical software. The remaining three studies described their studies as 'random' in design without further description of methods employed for randomisation.

Allocation concealment

One study had adequate allocation concealment (Gupta 2010) whereby allocation was carried out via sealed opaque envelopes with each patient's assignment made by an attending physician. The remaining four studies were unclear as the methods of allocation concealment were not reported.

Blinding

Blinding would be difficult given the nature of the study where intervention would use non-invasive ventilation. It is especially difficult to employ blinding of personnel as titration of the respiratory pressures in the ventilators requires expert knowledge. It is also likely that participants and personnel would be aware of the allocation of any sham NPPV. However, four of the five studies were judged to have been at low risk of performance bias since objective outcome measures were included and lack of blinding is unlikely to have influenced the outcome (Soroksky 2003; De Miranda 2004; Brandao 2009; Gupta 2010). Participants were blinded to the use of sham NPPV according to authors in Soroksky 2003. Filho 2009 was judged to have unclear risk of bias in this area as the full text of the published study was not available. In addition the authors reported on symptom scores, which are subjective outcome measures.

Incomplete outcome data

Incomplete outcome data were inadequately addressed in one study (Gupta 2010). Although participants were analysed on an intention-to-treat basis for this study, there was substantial departure from allocation with reasons for this departure considered to be related to the outcome. Missing variables (if any), were not reported in three studies (Soroksky 2003; De Miranda 2004; Brandao 2009), with the Soroksky 2003 study reporting that intention-to-treat analyses were carried out. Insufficient published data do not permit a clear judgement to be made in regards to incomplete outcome data for Filho 2009.

Selective reporting

Selective reporting was unclear in two studies (Brandao 2009; Gupta 2010), while in the Brandao 2009 study, graphs were available for comparison. However, there were missing data for relative/absolute improvement in lung function. In the Gupta 2010 study there were two secondary outcomes that were not reported as per protocol and important parameters of the lung function test (peak expiratory flow (PEF) and forced vital capacity (FVC)) were also not reported. In addition, FEV1, was not reported in %predicted, some outcome measures were reported using median, making them unsuitable for meta-analyses. No selective reporting was identified in the Soroksky 2003 study. As full publication in English was not available for both De Miranda 2004 and Filho 2009, the review authors were unable to assess selective reporting adequately.

Other potential sources of bias

Insufficient published data prevent judgement for other potential sources of bias to be carried out in the Filho 2009 study, whereas no other sources of bias were identified in the remaining four studies.

Effects of interventions

See: **Summary of findings for the main comparison** Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

A total of five studies met all of the inclusion criteria and combinations of these were able to assess the effectiveness of NPPV for various outcomes. These included mortality and tracheal intubation as primary outcomes in addition to the secondary outcomes of the number of hospital admissions, length of hospital stay, length of ICU/ITU stay, symptom scores, lung function tests, ABG, respiratory rate and complications. Data were analysed as per the pre-defined methods described in 'Subgroup analysis and investigation of heterogeneity'. For a summary of intervention effectiveness for each of these outcomes see Table 1 and Table 2. Narrative syntheses have been used to report primary outcomes, secondary outcomes and process measures for all studies (Table 3). One of the five included studies could not be meta-analysed due to insufficient published data (Filho 2009). Subgroup analysis based on admission pH could not be carried out as two studies did not report this outcome (De Miranda 2004; Brandao 2009) while the other two studies reported similar non-acidotic admission pH of more than 7.35 (Soroksky 2003; Gupta 2010).

Primary outcomes

Mortality during hospital admission

Two studies with 86 participants (45 in the NPPV arm and 41 in the control arm) were available to assess mortality (Soroksky 2003, Gupta 2010), although no incidences were reported in either group (Analysis 1.1), as such meta-analysis could not be performed.

Tracheal intubation

For the primary outcome of tracheal intubation, two studies with 45 participants in the NPPV and 41 in the control arms were assessed (RR 4.48; 95% CI 0.23 to 89.13) (Soroksky 2003; Gupta 2010), with no evidence of an effect between groups (Analysis 1.2).

Study location subgroup

In the location subgroup analysis, there were no statistically significant differences in risk of tracheal intubation in both the ICU (Gupta 2010) and ward (Soroksky 2003) subgroups.

Secondary outcomes

Number of hospital admissions

Thirty-three participants from one study (17 in NPPV and 16 in control) contributed to the data on number of hospital admissions (Soroksky 2003) (Analysis 1.3). The results were significant and favoured intervention although we were unable to pool data as we had results from a single trial.

Length of hospital stay

Two studies with 86 participants (Soroksky 2003; Gupta 2010) (45 in the NPPV arm and 41 in the control arm) reported on the length of hospital stay. We were unable to meta-analyse data for the following reasons. Gupta 2010 reported a statistically significant shortening of hospital stay favouring intervention; however, data were reported using median and interquartile range, which is unsuitable for meta-analysis. Soroksky 2003 reported that the mean stay in hospital was 2.5 days (SD 1.3 days) in the control group compared to 4 days (SD 0 days) for people receiving NIPV, but the authors were unable to calculate a P value as there was no variance for an independent sample t-test of days in hospital.

Length of ICU stay

One study conducted in the ICU with 53 participants (Gupta 2010) showed that NPPV provided a statistically significant benefit towards shortening of ICU stay. The data were reported using median and interquartile range, and as such meta-analysis was not possible. Another study (Soroksky 2003) reporting ICU stay in hours for 15 NPPV and 15 control participants found no difference between groups (MD 0.30; 95% CI -0.63 to 1.23; Analysis 1.4).

Symptom scores

None of the studies reported symptom scores.

Treatment failure

Two studies reported on treatment failure (Soroksky 2003; Gupta 2010) with 45 participants in the intervention group and 41 in the control. Overall, no statistically significant benefit was identified for this outcome on meta-analysis (RR 0.73; 95% CI 0.21 to 2.53; Analysis 1.5).

Complications

None of the studies formally assessed the complications of NPPV. One study with 53 participants reported that NPPV was well tolerated by all participants without serious adverse effects; however, frequent complaints of pain in the nasal bridge area were reported (Gupta 2010). The exact number of complaints was not mentioned.

Lung function tests

The parameters of lung function tests including PEF, FVC, FEV1), forced expiratory fraction 25-75% (FEF_{25-75}), minute ventilation (MV), tidal volume (TV) and inspiratory capacity (IC) were reported with largely mixed results (see Table 3 for more detailed information). Findings for MV, TV and IC could only be shown in Table 2 due to lack of available published data.

PEF

Four studies with 153 participants reported on PEF (Soroksky 2003; De Miranda 2004; Brandao 2009; Filho 2009), out of which three studies with 90 participants reported a statistically significant improvement in PEF in the intervention group (Soroksky 2003; Brandao 2009; Filho 2009). However, there was only enough data to meta-analysis for two of the four studies (66 participants) (Soroksky 2003; Brandao 2009), both of which were performed in the ward. NPPV was found to confer an absolute PEF improvement of 19.97 %predicted, which was both clinically and statistically significant (MD 19.97; 95% CI 15.01 to 24.93; Analysis 1.7). De Miranda 2004 reported peak expiratory flow rate (PEFR) using litres per minute and, as such, was unable to be meta-analysed with the other studies (Analysis 1.6). The results reported by De Miranda 2004 showed statistically significant improvements in PEF across both the control and intervention groups, with an

inter-group analysis showing a statistically significant advantage in the intervention group compared to the control group (P < 0.05).

FVC

Three studies with 90 participants reported on FVC with mixed results (Soroksky 2003; Brandao 2009; Filho 2009). Meta-analysis was carried out on two studies with 66 participants, both of which were conducted on the hospital ward (Soroksky 2003; Brandao 2009), producing a statistically and clinically significant improvement for FVC (MD 12.27; 95% CI 4.38 to 20.16; Analysis 1.8).

FEV1

Four studies with a total of 140 participants reported on FEV1 (Soroksky 2003; Brandao 2009; Filho 2009; Gupta 2010). Only two studies could be combined and meta-analysed, both of which were conducted on the hospital ward with 66 participants (Soroksky 2003; Brandao 2009). The meta-analysis found a statistically and clinically significant improvement of FEV1 %predicted (MD 14.02; 95% CI 7.73 to 20.32; Analysis 1.9). One study conducted in the ICU with 53 participants (Gupta 2010) did not find a statistically or clinically significant improvement in FEV1 %predicted (MD 0.12; 95% CI -0.38 to 0.14; Analysis 1.10).

FEF_{25-75}

Two studies with 57 participants (Brandao 2009; Filho 2009) reported on FEF_{25-75} although data were available for meta-analysis from only one study. Brandao 2009 reported statistically and clinically significant results favouring the intervention (MD 19.93; 95% CI 15.84 to 24.02; Analysis 1.11).

Arterial blood gas

One study with 53 participants compared ABG results at follow-up (Gupta 2010), reporting on various components, namely pH, $PaCO_2$ and PaO_2/FiO_2. Overall no statistically significant differences were found between control and intervention groups.

Respiratory rate

All five studies with 203 participants reported on changes in respiratory rate with mixed findings. Three studies with 146 participants provided data that could be meta-analysed (Soroksky 2003; De Miranda 2004; Gupta 2010) and indicated that the intervention provided a statistically but not clinically significant improvement in respiratory rate (MD -1.42; 95% CI -2.77 to -0.07; Analysis 1.15). In one study (Filho 2009) the intervention produced a significant improvement in respiratory rate, while in another it was reported that only one of two intervention groups had a significant improvement (Brandao 2009).

Study location subgroup

One study with 53 participants was conducted in an ICU setting (Gupta 2010) and two studies with 93 participants (Soroksky 2003; De Miranda 2004) were conducted in hospital wards. Neither ICU nor ward subgroups showed a statistically or clinically significant improvement in respiratory rate with NPPV (ICU: MD -1.60; 95% CI -3.75 to 0.55; ward: MD -1.30; 95% CI -3.04 to 0.44; Analysis 1.15).

DISCUSSION

Summary of main results

Five RCTs with a total of 203 participants were selected for inclusion in this review. A further RCT was identified as an ongoing study that could not be used for meta-analyses at the present time. Although there were some methodological variations between studies, all were conducted to evaluate the effectiveness of NPPV in the treatment of acute respiratory failure due to asthma. All six studies concluded that the addition of NPPV to standard therapy may be beneficial. The results did not show a clear benefit for NPPV when the primary outcomes, namely mortality rate and tracheal intubation, were examined. This could partly be explained by the fact that only two studies with a total of 86 participants could be meta-analysed. Both studies showed a mean admission pH that was above 7.35. At this non-acidotic range of pH (being neutral to slightly basic), significant mortality or tracheal intubation is not expected.

In general, NPPV provided favourable outcomes when used in conjunction with usual medical care in most secondary objectives. Treatment with NPPV provided statistically significant improvements for the number of hospital admissions, length of ICU stay and length of hospital stay. In addition, the use of NPPV in the ward setting had statistically and clinically significant positive impacts on many important lung function parameters, namely PEF, FVC, FEV1 and FEF_{25-75}. However, this did not translate into corresponding improvements in ABG results. As such, there is a need for more studies to be conducted to investigate the effectiveness of NPPV for these aspects. There was also a marginal statistically significant reduction in respiratory rate when NPPV was used. Subgroup analyses for respiratory rate showed a clinically significant improvement when given in the ward setting, although it was not statistically significant. Unfortunately, no data

were available to formally examine the symptom scores, treatment failure or complications associated with the use of NPPV.

Overall completeness and applicability of evidence

Following the update of this review additional studies have been identified to examine the effectiveness of NPPV in the treatment of respiratory failure due to severe acute exacerbations of asthma. NPPV certainly confers some degree of benefit for patients with severe acute asthmatic attacks. However, the lack of published data in terms of complications and treatment failure leaves questions regarding the overall safety of NPPV largely unresolved.

More studies are required to demonstrate the effectiveness of NPPV in terms of the primary outcomes, namely mortality and endotracheal intubation, particularly among patients who become acidotic due to respiratory failure. Studies addressing the effectiveness and safety of NPPV when conducted in a general ward setting versus an ICU setting are needed as some degree of expertise is required to monitor patients using NPPV. Further studies using different forms of NPPV, such as bi-PAP or CPAP are also required to allow subgroup analysis comparing specific forms of NPPV. Applying varying settings of NPPV in one study (Brandao 2009) provided some information regarding the benefit of using higher pressure ventilation settings versus lower pressure ventilation settings. This was a positive step towards understanding the benefit of NPPV in different ventilation settings and should be considered in future studies.

Quality of the evidence

Study quality was an issue in this review with all studies having at least one source of unclear or high risk of bias identified. The greatest barrier in the assessment of study quality was inadequate reporting by study authors. In addition, two RCTs had unclear allocation concealment and three had unclear random sequence generation. One study was translated from Portuguese (De Miranda 2004), with some aspects unable to be clearly translated. In summary, the body of evidence identified from the included six RCTs with 253 patients did not allow for a robust conclusion in favour of the use of NPPV for patients with acute severe asthma. For more information regarding the quality of included studies see Summary of findings table 1. The reasons or rationale for up- or downgrading the quality of a body of evidence in the Summary of findings for the main comparison are described in the table footnotes.

Potential biases in the review process

Selecting only RCTs ensures that only high-quality investigations are included. However, it has the potential of introducing selection bias by excluding relevant studies that do not fulfil the studies strict criteria. The review is also susceptible to publication bias, even though we attempted to search all relevant databases for published and non-published studies. Despite numerous attempts to contact study authors for raw data, the inability to obtain all relevant information might introduce a bias, which has the potential to alter the outcome of the meta-analysis. In addition, biases that occur because of methodological designs of included studies might not be adequately accounted for, despite the rigorous assessment by two independent review authors.

Agreements and disagreements with other studies or reviews

One review by Keenan 2009 identified two studies that examined the effects of NPPV in the treatment of respiratory failure due to severe asthma. The studies included were Soroksky 2003, which was also included in this review, and a second study Holley 2001, which was stopped early due owing to a recognised marked bias in recruitment of participants. The authors concluded that although the trials showed trends towards the benefits of NPPV, the small number of participants included rendered the evidence weak. Similarly more recent studies by Soroksky 2010 and Murase 2011 produced limited evidence to support the use of NPPV in carefully selected patients with severe asthma attack, although the authors reported that larger and higher-quality studies are required to confirm these findings. Our review did include a larger number of studies, however we agree that while the effects of intervention showed a trend towards the benefits of NPPV in asthma, the small number of trials and participants in the review highlights the paucity of data while making it impossible to provide any recommendations for the use of NPPV in the treatment of respiratory failure due to acute exacerbations of asthma.

AUTHORS' CONCLUSIONS

Implications for practice

This review highlights the paucity of evidence available to support NPPV for the treatment of respiratory failure due to severe acute asthma exacerbations and as such no implications for current practice can be made. Some promising results in favour of NPPV are evident; however, the weaknesses described above and the concern with prolonged hospitalisation suggest that the regular use of NPPV in status asthmaticus remains controversial and additional research is required before changes to practice can be made.

Implications for research

RCTs of good methodological design are needed to address the question of NPPV for treating respiratory failure in asthmatics

following acute exacerbations adequately. Researchers should consider:

- RCTs with a sample size large enough to demonstrate a meaningful result;

- attention should be paid to maximising the treatment of the control group with efficacious asthma treatments) such as early systemic corticosteroids, frequent short-acting beta-agonists combined with ipratropium bromide, inhaled corticosteroids and intravenous magnesium sulfate) and all treatment groups should have maximal medical management (i.e. best practice minimum);

- a core set of outcome measures for future studies need to be included with primary outcomes of endotracheal intubation and mortality during the hospital admission and secondary outcomes of respiratory rate, ABGs and pH, lung function measurements, length of hospital and ITU/ICU stay, treatment failure (adverse events and complications) and symptom scores (e.g. Borg scores);

- adequate reporting of methodology, outcomes and potential biases in the study design need to be included in the publications;

- clearly defined respiratory failure on based on the presence of hypoxaemia;

- attempts to mask NPPV treatment (as demonstrated by Soroksky 2003) are possible and should be encouraged to reduce the bias associated with a lack of blinding.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Brandao 2009

Methods	Country: Brazil Design: randomised, non-blinded, non-placebo controlled trial Study site: single centre, conducted in the emergency department of a hospital. Hospital not stated Methods of analysis: Kolmogorov-Smirnov test was used to analyse the distribution of the variables and the Levene test was used to evaluate the homogeneity of the data. The data were analysed with ANOVA to compare the treatment effect among the groups, and the Tukey HSD post-hoc test was selected a priori to analyse differences. Alpha was set at 0.05 Aim: to evaluate the effect of jet nebulisation administered during spontaneous breathing with that of nebulisation with NPPV at 2 levels of inspiratory and expiratory pressures resistance in patients experiencing an acute asthmatic episode
Participants	Eligible for study: number of asthma patients presented to the emergency department not reported. Successive patients admitted to the emergency department were invited to participate. 36 participants fulfilled the criteria for inclusion criteria for severe asthma Recruited: n = 24 for intervention (intervention had 2 groups, a and b; n = 12 for each group); n = 12 for control (n = 36 total) Completed: not stated* Age: control group: 40.75 ± 13.97 years; intervention group a: 33.75 ± 13.99 years; intervention group b: 41.00 ± 15.88 years Gender: control: 4 male, 8 female; intervention: 8 male, 16 female (group a: 4 male, 8 female; group b: 4 male, 8 female) Criteria used to define asthma: Study inclusion criteria: Participants were recruited if they were clinically diagnosed with severe asthma, with reversible bronchial obstruction (established objectively with bronchodilator therapy, pre-post FEV1 within 10%) and fulfil the following inclusion criteria: FEV1 < 60% predicted, asthma** at least 1 year, current crises lasting < 7 days Study exclusion criteria: patients with any of the following were excluded: smoked, used anti-inflammatory drugs, COPD, haemodynamically unstable (HR > 150 or systolic BP < 90 mmHg), congestive heart failure, pregnant, facial deformity or altered consciousness
Interventions	Before the study, patients were oriented and allowed to adapt to the mask. They were instructed in standardised slow deep diaphragmatic breathing with a post-inspiratory pause Intervention description: Conventional treatment delivered in the form of nebulisation solution (fenoterol 2.5 mg (now a withdrawn medication - see note below), ipratropium bromide 0.25 mg and 4 mL of physiological saline, 0.9% NaCl) given over 15 minutes, delivered via nebulisers (NS ST3, of NS, Sao Paulo, Brazil) with particles inhaled in the order of 0.9 microns. All participants were seated upright. Inhalation was performed with the use of a silicone face mask

	Intervention delivered via NPPV (BiPAP ventilator - Model Synchrony of Respironics, Murrysville, PA) while receiving nebulisation. The bi-level ventilator was connected to the nebuliser through a T-tube. The following inspiratory and expiratory airway pressures were established: Intervention group a: 15 cm H_2O and 5 cm H_2O Intervention group b: 15 cm H_2O and 10 cm H_2O Control description: Conventional treatment and oxygen flow at 8 L/minute Duration of intervention: 15 minutes
Outcomes	Method of outcome collection: Spirometric testing (before and 30 minutes after nebulisation) with 3 repeated trials was performed with a 1-minute interval between trials - acceptable results if less than 0.2 L difference. The recorded value was the best of 3 trials. RR, HR and peripheral SpO_2 (with pulse oximeter) were recorded before, during and 30 minutes after inhalation based on 3 measures of each variable between 1-minute intervals Pre-specified primary outcome: Protocol not available. In text outcome: spirometric testing results (FVC, FEV1, PEF, FEV25-75%) Pre-specified secondary outcome: Protocol not available. In text outcomes: RR, HR, SpO_2 Follow-up period: 30 minutes Number of follow-up periods reported in study: 3 (before treatment; during treatment; 30 minutes post treatment)
Notes	*Unsure whether all participants completed the study in each respective group **As no statement was made regarding which international criteria was used to define asthma, patients were assumed to have internationally accepted criteria for diagnosing asthma. Attempts were made to contact study authors to no avail NOTE: fenoterol, which was used as part of the conventional treatment, is now a withdrawn medication due to an increase in cardiovascular-related deaths

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not adequately described. Study stated to be a 'prospective randomised controlled study'
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	T-tube used for participants who required both NPPV and nebulisation. No sham NPPV employed. Highly likely that participants and personnel were aware of allocation. However, outcome is unlikely to be affected

Brandao 2009 (*Continued*)

Blinding of outcome assessment (detection bias) Spirometric testing	Low risk	Highly likely that assessors knew which group the patients belonged to as no sham NPPV was used. However, measurements for spirometric testing were unlikely to be affected as best of 3 trials with acceptable results < 0.2 L difference, whereas measurements of HR, RR, SpO_2 are all objective measurements
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of how missing variables, if any, were handled. Unsure whether all participants completed study
Selective reporting (reporting bias)	High risk	No data regarding the outcome were given for clear comparison. Comparison given in the form of graphs (with no exact data values written). No data given on relative/absolute improvement in lung function
Other bias	Low risk	No other sources of bias identified

De Miranda 2004

Methods	Country: Brazil Design: randomised controlled trial, block design Study site: single centre, recruited from the Federal University of Sao Paulo - Paulista School of Medicine Methods of analysis: Student t-test; ANOVA and percentual variation (Kruskall-Wallis) for variables of RR and PEF Aim: to evaluate the bronchodilator response in patients with acute asthma crisis when using CPAP with facial mask and bronchodilator inhaler therapy and to evaluate the subjective sensation of patient tolerance in relation to non-invasive ventilation support during bronchial asthma crisis
Participants	Eligible for study: unclear Recruited: 21 for control; 42 for intervention (intervention had 2 groups, A and B, 21 people in each); 21 for control (63 in total) Completed: 42 for intervention (63 in total) Age: minimum age of 18 years; control group: 53 ± 15.8 years; group A: 40 ± 14.9 years; group B: 41.9 ± 11.6 years (age ± SD) Gender (expressed as a ratio, male/female): control: 30/70; group A 28.5/71.5; group B: 28.5/71.5 Study inclusion criteria: • patients with a diagnosis of bronchial asthma crisis • minimum age of 18 years • PEF < 70% predicted • indication of therapeutic bronchodilation brought on by inhalation through

	aerosol dispenser Study exclusion criteria: • smoker or ex-smoker • any other type of associated pulmonary disease • severe cardiac disease • any difficulty performing PEF • illiterate or unable to understand the procedures performed
Interventions	Intervention description: Conventional treatment: each group was given 2 puffs of fenoterol (200 μg/puff; fenoterol now withdrawn - see note below) via a metered dose inhaler, without using a spacer except intervention group B Intervention in the form of CPAP: given to both intervention groups, A and B, using a face mask. However, the method of delivery of the conventional treatment was different: • group A: fenoterol was interconnected to CPAP and face mask to ensure CPAP delivery was seamless. CPAP was first given to the participants for 3 minutes. Without stopping CPAP, the first puff of fenoterol was then given, followed by a second puff after 1 minute. CPAP was then continued for another 5 minutes before the face mask was removed. A 15-minute interval was given before measurements were taken • group B: the delivery of fenoterol via metered dose inhaler was interspersed with the administration of CPAP. CPAP was given to the participants for 3 minutes. The face mask was then removed for the administration of the first puff of fenoterol via a spacer. This was then followed by CPAP for 1 minute before the face mask was again removed for a second puff of fenoterol via a spacer. Finally, CPAP was continued for another 5 minutes before being removed. A 15-minute interval was given before measurements were taken Control description: Conventional treatment was given. A 1-minute interval was allowed before the second puff of fenoterol was delivered. A 15-minute interval was then given before measurements were taken Duration of intervention: a total of 9 minutes of CPAP was given in each intervention group
Outcomes	Methods of outcome collection: not reported Pre-specified primary outcomes: protocol not available. In text outcomes: oxygen saturation, RR, HR and PEF Pre-specified secondary outcomes: protocol not available. Insufficient information available Follow-up period: 15 minutes after delivery of intervention/treatment Number of follow-up periods reported: unclear
Notes	Unable to obtain a complete translation of the full article, resulting in minor areas that could not be clarified NOTE: fenoterol, which was used as part of the conventional treatment, is now a withdrawn medication due to an increase in cardiovascular related deaths

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

De Miranda 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Sequence generated through random draw/ raffle
Allocation concealment (selection bias)	Unclear risk	No information reported regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Due to the nature of the intervention, blinding was not possible. No sham CPAP used. However, outcomes reported were objective outcomes and were unlikely to be affected
Blinding of outcome assessment (detection bias) Spirometric testing	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of participants lost to follow-up; no mention of how missing outcome data were handled
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of yes or no
Other bias	Low risk	No other bias identified

Filho 2009

Methods	Country: Brazil Design: randomised controlled trial Study site: single centre Methods of analysis: not reported Aim: to assess the effects of coupled nebulisation to bi-level non-invasive ventilation during asthma exacerbations on radio aerosol deposition and cardiopulmonary parameters
Participants	Eligible for study: unclear Recruited: 21 asthmatic patients were randomised into 2 groups, control and experimental Completed: 10 for Intervention; 11 for control (21 in total) Age: not reported Gender: not reported Criteria used to define asthma: clinical diagnosis of moderate to severe asthma (FEV1 < 60% predicted), history of asthma for at least 1 year
Interventions	Intervention description: Intervention: nebulisation (salbutamol 2.5 mg and ipratropium bromide 0.25 mg plus oxygen flow 7 L/minute for 9 minutes)) coupled with non-invasive ventilation IPAP and EPAP levels were set to 12 cm H_2O and 5 cm H_2O, respectively Control description: nebulisation (salbutamol 2.5 mg and ipratropium bromide 0.25

Filho 2009 (*Continued*)

	mg plus oxygen flow 7 L/minute) Duration of intervention: not reported
Outcomes	Methods of outcome collection: not reported Pre-specified primary outcomes: protocol not available. In text outcomes: RR, SpO_2, tidal volume, minute ventilation, inspiratory capacity Pre-specified secondary outcomes: protocol not available. In text outcomes: HR, BP Follow-up period: after intervention - timeline not known Number of follow-up periods: not reported
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned but methods not described
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of yes or no
Blinding of outcome assessment (detection bias) Spirometric testing	Unclear risk	Insufficient information to permit judgement of yes or no
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement of yes or no
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of yes or no
Other bias	Unclear risk	Insufficient information to permit judgement of yes or no

Gupta 2010

Methods	Country: India Design: randomised controlled trial Study site: single centre, in the respiratory ICU of a hospital in India Methods of analysis: statistical analysis was performed with statistics software (SPSS 10, SPSS, Chicago, IL, US). The analysis was based on intention to treat. Statistical significance was assumed at a P value of < 0.05. The normalcy of distribution was evaluated with the Kolmogorov-Smirnov test. The differences between continuous variables were analysed with the Mann-Whitney U test if not normally distributed, or with Student's t test if normally distributed. The differences between categorical variables were analysed with Fisher's exact test. Improvements in RR, HR, pH, PaO_2 and $PaCO_2$, were analysed with repeated-measures ANOVA. The within-groups factor was time (0, 1, 1, 2 and 4 hours) and the between-groups factor was the experimental group (NPPV vs. standard medical therapy). Kaplan-Meier curves were constructed to study the effect of NPPV on ICU and hospital stay. Differences between the 2 curves were analysed with the log-rank test
Participants	Aim: to evaluate the efficacy of NPPV in patients with severe acute asthma Eligible for study: 62 asthma patients admitted to the respiratory ICU, 53 fulfilled severe asthma inclusion criteria Recruited: 28 for intervention; 25 for control (53 in total) Completed: 28 for intervention; 25 for control (53 in total) *2 patients in the intervention group required invasive ventilation, 4 patients in the control group were crossed over to receive NPPV Age: all participants 44.1 ± 14.6 years; intervention: 46.2 ± 16.2 years; control: 41.6 ± 12.5 years Gender: intervention: 22 female, 6 male; control: 20 female, 5 male Study inclusion criteria:** History of asthma of at least 1 year, judged by the attending physician as having an asthma attack (acute respiratory distress with wheeze and inability to complete 1 sentence in 1 breath), RR > 30 breaths/minute, HR > 100 beats/minute, pulse oximetry saturation < 92% (or PaO_2 < 60 mmHg) Study exclusion criteria: Smoking history > 10 years, COPD, need for immediate endotracheal intubation, hypotension (systolic < 90 mmHg) or cardiac arrhythmias, pregnancy, inability to protect airway, abnormalities precluding proper fit of interface, pulmonary infiltrates suggestive of pulmonary oedema pneumonia, active tuberculosis or its sequelae
Interventions	Intervention description: Conventional treatment: all participants received (in first hour of respiratory ICU) 3 doses of nebulised albuterol (2.5 mg every 20 minutes), 1 dose of nebulised ipratropium bromide (0.25 mg), IV hydrocortisone (100 mg) or equivalent dose of methylprednisolone, and IV magnesium sulfate (2 g, slowly, over 10 minutes) Nebulised albuterol (2.5 mg hourly for the first 6 hours, then every 4 hours and as needed) Nebulised ipratropium (0.25 mg, every 6 hours and as needed) IV hydrocortisone (100 mg every 8 hours) Intervention: NPPV was administered with the non-invasive module of a critical care ventilator (Servo-i, Maquet, Germany) All NPPV patients used an oronasal mask as the interface

	Detailed procedure of NPPV explained to patient to improve patient adherence to therapy NPPV was delivered while the patient was in bed, with the head of the bed at an angle of 30° to 45° The fraction of inspired oxygen was titrated to maintain $SpO_2 \geq 92\%$ The patient was started on an inspiratory/expiratory pressure of 8/4 cm H_2O, and titrated in increments of 2 cm H_2O, based on continuous pulse oximetry, ABG values (at 1, 2 and 4 hours, and periodically thereafter, as clinically indicated), alleviation of dyspnoea, decrease in RR and patient-ventilator synchrony (Maximum inspiratory pressure was 20 cm H_2O, maximum expiratory pressure was 10 cm H_2O) Frequently checked for air leaks, and the patient was constantly encouraged and reassured. NPPV was applied continuously for as long as possible, and interruption of NPPV was allowed only for spirometry or secretion clearance, and for no more than 5 minutes. Inhaled bronchodilators were given via T-piece in the ventilator circuit, with the ventilator's built-in ultrasonic nebuliser, without discontinuing the circuit Control description: conventional treatment as described above and oxygen therapy to maintain blood SpO_2 (measured via pulse oximetry) > 92% Duration of intervention: weaning from NPPV was begun when there was clinical improvement of the severe acute asthma, RR was < 25 breaths/minute, and PaO_2 was > 60 mmHg. Mean ± SD of duration of intervention was 9 ± 5 hours Decision to move a patient to the next level (standard medical therapy to NPPV to invasive ventilation) was based on the following criteria: failure to improve clinical variables and gas exchange at 1 hour, development of alteration in sensorium, haemodynamic instability and inability to tolerate face mask. However, the final decision was left to the intensivist's clinical judgement
Outcomes	Methods of outcome collection: Arterial blood samples, via radial arterial catheter, were taken at baseline, 1, 2 and 4 hours Spirometry (PIKO-I, Ferraris Respiratory Europe, Hertford, UK) was performed at admission, and repeated at 1, 2 and 4 hours. At least 3 spirometry readings were taken. In accordance with the American Thoracic Society guidelines for spirometry reproducibility, at least 2 of the volumes differed by no more than 0.2 L, unless the FEV1 was < 0.2 L, in which case difference was < 10%. Best of the 3 spirometry results recorded Pre-specified primary outcomes: As per protocol: improvement in lung function defined as an increase of at least 50% in FEV1 as compared to baseline value on admission or an increase in FEV1 to > 60% of predicted value, ICU length of stay and hospital length of stay. This was largely similar to in-text primary outcomes. In-text outcomes: improvement in lung function test results (defined as an increase of at least 50% in FEV1 as compared to baseline values on hospital), length of ICU stay and length of hospital stay Pre-specified secondary outcomes: as per protocol: improvement in the clinical status, disappearance of pulsus paradoxus, improvement in ABGs, improvement in oxygen saturation, requirements of FiO_2 and medications, and need for mechanical ventilation. In-text outcomes: improvement in clinical status (with respect to RR and disappearance of use of accessory muscles of respiration): improvement in ABG values (pH, PaO_2, $PaCO_2$, PaO_2/FiO_2) from baseline

	at 1, 2 and 4 hours; requirements for inhaled albuterol and ipratropium; and failure of primary therapy (need for NPPV in the standard medical therapy arm, and endotracheal intubation and mechanical ventilation in the NPPV arm). Disappearance of pulsus paradoxus and improvement in oxygen saturation was not reported in text Follow-up period: not stated but presumably up to the end of hospital stay Number of follow-up periods reported: 5 (1, 2 and 4 hours post-NPPV application; upon ICU discharge; upon hospital discharge)
Notes	*Study uses intention-to-treat analysis **Study used GINA guidelines as part of assessment of baseline characteristics. Refer to study table 1 of study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation sequence generated with StatsDirect version 2.6.2 statistics software
Allocation concealment (selection bias)	Low risk	Assignments placed in sealed opaque envelopes with each patient's assignment made by attending physician on admission to respiratory ICU
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors stated that the patients and personnel were not blinded to the intervention. No sham NPPV was used. However, outcomes reported were objective outcomes and as such were unlikely to be affected
Blinding of outcome assessment (detection bias) Spirometric testing	Low risk	Assessors were not blinded to the intervention; however, outcomes measured were objective outcomes and were unlikely to be affected
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis. 2 of 28 participants in intervention group required intubation, 4 of 25 participants in the control group was crossed over to receive intervention
Selective reporting (reporting bias)	High risk	There were 2 secondary outcomes that were not reported as per protocol. Other important parameters of lung function test such as PEF and FVC were not reported. The reported lung function test result, FEV1, was not reported as %predicted, which would

Gupta 2010 (*Continued*)

		have better generalisability and would be suitable for meta-analysis. Outcome data mostly reported using median, rather than mean
Other bias	Low risk	No other sources of bias identified

Soroksky 2003

Methods	Country: Israel Design: randomised controlled trial Study site: single centre, conducted in the emergency department of the Asaf Harofe Medical Center Method of analysis: 2-tailed tests; categorical data analysed using Chi^2 test; Yates correction used for 2 × 2 table; intention-to-treat analysis performed using 2-tailed Fisher exact test; SPSS statistical software package used
Participants	Eligible for study: 124 asthma patients were seen in emergency department; 37 fulfilled the severe asthma inclusion criteria Recruited: 17 for intervention; 16 for control (33 in total) Completed: 15 for each arm (30 in total) Age: range 18 to 50 years; intervention 34.07 $\pm$ 8.55 years; control 32.53 $\pm$ 9.68 years Gender: intervention: 8 female, 7 male; control: 7 female, 8 male Criteria used to define asthma: FEV1 < 60% of predicted by age, height and gender; RR > 30 breaths/minute; history of asthma of at least 1 year and duration of current asthma attack of < 7 days
Interventions	Intervention descriptions: Conventional treatment combined with ventilator support with BPV Conventional treatment: salbutamol 2.5 mg and ipratropium 0.25 mg nebulised on average once an hour, and IV corticosteroids (either methylprednisolone or hydrocortisone) at the discretion of the attending physician; oxygen was administered as required Therapeutic BPV: applied through a nasal mask and secured with head straps with pre-determined pressures for no longer than 3 hours; inspiratory pressure was set at 8 cm H_2O and increased by 2 cm H_2O every 15 minutes to a maximum of 15 cm H_2O, or until an RR of < 25 breaths/minute was reached (whichever came first); Expiratory pressure was set at 3 cm H_2O and was increased by 1 cm H_2O every 15 minutes to a maximum of 5 cm H_2O; breathing through the mouth was discouraged and patients were instructed to breath only through the nasal mask Control descriptions: conventional treatment (as described above) plus sham BPV Sub-therapeutic (sham) BPV: was applied through a nasal mask and secured with head straps with pre-determined pressures (1 cm H_2O) for no longer than 3 hours; in addition, 4 holes (3 mm in diameter) were made in the tube connecting the apparatus and the nasal mask; patients were not instructed to breath solely through their nasal mask and oral breathing was allowed Duration of intervention: not longer than 3 hours

Soroksky 2003 (*Continued*)

Outcomes	Method of outcome collection: vital signs and bedside spirometry (best of 3 readings, with < 0.2 L variance allowed between tests) Pre-specified primary outcomes: protocol not available; in text outcome improvement in lung function test results defined as an increase of at least 50% in FEV1 as compared to baseline values on hospital admission or an increase in FEV1 to > 60% of the predicted value Pre-specified secondary outcomes: protocol not available; in text outcomes were need for hospitalisation and the occurrence of respiratory failure with the need for mechanical ventilation; re-admission rates Follow-up period: 1 month Number of follow-up periods reported: 3 at 3 hours post-BPV application, 1 hour later and 1 month following discharge
Notes	(Original review) Author reply received 01/06/2004 regarding allocation concealment, mortality and endotracheal intubation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised and confirmed by investigator, but further information was not available
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors state that the patients were blinded to the intervention
Blinding of outcome assessment (detection bias) Spirometric testing	Low risk	The investigating team could not be blinded due to the requirement to individually titrate respiratory pressures; however, outcome unlikely to be affected due to the nature of the outcomes measured
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of how missing variables were handled; Patients were analysed on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	Low risk	No other sources of bias identified

ABG: arterial blood gas; ANOVA: analysis of variance; BiPAP: bi-level positive airway pressure; BP: blood pressure; BPV: bi-level pressure ventilation; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; EPAP: expiratory positive airway pressure; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; HR: heart rate; ICU: intensive care unit; IPAP: inspiratory positive airway pressure; IV: intravenous; NPPV: non-invasive

positive pressure ventilation; PEF: peak expiratory flow; RR: respiratory rate; SD: standard deviation; SpO_2: peripheral oxygen saturation.

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

Study	Reason for exclusion
Akingbola 2002	Not a randomised controlled study - case series report
Archis 2001	Study not conducted in patients with asthma
Clark 1997	Not a randomised controlled study - case-control study
Compagnoni 2000	Intervention not NPPV - study was testing the delivery of beta-agonists and compared NPPV, inspiratory positive pressure breathing and spontaneous breathing
Ergun 2002	Not acute exacerbations of asthma - patients in stable state of disease and only includes patients with pachypleuritis and kyphoscoliosis
Fernandez 2001	Not a randomised controlled study - retrospective observational study
Meduri 1996	Not a randomised controlled study - retrospective patient record review
Pollack 1995	Intervention not NPPV - NPPV compared to small volume nebuliser for the delivery of beta-2 agonists
Soma 2002	Not a randomised controlled study - before and after study
Soma 2008	Not a randomised controlled study - recruitment of participants was random; however, assignment to the 3 study arms were through allocation in consecutive order
Thill 2004	Study included patients with COPD and data not analysed separately - all patients received both NPPV and usual medical care for 2 hours each using cross-over design - first arm data was not presented/analysed separately. Study combined patients with asthma and other obstructive lower airways disease
Thys 1999	Not a randomised controlled study - non-randomised trial

COPD: chronic obstructive pulmonary disease; NPPV: non-invasive positive pressure ventilation.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chaudhry 2010

Methods	Country: not reported Design: randomised controlled trial Study site: not reported Methods of analysis: not reported Aim: to study the role of NPPV in management of acute severe asthma
Participants	Eligible for study: 308 patients were seen; 62 fulfilled the severe asthma inclusion criteria Recruited: 51 participants divided into groups A and B (no information found on number of patients in each group) Completed: 50 (1 patient in group A deteriorated and was withdrawn) Age: not reported Gender: not reported Criteria used to define Asthma: Inclusion criteria: having asthma for at least 1 year' duration with exacerbation of < 7 days' duration, FEV1 < 50% of predicted, respiratory rate of > 25 breaths/minute, pulse rate > 110 beats/minute after 30 minutes of nebulised salbutamol 5 mg Exclusion criteria: patients with known COPD, history of smoking > 10 years, HR > 140, systolic BP < 90 mmHg, facial deformity, pulmonary oedema, pneumonia and pregnancy
Interventions	Intervention description: intervention group (group B) patients were given NPPV support in addition to usual medical therapy for 6 hours Control description: usual medical therapy was given to all patients in the form of nebulisation with salbutamol 5 mg and ipratropium bromide 0.5 mg and hydrocortisone 100 mg IV at 0 hours and later salbutamol 5 mg with small volume oxygen driven nebuliser at 6 L/minute at 1st, 2nd, 3rd and5th hour of study. All patients received oxygen at 6 to 8 L/minute for 6 hours Duration of intervention: 6 hours
Outcomes	Methods of outcome collection: spirometry, ABG, respiratory rate, accessory muscles of respiration and BORG dyspnoea score were assessed Pre-specified primary outcomes: protocol not available Pre-specified secondary outcomes: protocol not available In text outcomes: use of accessory muscles score, BORG dyspnoea score, respiratory rate, HR, FEV1 and ABG Follow-up period: 1 hour after intervention Number of follow-up periods reported: unclear
Notes	-

ABG: arterial blood gas; BP: blood pressure; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; HR: heart rate; NPPV: non-invasive positive pressure ventilation.

DATA AND ANALYSES

Comparison 1. NPPV versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality during hospital admission	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 ICU	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Ward	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Endotracheal intubation	2	86	Risk Ratio (M-H, Fixed, 95% CI)	4.48 [0.23, 89.13]
2.1 ICU	1	53	Risk Ratio (M-H, Fixed, 95% CI)	4.48 [0.23, 89.13]
2.2 Ward	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Number of hospital admissions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Length of ICU stay (hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Treatment failure	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.21, 2.53]
6 PEF (L/minute)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 PEF (% predicted)	2	66	Mean Difference (IV, Fixed, 95% CI)	19.97 [15.01, 24.93]
8 FVC (% predicted)	2	66	Mean Difference (IV, Fixed, 95% CI)	12.27 [4.38, 20.16]
9 FEV1 (% predicted)	2	66	Mean Difference (IV, Fixed, 95% CI)	14.02 [7.73, 20.32]
10 FEV1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 $FEF_{25-75\%}$ (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 ABG - pH	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.03, 0.01]
13 ABG - $PaCO_2$ (mmHg)	1	53	Mean Difference (IV, Fixed, 95% CI)	0.5 [-2.83, 3.83]
14 ABG - PaO_2/FiO_2 (mmHg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Respiratory rate	3	146	Mean Difference (IV, Fixed, 95% CI)	-1.42 [-2.77, -0.07]
15.1 ICU	1	53	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.75, 0.55]
15.2 Ward	2	93	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.04, 0.44]

Analysis 1.1. Comparison 1 NPPV versus usual care, Outcome 1 Mortality during hospital admission.

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 1 Mortality during hospital admission

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 ICU				
Gupta 2010	0/28	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**28**	**25**		**0.0 [0.0, 0.0]**
Total events: 0 (Intervention), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Ward				
Soroksky 2003	0/17	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**17**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Intervention), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**45**	**41**		**0.0 [0.0, 0.0]**
Total events: 0 (Intervention), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

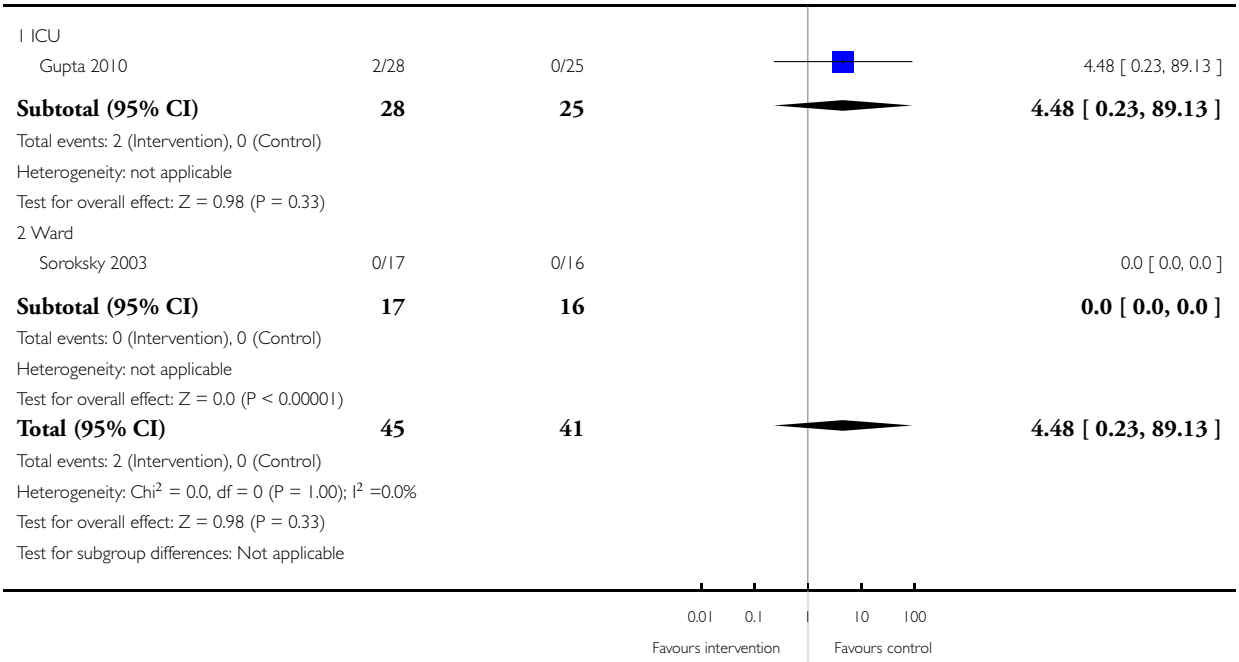
Analysis 1.2. Comparison 1 NPPV versus usual care, Outcome 2 Endotracheal intubation.

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 2 Endotracheal intubation

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 ICU				
Gupta 2010	2/28	0/25		4.48 [0.23, 89.13]
Subtotal (95% CI)	**28**	**25**		**4.48 [0.23, 89.13]**
Total events: 2 (Intervention), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.98 (P = 0.33)				
2 Ward				
Soroksky 2003	0/17	0/16		0.0 [0.0, 0.0]
Subtotal (95% CI)	**17**	**16**		**0.0 [0.0, 0.0]**
Total events: 0 (Intervention), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**45**	**41**		**4.48 [0.23, 89.13]**
Total events: 2 (Intervention), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.98 (P = 0.33)				
Test for subgroup differences: Not applicable				



Analysis 1.3. Comparison 1 NPPV versus usual care, Outcome 3 Number of hospital admissions.

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 3 Number of hospital admissions

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Soroksky 2003	3/17	10/16		0.28 [0.09, 0.84]

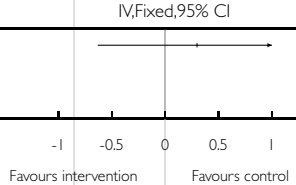
Analysis 1.4. Comparison 1 NPPV versus usual care, Outcome 4 Length of ICU stay (hours).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 4 Length of ICU stay (hours)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Soroksky 2003	15	5.9 (1.3)	15	5.6 (1.3)		0.30 [-0.63, 1.23]



Analysis 1.5. Comparison 1 NPPV versus usual care, Outcome 5 Treatment failure.

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 5 Treatment failure

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 2010	2/28	4/25		80.4 %	0.45 [0.09, 2.23]
Soroksky 2003	2/17	1/16		19.6 %	1.88 [0.19, 18.80]
Total (95% CI)	**45**	**41**		**100.0 %**	**0.73 [0.21, 2.53]**

Total events: 4 (Intervention), 5 (Control)

Heterogeneity: Chi^2 = 1.01, df = 1 (P = 0.32); I^2 =1%

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

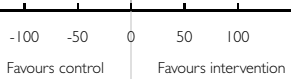
Analysis 1.6. Comparison 1 NPPV versus usual care, Outcome 6 PEF (L/minute).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 6 PEF (L/minute)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
De Miranda 2004	42	302.26 (84.54)	21	260.95 (88.08)		41.31 [-4.22, 86.84]



Analysis 1.7. Comparison 1 NPPV versus usual care, Outcome 7 PEF (% predicted).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 7 PEF (% predicted)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brandao 2009	24	42.92 (5.05)	12	22.37 (8.64)		87.8 %	20.55 [15.26, 25.84]
Soroksky 2003	15	59.9 (20.4)	15	44.1 (19.3)		12.2 %	15.80 [1.59, 30.01]
Total (95% CI)	**39**		**27**			**100.0 %**	**19.97 [15.01, 24.93]**

Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² =0.0%

Test for overall effect: Z = 7.90 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 NPPV versus usual care, Outcome 8 FVC (% predicted).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

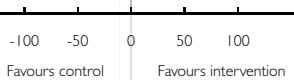
Outcome: 8 FVC (% predicted)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brandao 2009	24	53.79 (7.57)	12	41.26 (17.35)		59.0 %	12.53 [2.26, 22.80]
Soroksky 2003 (1)	15	70 (14.3)	15	58.1 (19.7)		41.0 %	11.90 [-0.42, 24.22]
Total (95% CI)	**39**		**27**			**100.0 %**	**12.27 [4.38, 20.16]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² =0.0%

Test for overall effect: Z = 3.05 (P = 0.0023)

Test for subgroup differences: Not applicable



(1) at 4 hours

Analysis 1.9. Comparison 1 NPPV versus usual care, Outcome 9 FEV1 (% predicted).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 9 FEV1 (% predicted)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brandao 2009	24	49.72 (5.91)	12	35.51 (12.26)		73.8 %	14.21 [6.88, 21.54]
Soroksky 2003 (1)	15	57.4 (17.7)	15	43.9 (16.7)		26.2 %	13.50 [1.19, 25.81]
Total (95% CI)	**39**		**27**			**100.0 %**	**14.02 [7.73, 20.32]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² =0.0%

Test for overall effect: Z = 4.36 (P = 0.000013)

Test for subgroup differences: Not applicable

(1) at 4 hour

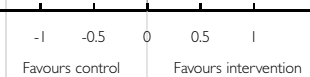
Analysis 1.10. Comparison 1 NPPV versus usual care, Outcome 10 FEV1 (litres).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 10 FEV1 (litres)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gupta 2010	28	1.02 (0.38)	25	1.14 (0.56)		-0.12 [-0.38, 0.14]

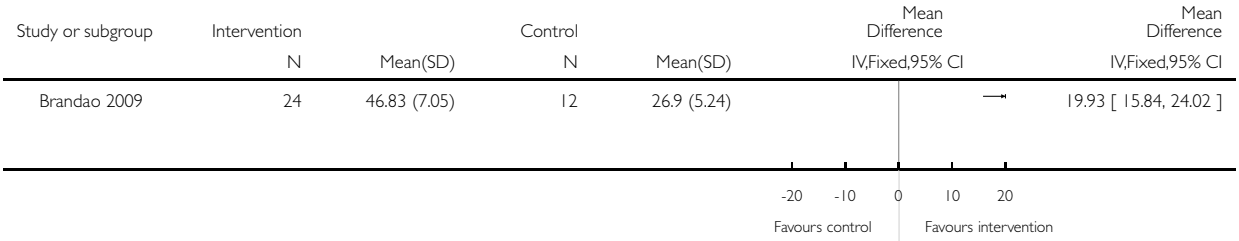


Analysis 1.11. Comparison 1 NPPV versus usual care, Outcome 11 $FEF_{25-75\%}$ (% predicted).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 11 $FEF_{25-75\%}$ (% predicted)

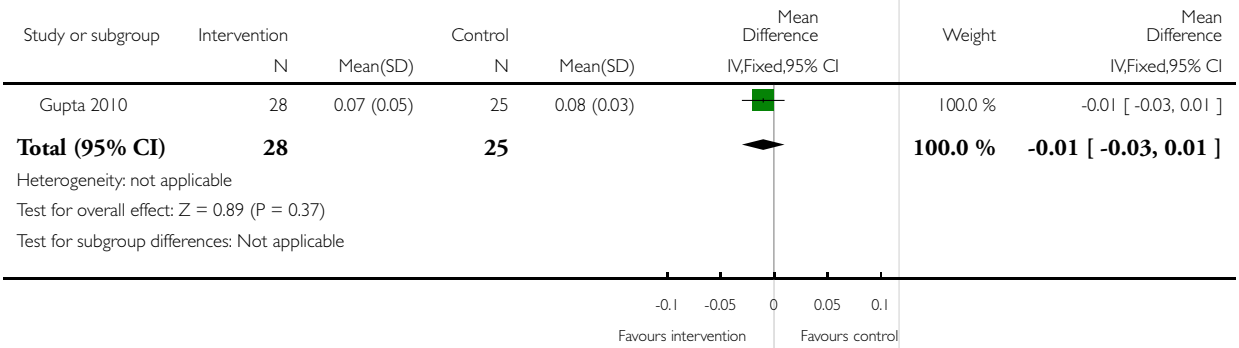


Analysis 1.12. Comparison 1 NPPV versus usual care, Outcome 12 ABG - pH.

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 12 ABG - pH



Analysis 1.13. Comparison 1 NPPV versus usual care, Outcome 13 ABG - $PaCO_2$ (mmHg).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 13 ABG - $PaCO_2$ (mmHg)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gupta 2010	28	35.3 (7.7)	25	34.8 (4.4)		100.0 %	0.50 [-2.83, 3.83]
Total (95% CI)	**28**		**25**			**100.0 %**	**0.50 [-2.83, 3.83]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable

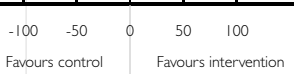
Analysis 1.14. Comparison 1 NPPV versus usual care, Outcome 14 ABG - PaO_2/FiO_2 (mmHg).

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 14 ABG - PaO_2/FiO_2 (mmHg)

Study or subgroup	Intervention N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Gupta 2010	28	329 (60)	25	371 (55)		-42.00 [-72.96, -11.04]

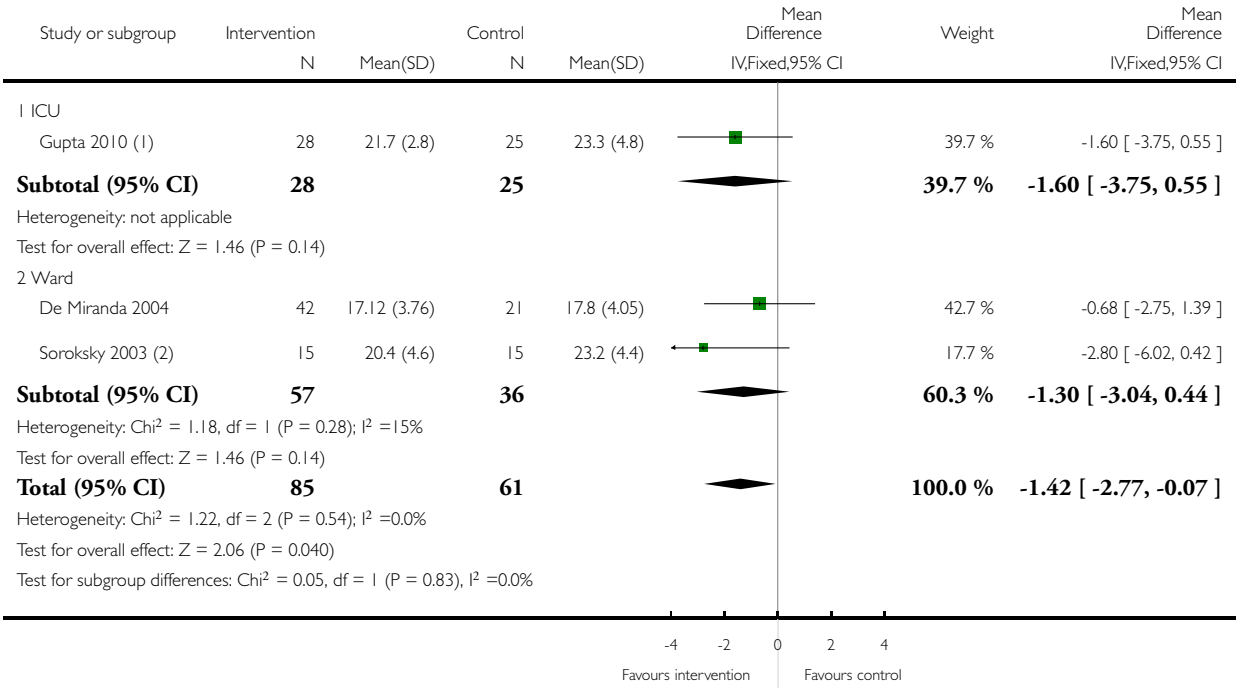


Analysis 1.15. Comparison 1 NPPV versus usual care, Outcome 15 Respiratory rate.

Review: Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma

Comparison: 1 NPPV versus usual care

Outcome: 15 Respiratory rate



(1) at 4 hours

(2) at 4 hours

ADDITIONAL TABLES

Table 1. Summary of intervention effectiveness: secondary outcomes

Study ID/ N-values	Outcome results (comparing intervention to control):								
	Number	Length of	Length of	Symptom	Treatment	Compli-	Lung function tests	ABG	Respira-

Table 1. Summary of intervention effectiveness: secondary outcomes (*Continued*)

	of hospital admissions	hospital stay	ICU stay	scores	failure	cations	PEF	FVC	FEV1	FEF_{25-}	MV	TV	IC	pH	$PaCO_2$	PaO_2/FiO_2	tory rate
Brandao 2009	-	-	-	-	-	-	Favour intervention	No evidence of effect	Favour intervention	Favour intervention	-	-	-	-	-	-	Favours intervention group a
Gupta 2010	-	Favour intervention	Favour intervention	-	No evidence of effect	-	-	-	No evidence of effect	-	-	-	-	No evidence of effect	No evidence of effect	No evidence of effect	No evidence of effect
Soroks 2003	Favour intervention	No evidence of effect	-	-	No evidence of effect	-	Favour Intervention	No evidence of effect	Favour Intervention	-	-	-	-	-	-	-	No evidence of effect
Filho 2009	-	-	-	-	1 patient deteriorated in control group and was withdrawn	-	Favour intervention	Favour intervention	Favour intervention	Not reported	Favour intervention	Favour intervention	Favour intervention	-	-	-	Favours intervention
De Miranda	-	-	-	-	-	-	No evi-	-	-	-	-	-	-	-	-	-	No

Table 1. Summary of intervention effectiveness: secondary outcomes (*Continued*)

2004							dence of effect										evidence of effect

Table 2. Narrative synthesis

Study ID/sub-headings	Detailed synthesis of intervention effectiveness
Brandao 2009 Primary outcome:	There were no reported outcome measures for intubation or mortality
Brandao 2009 Secondary outcomes:	The number of hospital admissions, length of hospital stays, symptoms scores, ABG results and complications were not reported. Compared to the effect of nebulisation in the control group, intervention group a: (IPAP 15 cm H_2O and EPAP 5 cm H_2O), had significantly higher PEF (P = 0.04) and lower respiratory rate (P = 0.04); whereas intervention group b (IPAP 15 cm H_2O and EPAP 10 cm H_2O) had significantly higher PEF (P = 0.03), FVC (P = 0.03), FEV1 (P = 0.03) and $FEF_{25-75\%}$ (P = 0.0001) with no evidence of effect for respiratory rate
Gupta 2010 Primary outcome:	The authors reported that there were no mortalities in any group. 2 patients in the intervention group were subsequently intubated. 4 patients in the control group were crossed over to receive the intervention, however, none were subsequently intubated
Gupta 2010 Secondary outcomes:	The median length of stay in hospital for the intervention group was 38 hours (interquartile range 24 to 48 hours) compared to 54 hours (interquartile range 48 to 72 hours) for the control group (P = 0.01). The median length of stay in the respiratory ICU was 10 hours (interquartile range 8 to 20 hours) for the intervention group compared to 24 hours (interquartile range 18 to 36 hours) in the control group (P = 0.01). 64% (16/25) of patients in the control group and 85.7% (24/28) of patients in the intervention group had a $\geq$ 50% improvement in FEV1 at 4 hours (P = 0.08). Time to disappearance of accessory muscle use was 2.3 (± 1.4) hours in the intervention group and 3.2 (± 1.7) hours in the control group (P = 0.06). The mean dose of inhaled salbutamol required during hospitalisation was 31.2 mg (± 14.5) in the NPPV group and 42.8 mg (± 10.4) in the control group (P = 0.008). This was significantly lower in the NPPV group. The mean dose of inhaled ipratropium required during hospitalisation was 5.2 mg (± 2.8) in the NPPV group and 7.6 mg (± 2.2) in the control group with a P value of 0.007. This was significantly lower in the NPPV group
Soroksky 2003 Primary outcome:	There were no reported outcome measures for intubation or mortality
Soroksky 2003 Secondary outcomes:	The number of hospital admissions was analysed on an intention-to-treat basis with 17.6% (3/17) participants in the intervention group and 62.5% (10/16) in the control group requiring hospitalisation (P = 0.0134). During follow-up (1 month), only 1 patient in each group was re-admitted to the emergency department and both were discharged after a short treatment without re-hospitalisation. Average length of stay in the emergency department

Table 2. Narrative synthesis (*Continued*)

	was 5.9 hours (± 1.3) for the intervention group and 5.6 hours (± 1.3) for the control (P = NS). There was an increase in FEV1 for the intervention group during the 3 hours of BPV treatment (mean ± SD; intervention: 56.1 ± 16.3; control: 42.3 ± 15.9; P = 0.03), which steadily increased for an additional hour after discontinuation of treatment (mean ± SD; intervention: 57.4 ± 17.7; control: 43.9 ± 16.7; P = 0.04). PEFR also increased in the intervention arm at both 3 and 4 hours post treatment (P = 0.03 and P = 0.04, respectively) , and although FVC showed a similar improvement at 3 hours for the intervention arm (P = 0.03) this was not maintained at 4 hours post BPV administration (P = NS). Respiratory rate decreased significantly in the BPV group (41.3 ± 12.8%) compared to the control group (31 ± 11.4%) at 4 hours' follow-up (P = 0.02). 2 patients in the intervention arm and 1 in the control arm could not tolerate the nasal mask and did not complete the 3-hour protocol, subsequently they were withdrawn from the study
De Miranda 2004 Primary outcome:	There were no reported outcome measures for intubation or mortality
De Miranda 2004 Secondary outcomes:	Only PEF (measured in L/minute) and respiratory rate were reported. Both outcomes were reported to have statistically significant improvements in each of the 3 groups; however, comparisons between groups were not reported in the study. Outcomes reported were intervention group A mean PEF 293.80 (SD 82.12; P < 0.001) and mean respiratory rate 17.57 (SD 4.29; P < 0.001), intervention group B mean PEF 310.71 (SD 88.08; P < 0.001) and mean respiratory rate 16.66 (SD 3.19; P < 0.001), control group mean PEF 260.95 (SD 88.08; P < 0.001) and mean respiratory rate 17.80 (SD 4.06; P < 0.007)
Filho 2009 Primary outcome:	There were no reported outcome measures for intubation or mortality
Filho 2009 Secondary outcomes:	A reduction of respiratory rate (P = 0.001), TV (P = 0.01) and MV (P = 0.01), as well as a gain in FEV1 (P = 0.001), FVC (P = 0.001), PEF (P = 0.001) and IC (P = 0.01) in the intervention group compared to the control group were reported. However, no data were available from the published abstract for meta-analysis

ABG: arterial blood gas; EPAP: expiratory positive airway pressure; $FEF_{25-75\%}$: forced expiratory fraction 25-75%; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; IC: inspiratory capacity; ICU: intensive care unit; IPAP: inspiratory positive airway pressure; MV: minute ventilation; NPPV: non-invasive positive pressure ventilation; NS: not significant; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; TV: tidal volume.

Table 3. Summary of intervention effectiveness: primary outcomes

Study ID	Outcome results (comparing intervention to control)	
	Mortality during hospital admission	Intubation
Brandao 2009	-	-
Gupta 2010	No evidence of effect	No evidence of effect

Table 3. Summary of intervention effectiveness: primary outcomes (*Continued*)

Soroksky 2003	No evidence of effect	No evidence of effect
Filho 2009	-	-
De Miranda 2004	-	-

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.

7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

WHAT'S NEW

Last assessed as up-to-date: 19 July 2012.

Date	Event	Description
8 March 2012	New citation required and conclusions have changed	Four new studies identified for inclusion (De Miranda 2004; Brandao 2009; Filho 2009; Gupta 2010) and combined with the single study previously included in the review (Soroksky 2003); manuscript updated; analyses conducted; conclusions changed
8 March 2012	New search has been performed	New literature search run.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 2, 2005

Date	Event	Description
2 July 2008	Amended	Converted to new review format.
10 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Bruce Lim - updated the protocol, reviewed the literature, identified studies for inclusion, extracted data, entered and analysed data, and updated the text of the manuscript.

Redhuan Mohammed Akram - updated the protocol, reviewed the literature, identified studies for inclusion, extracted data, entered and analysed data, and updated the text of the manuscript.

Kristin V Carson - updated the protocol, reviewed the literature, identified studies for inclusion, extracted data, entered and analysed data, updated the text of the manuscript and supervised the update.

Satya Mysore - updated the protocol, reviewed the literature, identified studies for inclusion, extracted data, entered and analysed data, and updated the text of the manuscript.

Nadina A Labiszewski - reviewed the literature and identified studies for inclusion.

Jadwiga A Wedzicha - updated the text of the manuscript.

Brian H Rowe - updated the text of the manuscript.

Brian J Smith - updated the text of the manuscript and supervised the update.

Previous authors: Dr Felix Ram initiated the idea of this review and wrote the protocol and updated the review in May 2005. Sheree Wellington assisted with assessment of studies and data extraction. Brian Rowe was the assigned Cochrane group editor who also helped with the writing up of the review. Jadwiga Wedzicha assisted with manuscript preparation.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

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Internal sources

- Respiratory Medicine Unit; The Queen Elizabeth Hospital, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Asthma [*complications]; Positive-Pressure Respiration [*methods]; Randomized Controlled Trials as Topic; Respiratory Insufficiency [etiology; *therapy]

MeSH check words

Adult; Humans