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[Intervention Review]

Continuous versus intermittent beta-agonists for acute asthma

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ABSTRACT

Background

Patients with acute asthma treated in the emergency department are frequently treated with intermittent inhaled beta-agonists delivered by nebulisation. The use of continuous beta-agonist (CBA) via nebulisation in the emergency setting may offer additional benefits in acute asthma.

Objectives

To determine the efficacy (e.g., reductions in admission, improvement in pulmonary functions) and risks (e.g., adverse events, effects on vital signs) of continuous versus intermittent inhaled beta-agonists for the treatment of patients with acute asthma managed in the emergency department.

Search methods

Randomised controlled trials were identified from the Cochrane Airways Group Specialised Register of trials. In addition, primary authors and content experts were contacted to identify eligible studies. Bibliographies from included studies, known reviews and texts were also searched. The search is considered updated to February 2011.

Selection criteria

Only randomised controlled trials (RCTs) were eligible for inclusion. Studies were included if patients presented with acute asthma and were treated with either continuous or intermittent inhaled beta-agonists early in the ED treatment. "Continuous" nebulisation was defined as truly continuous aerosol delivery of beta-agonist medication (e.g., using a commercially available large-volume nebuliser, or a small-volume nebuliser with infusion pump) or sufficiently frequent nebulisations that medication delivery was effectively continuous (i.e., 1 nebulisation every 15 minutes or > 4 nebulisations per hour). Studies also needed to report either pulmonary function or admission results. Two reviewers independently selected potentially relevant articles and two additional reviewers independently selected articles for inclusion. Methodological quality was independently assessed by two reviewers.

Data collection and analysis

Data were extracted independently by two reviewers if the authors were unable to verify the validity of information. Missing data were obtained from authors or calculated from other data presented in the paper. The data were analysed using the Cochrane Review Manager (Version 4.1). Relative risks (RR), weighted mean differences (WMD) and standardized mean differences (SMD) are reported with corresponding 95% confidence intervals (CI); both peak expiratory flow rates (PEFR) and forced expiratory volume in one second (FEV-1) data are reported.

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Main results

165 trials were reviewed and eight were included; a total of 461 patients have been studied (229 with CBA; 232 with intermittent beta-agonists). Overall, admission to hospital was reduced with CBA compared to intermittent beta-agonists (RR: 0.68; 95% CI: 0.5 to 0.9); patients with severe airway obstruction at presentation appeared to benefit most from this intervention (RR: 0.64; 95% CI: 0.5 to 0.9). Patients receiving CBA demonstrated small but statistically significant improvements in pulmonary function tests when all studies were pooled. Patients receiving CBA had greater improvements in % predicted FEV-1 (SMD: 0.3; 95% CI: 0.03 to 0.5) and PEFR (SMD: 0.33; 95% CI: 0.1 to 0.5); this effect was observed by 2-3 hours. Continuous treatment was generally well tolerated, with no clinically important differences observed in pulse rate (WMD: -2.87; 95% CI: -6.0 to 0.3) or blood pressure (WMD: -1.75; 95% CI: -5.6 to 2.1) between the treatment groups. Tremor was equally common in both groups (OR: 0.81; 95% CI: 0.5 to 1.3) and potassium concentration was unchanged (WMD: 0.02; 95% CI: -0.2 to 0.2).

Authors' conclusions

Current evidence supports the use of CBA in patients with severe acute asthma who present to the emergency department to increase their pulmonary functions and reduce hospitalisation. Moreover, CBA treatment appears to be safe and well tolerated in patients who receive it.

PLAIN LANGUAGE SUMMARY

Continuous versus intermittent beta-agonists for acute asthma

During acute asthma attacks, inhaled beta-agonists (reliever medications) are used to treat spasm in the airways in the lungs. The medication can be administered by wet nebulisation or from an inhaler with a holding chamber; wet nebulisation may be delivered in a continuous or intermittent fashion. This review has collected information from randomised controlled trials comparing continuous to intermittent nebulised delivery methods in acute asthma attacks. Overall, differences were found between the two methods, with continuous nebulisers producing a modest reduction in admissions compared to intermittent beta-agonist therapy. This finding was especially pronounced in severe acute asthma. Continuous nebuliser therapy may be more effective than intermittent nebulisers for delivering beta-agonist drugs to relieve airway spasm in selected asthma populations.

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BACKGROUND

Acute asthma is a common presenting complaint to the emergency department (ED). In the United States, acute asthma accounts for approximately 2 million ED visits per year (Mannino 1998). Approximately 20-30% of these patients will require admission to the hospital; of those discharged from the ED after apparently successful treatment, approximately 10-20% will relapse within two weeks (Camargo 1998). The cost of asthma care is enormous, and care of the acute episode (e.g., emergency department and hospitalizations) represents approximately 25% of all care for this problem (Weiss 2001).

The enormity of asthma as a health care problem worldwide has led to the creation of several national (Boulet 1999; NAEPP 1997; BTS 1997) and international (GINA 2002) asthma guidelines. These guidelines generally include sections that focus care in the acute setting. There is general agreement that beta-agonists, such as albuterol (salbutamol), and corticosteroids, such as prednisone, are first-line agents for acute asthma. Beta-agonists are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. Although both agents are widely used in the acute setting, there remain numerous controversies regarding the appropriate dose, frequency, and route of beta-agonist delivery.

With regard to beta-agonists, most experts (NAEPP 1997; Boulet 1999) suggest that the inhaled route is superior to parenteral routes; this assertion is the focus of another systematic review by the members of the Cochrane Airways Group (Travers 2001). Even among those who contend that inhaled therapy is superior, there are controversies concerning the route of inhaled beta-agonist delivery. A recent systematic review found no material difference in the clinical efficacy of metered-dose inhalers (MDIs) with holding chambers versus wet nebulisers in acute asthma (Cates 2006). Current recommendations suggest that either MDI or nebulisation may be used in acute asthma.

The focus of the present review is the assertion that "continuous" inhaled beta-agonist therapy is more efficacious for acute asthma than the conventional (intermittent) method of beta-agonist delivery (e.g., 2.5 mg albuterol nebulisations every 20-30 minutes, or < or = to 3 nebulisations per hour). Given current practice patterns, the most important comparison is between continuous nebulisation and intermittent nebulisation. Continuous nebulisation may be delivered using commercially-available machines or through nebulisation systems devised locally (e.g., using an infusion pump). Potential advantages of continuous nebulisation include reduced time and labor costs (by obviating multiple refills of the nebuliser) and more consistent medication delivery; the latter feature may allow deeper penetration into the patient's airways and greater reduction of bronchoconstriction. Moreover, continuous nebulisation may result in fewer side effects due to consistent (rather than bolus) beta-agonist delivery.

To date, only a limited number of trials have examined continuous versus intermittent nebulisation and they have yielded inconsistent results. We are aware of one published systematic review on the role of continuous versus intermittent nebulisation in the treatment of acute asthma in the ED (Rodrigo 2002); however, our review includes other recent primary publications, uses Cochrane methods and was designed to further clarify the role of CBA in acute asthma.

OBJECTIVES

The objective of this review was to determine the effect (on pulmonary function, admission, and other outcomes) of treatment with continuous versus intermittent inhaled beta-agonist therapy in the first two hours of ED treatment for acute asthma.

Specific Aims: To quantify the effect of continuous inhaled beta-agonist therapy compared to the effect of these agents given intermittently. The specific outcomes included the effect of different beta-agonist delivery techniques on: (1) pulmonary function (e.g., peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV-1]) (2) admission (e.g., time to decision, % admission). (3) other clinical outcomes (e.g., vital signs, symptom scores, adverse effects). (4) economic endpoints.

METHODS

Criteria for considering studies for this review

Types of studies

To be considered, reported studies had to be randomised controlled clinical trials (RCT). We accepted blinded and unblinded trials, but not cohort or pseudo-randomised trials.

Types of participants

Studies including only patients presenting to an ED or its equivalent were considered for inclusion in the review. If patients from other settings could be removed easily from the study (for example if stratified randomisation was employed) these data were also considered. Studies recruiting either children or adult patients were reviewed and patient age formed one of the subgroup analyses.

Types of interventions

Patients in studies had to be randomised to receive either continuous or intermittent inhaled beta-agonists early in the ED treatment. "Continuous" nebulisation was defined as truly continuous aerosol delivery of beta-agonist medication (e.g., using a commercially available large-volume nebuliser, or a small-volume nebuliser with infusion pump) or sufficiently frequent nebulisations that medication delivery was effectively continuous (i.e., 1 nebulisation every 15 minutes or > 4 nebulisations per hour). Since acute asthmatics require additional treatments (e.g., corticosteroids, ipratropium bromide, magnesium sulfate, etc.) data for any co-interventions were recorded or requested from the authors when not reported in the studies.

Types of outcome measures

Primary outcomes

Change in pulmonary function

Secondary outcomes

1. Admission to the hospital or discharge from ED
2. Other clinical outcomes (e.g., vital signs, symptom scores)
3. Adverse effects (e.g., tremor, nausea, etc).

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4. We searched for results from economic analyses; however, few were identified.

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, 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 (please see the Airways Group Module for further details). The Register contains a variety of studies published in foreign languages, and we did not exclude trials on the basis of language. All records in the Specialised Register coded as 'asthma' were searched using the following terms:

(emerg* or acute or status or sever* or emerg* or exacerbat*) AND ("beta* agonist*" or bronchodilat* or albuterol or salbutamol or ventolin or proventil or metaproterenol or alupent or terbutaline or bricanyl or isoproterenol or epinephrine or adrenaline or isoprenaline or hexoprenaline or reproterol or broxaterol or carbuterol or fenoterol or formeterol or pirbuterol or rimiterol or salmeterol or tolubuterol or *terol)

The most recent serach was conducted in February 2011.

Searching other resources

Additional efforts to locate potential trials were as follows:

1. Reference lists of all available primary studies and review articles were reviewed to identify potentially relevant citations.
2. Inquiries were made regarding other published or unpublished trials known or supported by the authors of the primary studies so that these results could be included in this review.
3. The scientific advisors of the various pharmaceutical companies that manufacture aerosol delivery devices were contacted for any unpublished or interim results on relevant research.
4. Search of CENTRAL was completed using the following terms: asthma AND continuous AND (albuterol OR salbutamol OR ventolin OR proventil OR metaproterenol OR alupent OR terbutaline OR bricanyl).
5. Finally, personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, two reviewers (CAC, BHR) independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text, using specific criteria, two reviewers (CAC, BHR) independently selected trials for inclusion in this review. Inter-rater reliability was measured by using simple agreement and kappa statistics. Disagreement was resolved by consensus or third party adjudication (CHS).

Data extraction and management

Data for the trials were extracted by two reviewers (CAC, BHR) and entered into the Cochrane Collaboration software program (Review Manager). Primary study authors were requested to confirm data extraction and provide additional clarification and information for the review whenever there was a need. In some cases, expansion of graphic representations of data from the manuscripts were used to estimate missing data. All data, numeric calculations and graphic extrapolations were independently confirmed (CHS).

Assessment of risk of bias in included studies

Methodological quality assessment was performed by two reviewers working independently (CAC, BHR). Inter-rater reliability was measured by using simple agreement and kappa statistics. Both reviewers used two approaches to grade quality:

1. Allocation concealment. Using the Cochrane (Shultz 1995) approach to assessment of allocation concealment, all trials were scored and entered using the following principles:
Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment

2. Quality assessment. Quality was assessed using a 5 part score (Jadad 1996) and summarised as follows:
Was the study described as randomised (1=yes; 0=no)
Was the study described as double-blind (1=yes; 0=no)
Was there a description of withdrawals and dropouts (1=yes; 0=no)
Was the method of randomisation well described and appropriate (1=yes; 0=no)
Was the method of double blinding well described and appropriate (1=yes; 0=no)
Points were deducted for either inappropriate randomisation or blinding.

Dealing with missing data

Attempts were made to contact the primary investigators of included studies to obtain individual patient data, however this was largely unsuccessful.

When the standard deviation (SD) for a measure was missing from a study, an estimate was imputed. The estimate was based on the weighted average (by sample size) of the deviations from other included studies for that category. Data from several studies were not reported in tabular format; however, they were demonstrated in charts. To extract these data values the graphs were enlarged and data points were extracted using exact calipers; results were checked for reliability twice. Some graphs and tables displayed a point estimate measure with standard errors of the mean (SEM). SEM's for these trials were converted to SD's thus: SD(Xbar) = SEM(Xbar)*sqrt(n).

Assessment of heterogeneity

For pooled effects, heterogeneity was tested using the Breslow-Day test; in settings where the chi-square heterogeneity statistic revealed a $P < 0.1$, a random effects model was reported. Sensitivity analyses were conducted on fixed vs. random effects models and methodological quality (high vs. low).

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Data synthesis

All trials were combined using the RevMan. For continuous outcomes, individual and pooled statistics were calculated as weighted mean differences (WMD) and 95% confidence intervals (CIs) using a fixed effect model. For dichotomous variables, individual and pooled statistics were calculated as relative risks (RR) with 95% CIs; again, a fixed effect model was used.

Subgroup analysis and investigation of heterogeneity

Three specific subgroups were planned a priori: (a) patient age (adults vs. children); (b) acute asthma severity (severe vs. not severe); and (c) type of continuous nebuliser (commercially available model vs. intermittent nebuliser with infusion pump). A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Description of studies

Results of the search

The original search in 1999 revealed 165 abstracts from trials; all were reviewed and 26 potentially relevant studies were identified (kappa = 1.0). In addition, from the CCTR search, 42 abstracts, and 10 potentially relevant studies were identified (kappa = 0.94). In 2002 an updated search revealed two additional studies (Besbes-Ouanes 2000; Innes 2002). One excluded study has been added to the review from searches between 2002 and 2009. The current systematic review includes Register search updates to February 2011. The 2011 update search returned a potentially eligible abstract and we await publication in full (Rose 2010).

Included studies

All studies were published after 1990; six were from centres in the United States, one each was from Canada and Tunisia. All studies were convenience or consecutive patients from a single centre. Overall, the studies enrolled small samples (range: 22-170 patients) with all but 2 under 100 patients.

Populations: One study enrolled children (Khine 1996), one enrolled a mix of adults and children (Reisner 1995), and 6 enrolled adults only (Colacone 1990; Lin 1993; Rudnitsky 1993; Shrestha 1996; Besbes-Ouanes 2000; Innes 2002). The populations varied from patients with mild-moderate acute asthma (n = 3), to only those with "severe" attacks only (n = 5). Examination of the definitions used to designate the severe group reveals that patients had a combination of clinical findings, airflow measurements, or response to therapy that placed them in the severe category. The unadjusted admission proportion in the placebo group was 40% in the severe group vs. 11% in the mild-moderate group, which serves to partially validate this subgroup designation.

Interventions: Continuous inhaled beta-agonist treatment was administered early in the course of the ED treatment. One study used a small volume nebuliser and by increasing the amount of normal saline lengthened the nebulisation to 20 minutes, thereby creating back-to-back treatments and an effectively continuous nebulisation under these research conditions. The dosage of beta-agonist varied across studies; however, the dose of continuous beta-agonist (CBA) and intermittent beta-agonists administered were equivalent over the course of the studies. The dose in adults ranged from 5 mg to 30 mg and was generally administered over 120 minutes. In the sole pediatric study, children received 15 mg (Khine 1996). The studies lasted from 110 minutes (Lin 1993) to 6 hours (Besbes-Ouanes 2000).

Co-interventions: Co-interventions were reported in all studies. Theophylline administration was not permitted (n = 3) or not reported (n = 3) in most studies. Corticosteroids were routinely administered to all patients in most studies (n = 6; Besbes-Ouanes 2000; Innes 2002; Reisner 1995; Khine 1996; Shrestha 1996), and at the discretion of physicians in older studies (n = 2; Colacone 1990; Lin 1993). Supplemental oxygen was routinely administered in two studies (Besbes-Ouanes 2000; Shrestha 1996). Ipratropium bromide was administered at the discretion of the treating physician in one study (Besbes-Ouanes 2000).

Outcomes: Outcomes were determined at variable times, but usually included a variety of pulmonary function results and admission to hospital or discharge to home. Short-term follow-up (up to 6 hours) was provided in all studies and at intermediate times (up to 24 hours) in several (Innes 2002;) to determine the rate of relapse to additional care. However, the variability of treatment approaches following discharge makes comparisons problematic after discharge. Adverse effects and vital signs were reported frequently enough to permit pooling. There were limited alternative outcomes such as symptom scores and quality of life measure; no economic endpoints were reported.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

A full manuscript was available from each study on which to base quality assessments. Overall, the methodological quality of the included studies was rated as poor. Randomisation was poorly described in most studies. No studies were double-blind and only two were single-blind (Besbes-Ouanes 2000; Reisner 1995); all were controlled. However, few reported clearly on concealment of allocation, and many reported an insufficient number of outcomes. Four studies were rated as "strong" using the Jadad (scores = 3-5) method (Lin 1993; Reisner 1995; Rudnitsky 1993; Besbes-Ouanes 2000), and 4 were rated as "weak" (Colacone 1990; Khine 1996; Shrestha 1996; Innes 2002). Using the Cochrane methodology, 2 studies were rated as blinded allocation (Innes 2002; Besbes-Ouanes 2000) while 5 studies were rated as having unclear allocation (Colacone 1990; Lin 1993; Reisner 1995; Rudnitsky 1993; Shrestha 1996). In one study, allocation was clearly unblinded (Khine 1996).

Effects of interventions

Results from this meta-analysis are reported by outcome. The main results are reported as overall effects of continuous vs. intermittent inhaled beta-agonist. In addition, the main subgroup based on asthma severity is also reported.

ED Pulmonary Function Results

A variety of short-term pulmonary function tests were reported in the included trials. Most commonly, PEFR and FEV-1 were reported at the completion of the trial (or as close to 6 hours as possible). Patients receiving CBA demonstrated significant improvements in PEFR (SMD = 0.33; 95% CI: 0.1 to 0.5, Figure 1), absolute FEV-1 (WMD = 0.37; 95% CI: 0.1 to 0.6), and % predicted FEV-1 (WMD

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= 0.28; 95% CI: 0.03 to 0.5) when all studies were pooled (Figure 2). No statistically significant heterogeneity was identified for the results when all studies were pooled using PEFR (P= 0.57), FEV-1 (P = 0.61) or % predicted FEV-1 (P = 0.45). Insufficient information was available to dissect these data to examine response based on severity of disease at presentation.

Figure 1. Absolute PEFR values (end of study)

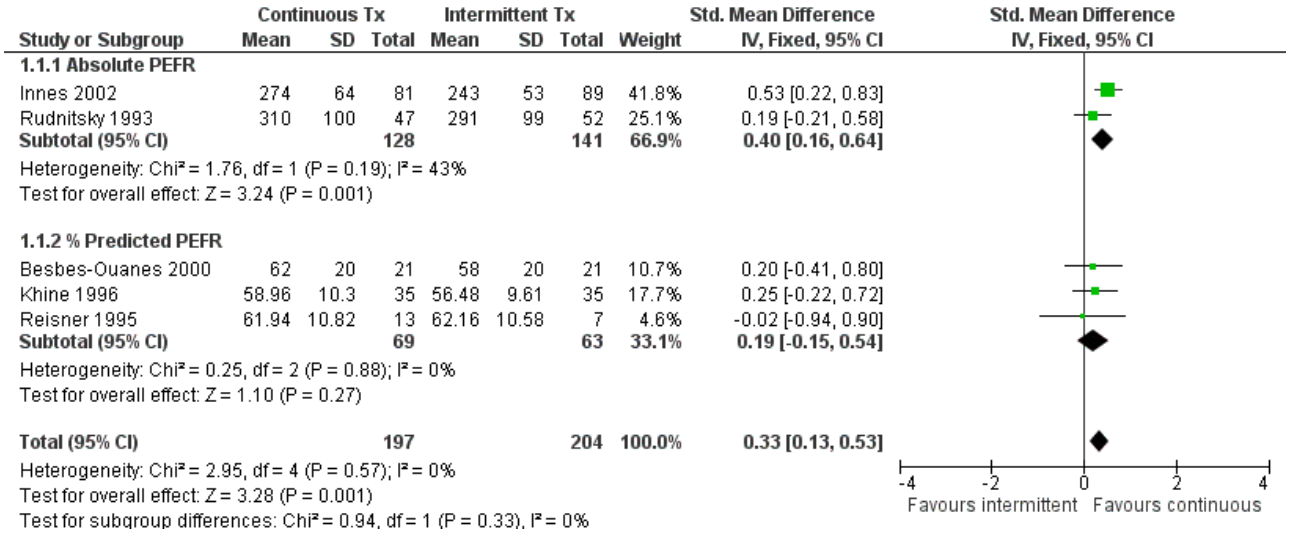
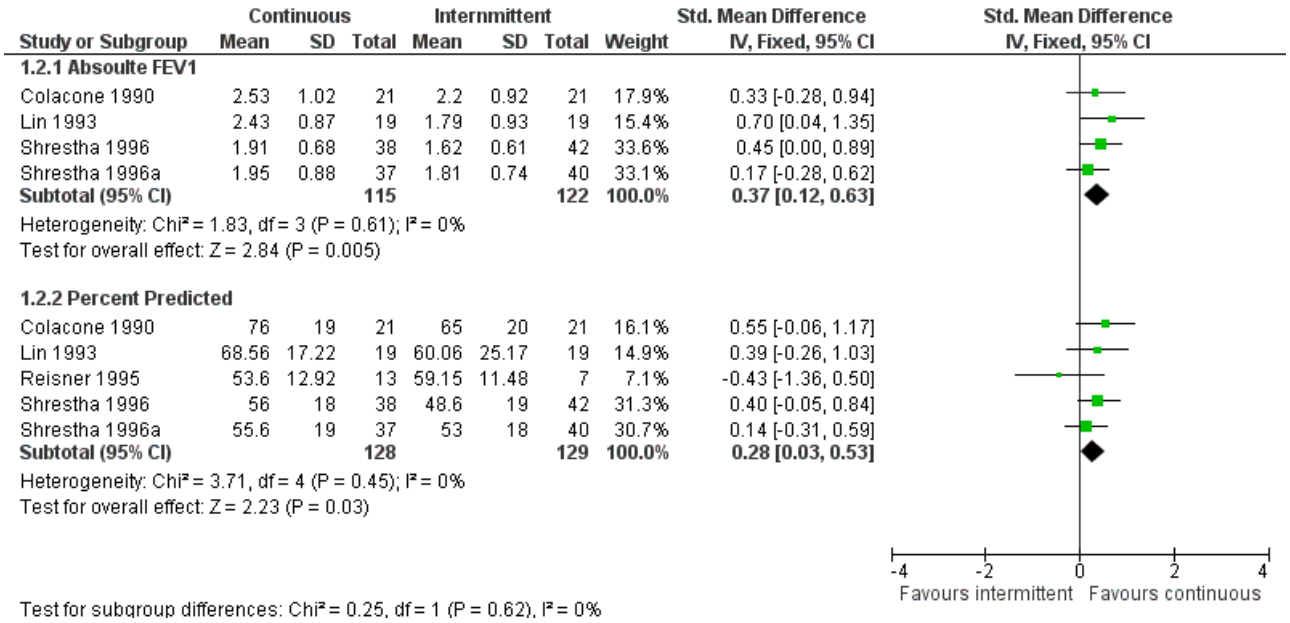


Figure 2. Absolute FEV1 values (end of study)



Time course of ED Pulmonary Function Improvements

Sufficient information was available to examine the time course for the changes observed at the end of the trial period reported above. In the first 60 minutes, differences between CBA and intermittent treatment were not obvious in PEFR (SMD: 0.14; 95% CI: -0.05 to 0.3) and were small when FEV-1 was reported (SMD: 0.30; 95% CI: 0.05 to 0.5). By 2-3 hours, the difference was significant in both measures, favouring treatment with CBA (PEFR SMD: 0.37; 95% CI: 0.2 to 0.6; FEV-1 SMD: 0.33; 95% CI: 0.1 to 0.6). There were a limited number of studies (n = 3) which reported times beyond 4 hours, making results from this group less reliable. Nonetheless, the PEFR and FEV-1 SMDs were insignificant at 4-6 hours.

Admission to Hospital

A significant difference was identified between patients treated with CBA vs. intermittent beta-agonist with respect to hospital admission at the end of the study period (RR: 0.68; 95% CI: 0.5 to 0.9). This result was similar if they were displayed as a odds ratio (OR: 0.57; 95% CI: 0.4 to 0.9) or number needed to treat (NNT: 10; 95% CI: 6, 34). This pooled result demonstrated no significant heterogeneity (chi square = 5.6; df = 7; P = 0.58). There

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was no apparent difference in hospitalisation for the studies where participants had mild-moderate asthma (RR: 1.12; 95% CI: 0.4 to 2.9); however, the confidence intervals are wide and the sample is small. Patients with severe asthma had fewer hospital admissions when treated with CBA (RR: 0.64; 95% CI: 0.5 to 0.9). This pooled result did not demonstrate significant heterogeneity (chi square = 2.95; df = 4; P = 0.56).

Tolerability

Vital signs were recorded and reported in many of the included studies; pooled results did not demonstrate statistical or clinical heterogeneity. Continuous treatment was generally well tolerated, with no clinically important differences observed in pulse rate (WMD: -2.87; 95% CI: -6.1 to 0.3) or respiratory rate (WMD: 1.00; 95% CI: -1.6 to 3.6) between the treatment groups. Systolic blood pressure was similar in both groups (WMD: -1.75; 95% CI: -6.6 to 2.1); however, this result demonstrated heterogeneity and is reported using a random effects model. Overall, vital signs remained "stable" during the period immediately after treatment with CBA.

Side Effects

Some side effect monitoring was common in these studies, but comprehensive lists of adverse events were rarely reported. CBA appears to be a safe treatment approach for acute asthma; general adverse events were similarly rare across multiple trials (WMD = 0.2; 95% CI: 0.03 to 1.6). Four trials (n = 307 patients) reported tremor as a specific side effect; pooled results failed to demonstrate differences between treatment groups (RR: 0.81; 95% CI: 0.5 to 1.3). Nausea and palpitations were reported in only one trial each; however, in both cases, these side effects were more common in the intermittent beta-agonists group than the CBA group. Potassium concentrations were reported in 3 trials and pooled results failed to demonstrate differences between treatment groups (WMD: 0.02; 95% CI: -0.2 to 0.2). However, an insufficient number of studies were available to provide meaningful sensitivity or sub-group comparisons, or firm conclusions about side effects or adverse events.

Subgroup/Sensitivity Analyses

Due to an insufficient number of paediatric trials, a subgroup analysis based on age was not possible. The random (RE) and fixed effects (FE) models did not affect reported results; especially for the admission data where sufficient trials reported this outcome (FE RR: 0.68; 95% CI: 0.5 to 0.9 vs RE RR: 0.69; 95% CI: 0.5 to 0.9). Higher severity at initial presentation appeared to increase the response to CBA (RR: 0.64; 95% CI: 0.5 to 0.9). Finally, study quality was not found to influence pooled results for admissions. With all trials included in the analysis the OR = 0.57 (95% CI: 0.34 to 0.9) compared to OR = 0.55 (95% CI: 0.4 to 0.9) when the weakest trials were excluded.

DISCUSSION

This systematic review examined the use of continuous nebulised beta-agonists in the ED management of acute asthma. The pooled results demonstrate a modest (effect size = 0.3), yet statistically significant beneficial effect of CBA in terms of pulmonary functions by 2-3 hours of therapy. The clinical significance of the magnitude of this pulmonary function improvement is difficult to determine, since the minimally clinically important difference for pulmonary functions in acute asthma have been infrequently studied. However, in chronic asthma an improvement of 12% predicted has been used (NAEPP 1997) and for acute studies, some have suggested an increase in PEFR of 30 L/min is clinically important (Tiffany 1993). The improvement of approximately 10% predicted FEV-1 or 50 L/min PEFR represent what we believe are important PF changes, especially considering the severity at the start of therapy. Moreover, these PFT changes appear important enough to reduce admissions. The effect of CBA can be restated using NNT as follows: 10 patients would have to receive CBA to prevent 1 admission to hospital, compared to intermittent beta-agonist nebulisation.

While the CBA delivery was well tolerated, with good efficacy in patients with severe asthma, its possible expense compared to other therapies and its more complex nature argues against its indiscriminate use in the emergency department treatment of acute asthma. Despite the lack of cost data, changing treatment approaches across EDs for all patients would not be appropriate; however, there is considerable evidence to suggest that the sub-group of patients presenting with severe acute asthma respond differently to the use of CBA. Patients who presented with severe asthma benefit from the use of CBA, both in terms of pulmonary functions and admission rates.

LIMITATIONS

There is a possibility of publication bias in this meta-analysis. For example, by missing unpublished negative trials we may be over-estimating the efficacy of CBA treatment. However, a comprehensive search of the published literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. This was followed by attempts to contact corresponding and first authors. No unpublished trial was identified; however, several negative trials were uncovered. While we recognise that more of these types of trials may exist, the funnel plot for admission provide some additional reassurance that publication bias was not a threat to the conclusions reported here.

There is also a possibility of study selection bias. However, we employed two independent reviewers, and feel confident that the studies excluded were done so for consistent and appropriate reasons. Our search was comprehensive and has been updated, so it is unlikely that there are any trials in publication which were missed.

Finally, these results are discordant from the results presented in a published systematic review (Rodrigo 2002). These authors claimed equivalence of CBA and such a claim is difficult to understand given the wide confidence intervals and small number of trials they presented. Such evidence does not demonstrate "equivalence"; rather, it supports the conclusion of a "lack of evidence of benefit" for the treatment. Our systematic review included more studies (8 vs 6) and this may explain the benefit demonstrated here with respect to admissions (RR: 0.69; 95% CI: 0.52 to 0.93). This result is compared to the reported "equivalence" (RR = 0.68; 95% CI: 0.33 to 1.38) by the earlier review (Rodrigo 2002).

AUTHORS' CONCLUSIONS

Implications for practice

- Most patients who present for assessment and treatment with an asthmatic exacerbation do not benefit from early treatment with CBA compared to intermittent beta-agonists in the emergency department.

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- In patients with "severe" acute asthma, benefits (e.g. pulmonary function improvements, reduced admissions) from treatment with CBA were observed. A practical clinical approach may be to identify those patients who fail to respond to initial beta-agonists or who have severe airflow limitations in the ED as being candidates for CBA therapy.
- In addition to the CBA intervention, standard acute asthma therapy must be administered to these patients early in the ED treatment (including corticosteroids, oxygen, ipratropium bromide, etc.).
- In this review, CBA nebulisation was provided as 5-15 mg over the first hour in adults, with lower doses in children.
- Only 1 study was identified which examined the use of CBA in children. Given the small numbers involved in this study, readers should be cautious when extrapolating results to children, especially the very young.

Implications for research

Many questions regarding the treatment of acute asthma with CBA remain unanswered.

- Additional research is required to determine the optimal dose (high vs low) and duration of therapy.
- Additional studies are needed to confirm the sub-group findings from this review suggesting a beneficial effect of CBA in severe acute asthma. In future studies, severity must be clearly defined and based on presenting pulmonary function results AND response to initial beta-agonist therapy whenever possible.
- Studies involving very young children need to be performed to determine the effect of CBA in this age group.
- Future research should examine the effect of CBA while maximising the use of known effective co-intervention therapies in acute asthma (e.g., systemic corticosteroids, inhaled corticosteroids, IV MgSO4, ipratropium bromide, etc). The effect of CBA treatment may differ based on administration of these therapies.
- Future research on acute asthma must concentrate on well defined outcomes which may lead to more informative reviews in the future. More specifically, criteria for admission/discharge and reporting of pulmonary function data in a systematic fashion would assist in further work. Finally, better description of the methodology would also be beneficial.

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CHARACTERISTICS OF STUDIES

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

Besbes-Ouanes 2000

Methods	Design: RCT. Method of randomisation: random numbers table, opaque envelopes. Blinding: patients and treating MDs blind to treatment. Objective: Safety & efficacy of continuous salbutamol in ED tx of acute adult asthma. Withdrawals: none described Baseline: groups similar at the start of the study.
Participants	Location: one hospital ED, Tunisia. Recruitment: consecutive eligible pts. Sample size: 42 (CN=21, IN =21) Age: "adults" Gender: 60% Female. Inclusion: Dx asthma - clinical definition; < 50% predicted PEFR plus 2 or more of: PR > 119/min, RR> 29/min, pulsus paradoxicus > 14, accessory muscle use, SaO2 < 92%, hypercapnia (>42 mm Hg). Exclusion: chronic cough, cardiac or hepatic disease, or pregnancy. Severity: moderate-severe asthma.
Interventions	Duration: 6 hrs. Intervention: Control: intermittent salbutamol 5mg q 20 minutes in 1st hour, then 2.5 mg hourly afterwards via pneumatic nebulization. Total given in 6 hrs = 27.5 mg salbutamol. CBA: salbutamol 15mg over 1st hour, repeated 2.5 mg/hr for 5 hours via continuous pneumatic nebulizer. Total given in 6 hrs = 27.5 mg salbutamol. Co-intervention: 200 mg IV hydrocortisone q4 hrs and oxygen at 6 L/min for all pts.
Outcomes	Outcomes reported: Admission (to ICU or floor). Clinical: 5-component scale. PEFR: at 0. 40 min, 1, 3 and 6 hours. Vital signs: PR, BP@ 60 & 120 min ADR: Potassium levels and ECG at 0 and 6 hrs. Arrhythmias (continuous monitoring) reported.
Notes	Jadad Score: 3 Patients had to reach a set of criteria at 6 hours to achieve admission.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random numbers table
Allocation concealment?	Low risk	Opaque envelopes.

Colacone 1990

Methods	Design: RCT. Method of randomisation: N/D Objective: Safety & efficacy of continuous albuterol in ED tx of acute adult asthma. Withdrawals: 4/46, described

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Colacone 1990 *(Continued)*

	Baseline: BN group lower FEV1 values P=0.06) otherwise similar
Participants	Location: General Hospital ED, Montreal, Canada. Recruitment: consecutive eligible pts. Sample size: 46 (CN=21, IN =21) Age: > 18 Gender: 22M, 20F Inclusion: Dx asthma - ATS criteria, Exclusion: comorbidity: pneumonia, heart disease, diabetes, pregnant or nursing women Severity: not described
Interventions	Duration: 2 hr. Intervention: Control: intermittent (BN)- albuterol 5.0mg (1.0mg diluted in 2.0mg saline) at time 0 & 1 hr. via face-mask & Airlife-Misty Neb., 100% O2 at 8L/min x 10-15 min. Total given in 2 hrs = 10mg albuterol . CBA: albuterol 100mg (20ml) in 480 ml saline continuously via facemask & Jet neb, O2 5-8 L/min. Total given in 2 hrs ˜ 10.07 +- 0.52mg albuterol . Co-intervention: only IV aminophylline &/or corticosteroids allowed.
Outcomes	Outcomes reported: FEV1: absolute values 0-120 min, % predicted 0-120 min Vital signs: PR, RR, BP@30, 60, 90, 120 min ADR: Tremor
Notes	Jadad Score: 2 Statistical issues: End of trial % predicted PFT calculated & adjusted for baseline differences. Used baseline SD Author contact: ADRs: none noted

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Information not available
Allocation concealment?	Unclear risk	Information not available

Innes 2002

Methods	Design: RCT. Method of randomisation: N/D Objective: Safety & efficacy of continuous albuterol in ED tx of acute adult asthma. Withdrawals: not well described Baseline: groups similar at the start of the study
Participants	Location: Two Hospital EDs, Ipswich, UK. Recruitment: consecutive eligible pts. Sample size: 170 CN=81, IN =89 Age: 18-64 Gender: 56% Female. Inclusion: Dx asthma - clinical definition; < or = to 75% predicted PEFR. Exclusion: comorbidity: pregnancy, lung pathology, heart disease or arrhythmia, diabetes, status asthmaticus.

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Innes 2002 *(Continued)*

	Severity: not described
Interventions	Duration: 2 hr. Intervention: Control: Oral prednisolone 40 mg; intermittent salbutamol 5.0mg (@ time 0) and 30 minutes) then q4 hourly nebulization. Total given in 2 hrs = 10 mg salbutamol. CBA: 60 mg oral prednisolone. Salbutamol 10mg over 1 hour, repeated over the second hour continuously via nebulizer. Total given in 2 hrs ~ 20 mg albuterol . Co-intervention: ipratropium bromide and IV beta-agonists were allowed.
Outcomes	Outcomes reported: Admission, relapse if discharged, and length of stay is admitted. PEFR: change at 1 and 2 hours Vital signs: PR, BP@ 60 & 120 min ADR: Potassium levels and arrhythmias
Notes	Jadad Score: 2 This study had an in-patient component; however, we only examined the 2 hours data for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised by blocking
Allocation concealment?	Low risk	'sequential opaque sealed envelopes in which treatment allocation had been predetermined (...) by a statistician (EB) unconnected to the study.'

Khine 1996

Methods	Design: RCT, SB (treating physician). Method of randomisation: block (poorly reported). Objective: Safety & efficacy of continuous albuterol in ED tx of acute asthma in children Withdrawals: 3/73 were excluded. Baseline groups similar.
Participants	Location: Pediatric ED, Philadelphia, USA. Recruitment: children presenting to ED with mod - severe asthma exacerbation. Sample size: 70 CN =35, IN =35 Age: ages 2-18, mean = 7.6 y (SD 4). Gender: 52 M, 18 F Inclusion: At least 1 prior episode of wheezing Exclusion: hypersensitivity to albuterol, pre-existing diagnosis with congenital heart disease, BPD, CF, sickle-cell disease, possible foreign body aspiration, corticosteroid therapy in the past 6 hours, use of subQ epinephrine in preceding 20 min., concurrent stridor & wheeze, +ve RSV culture. Severity: clinical asthma score >=8
Interventions	All received corticosteroids at entry. Intervention: Control: Control: albuterol 0.15 mg/kg/dose (minimum of 2.5 mg/dose and a maximum of 7.5 mg/dose) q 30 min. Total dose /hr over 2 hours equivalent in both groups. Maximum of 2 hours of treatment and 30 minutes of observation. CBA: albuterol 0.3 mg/kg/hr (minimum 5 mg/hr, maximum 15mg/hr) achieved using facemask & HEART nebulizer

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Khine 1996 *(Continued)*

	Co-intervention: oral or intravenous corticosteroid. O2 via neb if pulse symmetry showed hypoxemia. Theophylline allowed.
Outcomes	Outcomes reported: PEF: % mean change Admission to hospital: criteria - persistent asthma score >=8 and/or oxygen saturation <94% on room air. Assessed independently by physician and investigator. Vital signs: PR, RR, BP. Mean increase ADR: tremor and vomiting Timing: time in ED
Notes	Jadad Score: 2 Statistical issues: no baseline data to compute end of trial results Author contact:

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised by blocks.
Allocation concealment?	High risk	Single-blind study; respiratory therapist administered treatment from behind curtain.

Lin 1993

Methods	Design: RCT, Method of randomisation: Computer generated pseudo-random numbers. Blinding: non-blinded. Objective: Safety & efficacy of continuous vs intermittent albuterol in ED tx of acute adult asthma exacerbation. Withdrawals: none Baseline groups similar.
Participants	Location: Public hospital ED, New York, USA. Recruitment: volunteers Sample size: 38 CN=19, IN=19 Age: 40.2 (SD 13.7) Gender: 20M, 18F Inclusion: Dx of asthma by ATS criteria, smoked < 20 pack yr of cigarettes, >=18yr. Severity: males with PEFR <300 L/min., females with PEFRs <250 L/min, pulse rate <=180 per min,BP <= 180/100 mm mercury. Exclusion: Symptomatic angina pectorus or atherosclerotic heart disease, pregnancy,
Interventions	Intervention: Control: albuterol 5mg/ml (1ml in 2 ml saline) over 10 min. q 20 min. x 6 tx periods via facemask & standard acorn-type jet neb. Delivered by pressurized O2 at 6-8 L/min. CBA: albuterol 5MG/ML (6 ml in 34 ml saline) via facemask & HEART system. Delivered by pressurized O2 at 10 L/min. Both groups received 30 mg of albuterol over 110 min. Co-intervention: Corticosteroids allowed. Aminophylline not allowed.
Outcomes	Outcomes reported: FEV1: % predicted, absolute values 0 -110 min Admission to hospital: no criteria applied. Vital signs: PR.

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Lin 1993 *(Continued)*

	ADRs: tremor, palpitations, agitation, headache.
Notes	Jadad Score: 3 Statistical issues: 1 pt in CN recommended for admission but refused. Included as an admission. Author contact: Correspondence pending from the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated pseudo-random numbers
Allocation concealment?	Unclear risk	Information not available

Reisner 1995

Methods	Design: RCT, SB (MD reading spirometry & ECG tracings) Method of randomisation: N/D Objective: Safety & efficacy of high dose CN neb albuterol vs high dose IN neb albuterol over 4 hrs Withdrawals: 2/22. 1 pt from each group.
Participants	Location: ED Danbury, Conneticut, USA. Recruitment: adult asthmatics with acute asthma Sample size: 22 CN=14, IN=8 Age: mean 34.5 y (SD 15) Gender: 5M, 15F Inclusion: between 10-65 yr., PEFR less than 60% predicted. Exclusions: Fever > 100 F, >10-pack year history of smoking. Pregnant or nursing mothers, women in child-bearing age. Intolerance to beta-agonists: co-morbid renal, cardiovascular, endocrine, hepatic, metabolic, neurologic or systemic disease prior to participation in this study.
Interventions	Intervention: Control: 2.5 mg albuterol at time zero then q 20 min. x 4 hrs. Total= 30 mg in 12 Tx periods. The solution was administered via an Airlife Misty Nebulizer driven by 100% at a flow rate of 8 L/min. CBA: 30 mg albuterol over 4 hours using a Travenol volumetric infusion pump. Nebulizer was driven by 100% oxygen at 8 L/ min. Co-intervention: All received intravenous 125 mg of methyl- prednisolone on start of the study. No aminophylline.
Outcomes	Outcomes reported: PEF, FEV-1: % change 0-240 min. Vital signs: PR, RR, BP @ 240 min.
Notes	Jadad Score: 3 Statistical issues: Calculated end of trial result % predicted from % change scores. Used baseline SD. 1 pt (IN) recommended for admission but refused. Included as an admission. Author contact: Pending author response. ADR: 1 pt had abdominal pain, Tx group not specified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available

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Reisner 1995 *(Continued)*

Allocation concealment?	Unclear risk	Information not available

Rudnitsky 1993

Methods	Design: RCT, non-blinded Method of randomisation: block in groups of 10 Objective: Safety & efficacy of continuous vs intermittent albuterol in ED tx of acute adult asthma exacerbation. Withdrawals: 8. 4= >1 enrolment, 4 lost to follow-up.
Participants	Location: ED Philadelphia, USA. Recruitment: Consecutive eligible pts. Sample size: 99. 47= CN, 52= IN. Age: mean 35.5 y (SD14.5) Gender: 30M, 69F Inclusion: Adults with an acute exacerbation of asthma (ATS criteria), & a non-response to one tx of 2.5 mg neb albuterol Exclusion: COPD, T > 38.3C, evidence of pneumonia, heart failure, renal failure, pregnancy. Severity: no severity rating.
Interventions	Intervention: Control: 2.5 mg albuterol in 3ml saline via neb at time zero, 30, 60, 90 and 120 min. CBA: 10 mg albuterol in 70 ml saline via Vortran Heart Nebulizer Co-intervention: All received 2.5 mg neb albuterol and 125 mg of IV methylprednisolone. No other meds allowed.
Outcomes	Outcomes reported: Clinical Scoring: official index at 120 minutes. Hospital Admission PEFR: absolute & SD @ 0, 30, 60, 90, 120 min. Vital signs: PR
Notes	Jadad Score: 3 Statistical issues: none Author contact: Authors response still pending.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Described as randomised by blocking groups of 10
Allocation concealment?	Unclear risk	Information not available

Rudnitsky 1993a

Methods	Results from severe cases
Participants	
Interventions	
Outcomes	

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Rudnitsky 1993a *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	As for Rudnitsky 1993
Allocation concealment?	Unclear risk	As for Rudnitsky 1993

Shrestha 1996

Methods	Design: RCT, DB Method of randomisation: N/D Objective: Safety & efficacy of high & low dose albuterol via CN & IN. Withdrawals: none mentioned Standard values
Participants	Location: ED, U of Texas Medical Centre. USA Recruitment: Sample size: 157. CN: hi-dose =37, Std-dose =38, IN: hi-dose = 40, std-dose = 42 Age: mean 34.4 (SD 10.6) Gender: 77 M, 80 F Inclusion: Dx acute asthma: FEV1 < 40% predicted, Dx < 45 yrs.old, age =>=18, Exclusion: not pregnant, nursing or incarcerated, no Hx of allergy to albuterol, English speaking.
Interventions	4 groups Tx x 4 hr. Intervention: Control: hi-dose: 7.5 mg q 1h (1.5 ml in 1.5 ml saline) @ 6 L/min. Control standard: 2.5 mg q 1h (0.5 ml in 2.5 ml saline). CBA: hi-dose: 7.5 mg/h albuterol (1.5 ml in 13.5 ml saline) CBA standard: 2.5 mg/h (0.5 ml in 14.5 ml saline) via Airlife Misty-neb @ 6L/min Co-intervention: O2 if O2 sat < 92%
Outcomes	Outcomes reported: FEV1: absolute, % predicted, % change @ 1 & 2 hr.
Notes	Jadad Score: 2 Statistical issues: Author contact:

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

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Shrestha 1996a

Methods	See Shrestha 1996 High dose-values
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	As for Shrestha 1996
Allocation concealment?	Unclear risk	As for Shrestha 1996

RCT = Randomised Control trial
DB = double blind
neb=nebuliser or nebulisation
N/D = not described
IN=intermittent nebulisation
CBA=continuous nebulisation
ADR = adverse reactions
PEF =Peak expiry flow
FEV1= forced expiratory flow in one second

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

Study	Reason for exclusion
Andrews 2007	Comparison of continuous racemic versus continuous levalbuterol.
Levitt 1995	Continuous nebulization vs continuous metered dose inhaler with spacer in acute dyspnea. Mixed patient groups of COPD and asthma.
Moler 1988	Case series; not a randomized controlled trial and has no control group.
Moler 1995	In-patient study of children with continuous agents delivered over 8 hours and more.
Nelson 1990	No continuous arm of the trial; comparison of single to multiple doses.
Oshlaker 1993	No control group; not a randomized controlled trial.
Papo 1993	In-patient study of pediatric patients admitted to the intensive care unit.
Portney 1988	Case series; not a randomized controlled trial and has no controls.
Portney 1992	Review article.
Schuh 1989	High vs low dose "frequently" administered albuterol (not "continuous" vs intermittent)

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Study	Reason for exclusion
Stein 2003	Both groups received continuous nebulization.
Weber 1999	Continuous nebulization of albuterol plus ipratropium bromide compared to albuterol alone.

COPD = chronic obstructive pulmonary disease;

DATA AND ANALYSES

Comparison 1. Continuous vs intermittent nebulisation (end of study)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PEFR values (end of study)	5	401	Std. Mean Difference (IV, Fixed, 95% CI)	0.33 [0.13, 0.53]
1.1 Absolute PEFR	2	269	Std. Mean Difference (IV, Fixed, 95% CI)	0.40 [0.16, 0.64]
1.2 % Predicted PEFR	3	132	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.15, 0.54]
2 FEV1 values (end of study)	5		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Absoulte FEV1	4	237	Std. Mean Difference (IV, Fixed, 95% CI)	0.37 [0.12, 0.63]
2.2 Percent Predicted	5	257	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [0.03, 0.53]
3 Admission to hospital (end of observation period)	6	461	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.92]
3.1 Moderate-severe	5	341	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.87]
3.2 Less severe	3	120	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.44, 2.85]
4 Adverse effects	4	292	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.55]
5 ED treatment time	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Respiratory therapist time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Symptom scores	2	112	Std. Mean Difference (IV, Fixed, 95% CI)	0.43 [0.05, 0.81]
8 Potassium concentration	3	206	Mean Difference (IV, Random, 95% CI)	0.02 [-0.16, 0.19]
9 Pulse rate	5	373	Mean Difference (IV, Fixed, 95% CI)	-2.87 [-6.07, 0.34]

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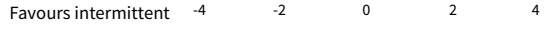
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Respiratory rate (end of study)	2	62	Mean Difference (IV, Fixed, 95% CI)	1.0 [-1.55, 3.55]
11 Blood pressure (end of study)	2	212	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-5.55, 2.05]
12 Tremor	5	307	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.51, 1.28]
13 Palpitations	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14 Nausea/vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

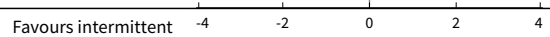
Analysis 1.1. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 1 PEFR values (end of study).

Study or subgroup	Continuous Tx N	Continuous Tx Mean(SD)	Intermittent Tx N	Intermittent Tx Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.1.1 Absolute PEFR							
Innes 2002	81	274 (64)	89	243 (53)		41.84%	0.53[0.22,0.83]
Rudnitsky 1993	47	310 (100)	52	291 (99)		25.11%	0.19[-0.21,0.58]
Subtotal ***	**128**		**141**			**66.94%**	**0.4[0.16,0.64]**
Heterogeneity: Tau^2=0; Chi^2=1.76, df=1(P=0.19); I^2=43.02%							
Test for overall effect: Z=3.24(P=0)							
1.1.2 % Predicted PEFR							
Besbes-Ouanes 2000	21	62 (20)	21	58 (20)		10.67%	0.2[-0.41,0.8]
Khine 1996	35	59 (10.3)	35	56.5 (9.6)		17.74%	0.25[-0.22,0.72]
Reisner 1995	13	61.9 (10.8)	7	62.2 (10.6)		4.65%	-0.02[-0.94,0.9]
Subtotal ***	**69**		**63**			**33.06%**	**0.19[-0.15,0.54]**
Heterogeneity: Tau^2=0; Chi^2=0.25, df=2(P=0.88); I^2=0%							
Test for overall effect: Z=1.1(P=0.27)							
Total ***	**197**		**204**			**100%**	**0.33[0.13,0.53]**
Heterogeneity: Tau^2=0; Chi^2=2.95, df=4(P=0.57); I^2=0%							
Test for overall effect: Z=3.28(P=0)							
Test for subgroup differences: Chi^2=0.94, df=1 (P=0.33), I^2=0%							



Analysis 1.2. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 2 FEV1 values (end of study).

Study or subgroup	Continuous N	Continuous Mean(SD)	Internmittent N	Internmittent Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.2.1 Absoulte FEV1							
Colacone 1990	21	2.5 (1)	21	2.2 (0.9)		17.88%	0.33[-0.28,0.94]
Lin 1993	19	2.4 (0.9)	19	1.8 (0.9)		15.39%	0.7[0.04,1.35]



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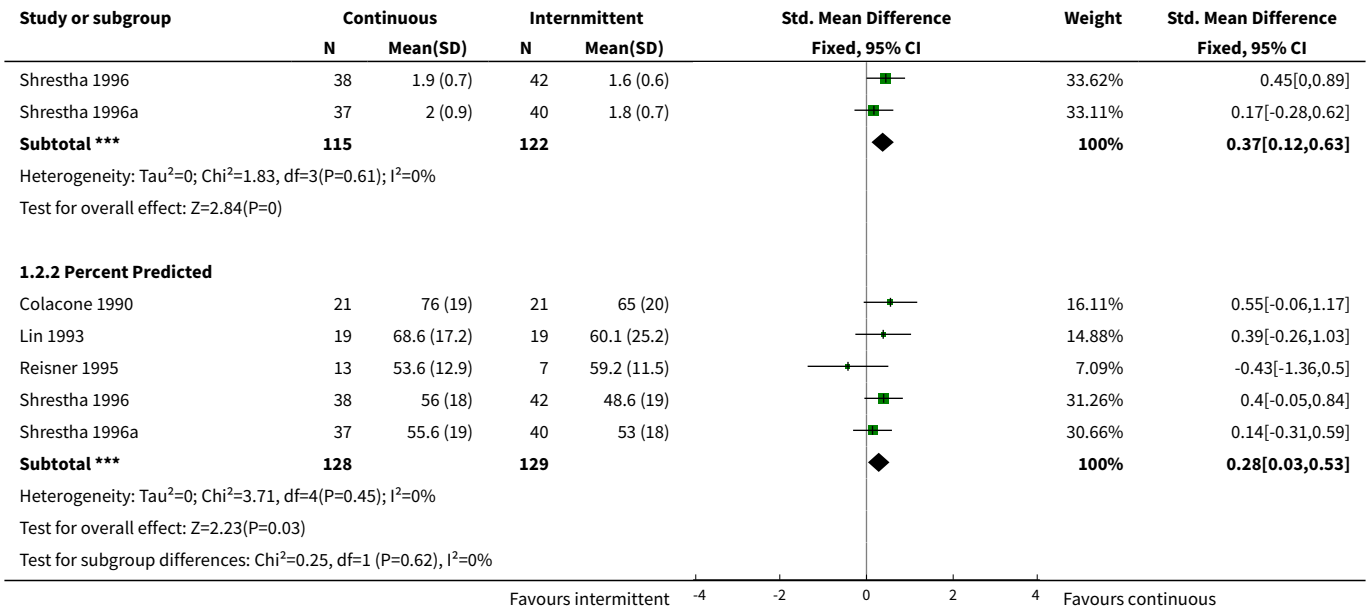
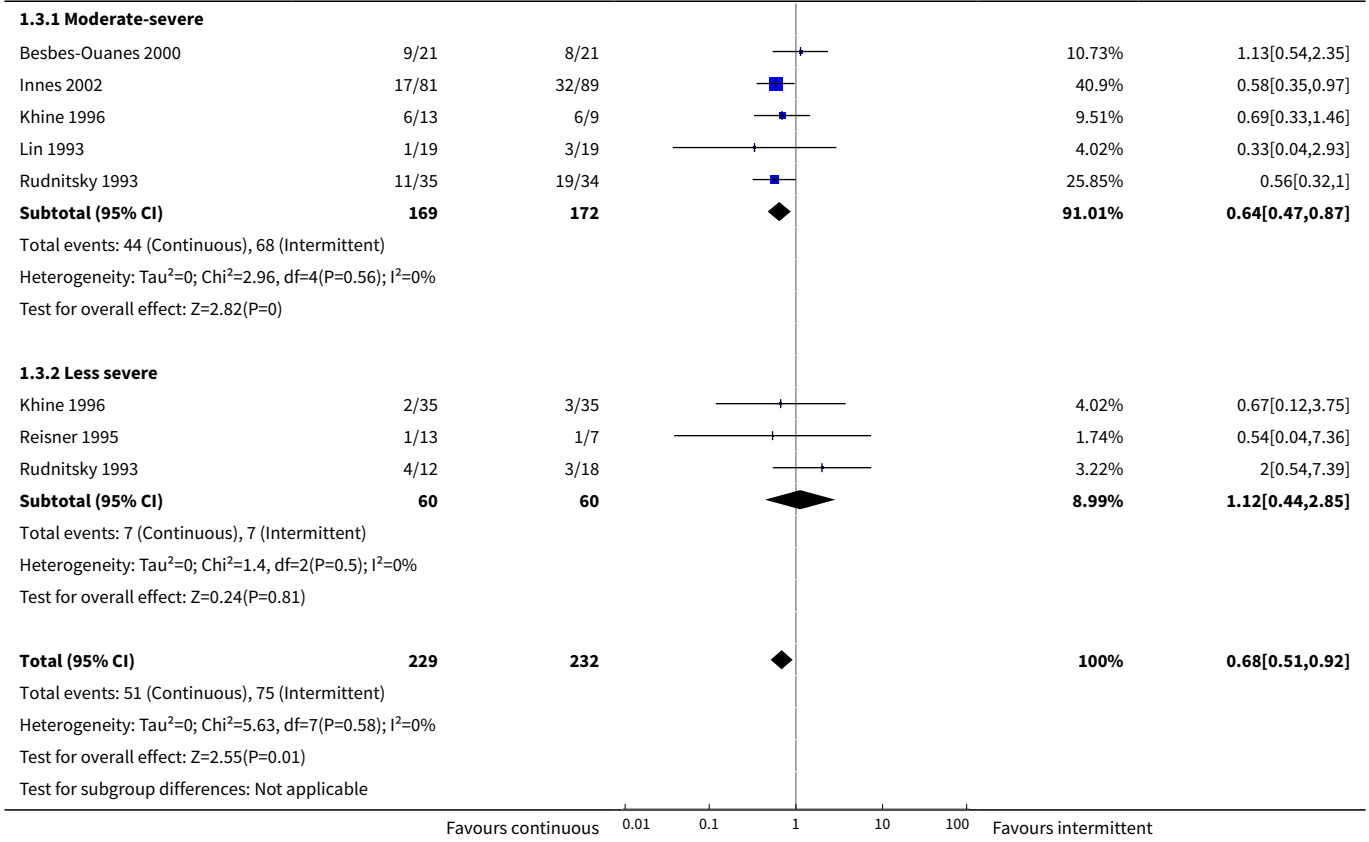


Study or subgroup	Continuous N	Continuous Mean(SD)	Internmittent N	Internmittent Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Shrestha 1996	38	1.9 (0.7)	42	1.6 (0.6)		33.62%	0.45[0,0.89]
Shrestha 1996a	37	2 (0.9)	40	1.8 (0.7)		33.11%	0.17[-0.28,0.62]
Subtotal ***	**115**		**122**			**100%**	**0.37[0.12,0.63]**
Heterogeneity: Tau²=0; Chi²=1.83, df=3(P=0.61); I²=0%							
Test for overall effect: Z=2.84(P=0)							
1.2.2 Percent Predicted							
Colacone 1990	21	76 (19)	21	65 (20)		16.11%	0.55[-0.06,1.17]
Lin 1993	19	68.6 (17.2)	19	60.1 (25.2)		14.88%	0.39[-0.26,1.03]
Reisner 1995	13	53.6 (12.9)	7	59.2 (11.5)		7.09%	-0.43[-1.36,0.5]
Shrestha 1996	38	56 (18)	42	48.6 (19)		31.26%	0.4[-0.05,0.84]
Shrestha 1996a	37	55.6 (19)	40	53 (18)		30.66%	0.14[-0.31,0.59]
Subtotal ***	**128**		**129**			**100%**	**0.28[0.03,0.53]**
Heterogeneity: Tau²=0; Chi²=3.71, df=4(P=0.45); I²=0%							
Test for overall effect: Z=2.23(P=0.03)							
Test for subgroup differences: Chi²=0.25, df=1 (P=0.62), I²=0%							

Analysis 1.3. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 3 Admission to hospital (end of observation period).



Study or subgroup	Continuous n/N	Intermittent n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Moderate-severe					
Besbes-Ouanes 2000	9/21	8/21		10.73%	1.13[0.54,2.35]
Innes 2002	17/81	32/89		40.9%	0.58[0.35,0.97]
Khine 1996	6/13	6/9		9.51%	0.69[0.33,1.46]
Lin 1993	1/19	3/19		4.02%	0.33[0.04,2.93]
Rudnitsky 1993	11/35	19/34		25.85%	0.56[0.32,1]
Subtotal (95% CI)	**169**	**172**		**91.01%**	**0.64[0.47,0.87]**
Total events: 44 (Continuous), 68 (Intermittent)					
Heterogeneity: Tau²=0; Chi²=2.96, df=4(P=0.56); I²=0%					
Test for overall effect: Z=2.82(P=0)					
1.3.2 Less severe					
Khine 1996	2/35	3/35		4.02%	0.67[0.12,3.75]
Reisner 1995	1/13	1/7		1.74%	0.54[0.04,7.36]
Rudnitsky 1993	4/12	3/18		3.22%	2[0.54,7.39]
Subtotal (95% CI)	**60**	**60**		**8.99%**	**1.12[0.44,2.85]**
Total events: 7 (Continuous), 7 (Intermittent)					
Heterogeneity: Tau²=0; Chi²=1.4, df=2(P=0.5); I²=0%					
Test for overall effect: Z=0.24(P=0.81)					
Total (95% CI)	**229**	**232**		**100%**	**0.68[0.51,0.92]**
Total events: 51 (Continuous), 75 (Intermittent)					
Heterogeneity: Tau²=0; Chi²=5.63, df=7(P=0.58); I²=0%					
Test for overall effect: Z=2.55(P=0.01)					
Test for subgroup differences: Not applicable					

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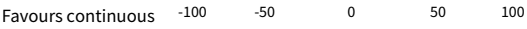
Analysis 1.4. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 4 Adverse effects.

Study or subgroup	Continuous n/N	Intermittent n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Besbes-Ouanes 2000	0/21	0/21			Not estimable
Colacone 1990	0/21	0/21			Not estimable
Innes 2002	0/81	0/89			Not estimable
Lin 1993	1/19	5/19		100%	0.2[0.03,1.55]
Total (95% CI)	**142**	**150**		**100%**	**0.2[0.03,1.55]**
Total events: 1 (Continuous), 5 (Intermittent)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.54(P=0.12)					

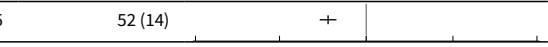
Analysis 1.5. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 5 ED treatment time.

Study or subgroup	Continuous N	Continuous Mean(SD)	Intermittent N	Intermittent Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Khine 1996	35	123 (23.9)	35	124 (29.2)		0%	-1[-13.5,11.5]



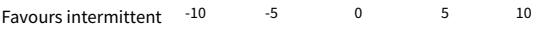
Analysis 1.6. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 6 Respiratory therapist time.

Study or subgroup	Intermittent N	Intermittent Mean(SD)	Continuous N	Continuous Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Khine 1996	35	30 (4)	35	52 (14)		-22[-26.82,-17.18]



Analysis 1.7. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 7 Symptom scores.

Study or subgroup	Continuous N	Continuous Mean(SD)	Intermittent N	Intermittent Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Besbes-Ouanes 2000	21	6.3 (3.1)	21	6.1 (2.9)		38.81%	0.07[-0.54,0.67]
Khine 1996	35	7 (3.1)	35	5 (2.9)		61.19%	0.66[0.18,1.14]
Total ***	**56**		**56**			**100%**	**0.43[0.05,0.81]**
Heterogeneity: Tau^2=0; Chi^2=2.26, df=1(P=0.13); I^2=55.8%							
Test for overall effect: Z=2.23(P=0.03)							



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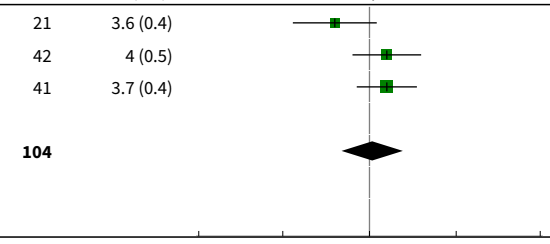
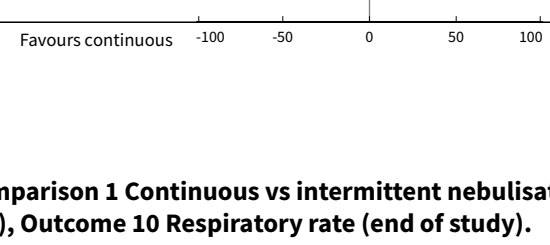
Analysis 1.8. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 8 Potassium concentration.

Study or subgroup	Intermittent		Continuous		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Besbes-Ouanes 2000	21	3.4 (0.4)	21	3.6 (0.4)		28.13%	-0.2[-0.44,0.04]
Shrestha 1996	41	4.1 (0.5)	42	4 (0.5)		34.06%	0.1[-0.1,0.3]
Shrestha 1996a	40	3.8 (0.4)	41	3.7 (0.4)		37.81%	0.1[-0.07,0.27]
Total ***	**102**		**104**			**100%**	**0.02[-0.16,0.19]**
Heterogeneity: Tau²=0.01; Chi²=4.58, df=2(P=0.1); I²=56.3%							
Test for overall effect: Z=0.17(P=0.86)							



Analysis 1.9. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 9 Pulse rate.

Study or subgroup	Continuous		Intermittent		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Besbes-Ouanes 2000	21	102 (16)	21	109 (16)		10.97%	-7[-16.68,2.68]
Colacone 1990	21	95 (14)	21	96 (14)		14.33%	-1[-9.47,7.47]
Innes 2002	81	98 (16.4)	89	98 (14.9)		46.01%	0[-4.73,4.73]
Reisner 1995	13	115 (13.7)	7	116 (16.9)		4.83%	-1[-15.59,13.59]
Rudnitsky 1993	47	93 (18)	52	101 (15)		23.85%	-8[-14.57,-1.43]
Total ***	**183**		**190**			**100%**	**-2.87[-6.07,0.34]**
Heterogeneity: Tau²=0; Chi²=4.71, df=4(P=0.32); I²=15.11%							
Test for overall effect: Z=1.75(P=0.08)							



Analysis 1.10. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 10 Respiratory rate (end of study).

Study or subgroup	Treatment		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Colacone 1990	21	22 (5)	21	21 (5)		71.11%	1[-2.02,4.02]
Reisner 1995	13	18 (6.9)	7	17 (4)		28.89%	1[-3.74,5.74]
Total ***	**34**		**28**			**100%**	**1[-1.55,3.55]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Z=0.77(P=0.44)							

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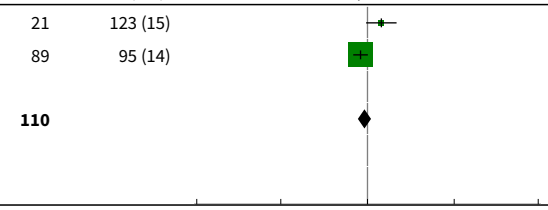
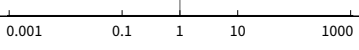
Analysis 1.11. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 11 Blood pressure (end of study).

Study or subgroup	Continuous N	Continuous Mean(SD)	Intermittent N	Intermittent Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Colacone 1990	21	131 (14)	21	123 (15)		18.74%	8[-0.78,16.78]
Innes 2002	81	91 (14)	89	95 (14)		81.26%	-4[-8.21,0.21]
Total ***	**102**		**110**			**100%**	**-1.75[-5.55,2.05]**
Heterogeneity: Tau^2=0; Chi^2=5.84, df=1(P=0.02); I^2=82.87%							
Test for overall effect: Z=0.9(P=0.37)							



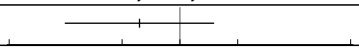
Analysis 1.12. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 12 Tremor.

Study or subgroup	Continuous n/N	Intermittent n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Colacone 1990	9/21	6/21		19.1%	1.5[0.65,3.47]
Khine 1996	5/35	9/35		28.65%	0.56[0.21,1.49]
Lin 1993	3/19	3/19		9.55%	1[0.23,4.34]
Shrestha 1996	1/38	4/42		12.1%	0.28[0.03,2.36]
Shrestha 1996a	7/37	10/40		30.6%	0.76[0.32,1.78]
Total (95% CI)	**150**	**157**		**100%**	**0.81[0.51,1.28]**
Total events: 25 (Continuous), 32 (Intermittent)					
Heterogeneity: Tau^2=0; Chi^2=3.72, df=4(P=0.45); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					



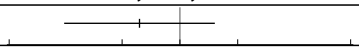
Analysis 1.13. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 13 Palpitations.

Study or subgroup	Continuous n/N	Intermittent n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Lin 1993	0/19	2/19		0%	0.2[0.01,3.91]



Analysis 1.14. Comparison 1 Continuous vs intermittent nebulisation (end of study), Outcome 14 Nausea/vomiting.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Khine 1996	0/35	2/35		0%	0.2[0.01,4.02]



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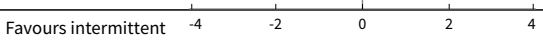
Comparison 2. Continuous vs Intermittent PFT time line

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Early (1 hour or less)	9		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 PEFR	5	400	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.05, 0.34]
1.2 FEV-1	5	257	Std. Mean Difference (IV, Fixed, 95% CI)	0.30 [0.05, 0.54]
2 2-3 hours	9		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 PEFR	5	400	Std. Mean Difference (IV, Fixed, 95% CI)	0.37 [0.17, 0.57]
2.2 FEV-1	5	257	Std. Mean Difference (IV, Fixed, 95% CI)	0.33 [0.08, 0.58]
3 4-6 hours	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 PEFR	2	62	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.34, 0.67]
3.2 FEV-1	1	20	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-1.31, 0.55]

Analysis 2.1. Comparison 2 Continuous vs Intermittent PFT time line, Outcome 1 Early (1 hour or less).

Study or subgroup	Continuous N	Continuous Mean(SD)	Intermittent N	Intermittent Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.1.1 PEFR							
Besbes-Ouanes 2000	21	44 (18)	21	42 (14)		10.61%	0.12[-0.48,0.73]
Innes 2002	81	239 (64)	89	236 (53)		42.91%	0.05[-0.25,0.35]
Reisner 1995	13	58.9 (10.8)	7	57.7 (10.6)		4.6%	0.11[-0.81,1.02]
Rudnitsky 1993	47	256 (87)	52	248 (95)		24.96%	0.09[-0.31,0.48]
Rudnitsky 1993a	35	239 (83)	34	202 (65)		16.92%	0.49[0.01,0.97]
Subtotal ***	**197**		**203**			**100%**	**0.14[-0.05,0.34]**
Heterogeneity: Tau^2=0; Chi^2=2.46, df=4(P=0.65); I^2=0%							
Test for overall effect: Z=1.43(P=0.15)							
2.1.2 FEV-1							
Colacone 1990	21	2.2 (0.9)	21	2.1 (0.9)		16.8%	0.13[-0.48,0.74]
Lin 1993	19	2.4 (0.9)	19	1.7 (0.9)		14.22%	0.72[0.06,1.37]
Reisner 1995	13	47.7 (14.4)	7	50.8 (13.2)		7.25%	-0.21[-1.13,0.71]
Shrestha 1996	38	1.7 (0.6)	42	1.4 (0.5)		30.94%	0.51[0.06,0.95]
Shrestha 1996a	37	1.6 (0.8)	40	1.6 (0.7)		30.79%	0.1[-0.35,0.54]
Subtotal ***	**128**		**129**			**100%**	**0.3[0.05,0.54]**
Heterogeneity: Tau^2=0; Chi^2=4.64, df=4(P=0.33); I^2=13.8%							
Test for overall effect: Z=2.33(P=0.02)							
Test for subgroup differences: Chi^2=0.87, df=1 (P=0.35), I^2=0%							



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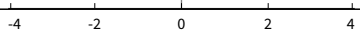
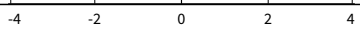
Analysis 2.2. Comparison 2 Continuous vs Intermittent PFT time line, Outcome 2 2-3 hours.

Study or subgroup	Continuous N	Continuous Mean(SD)	Intermittent N	Intermittent Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.2.1 PEFR							
Besbes-Ouanes 2000	21	52 (18)	21	52 (14)		10.81%	0[-0.6,0.6]
Innes 2002	81	274 (64)	89	243 (53)		42.17%	0.53[0.22,0.83]
Reisner 1995	13	61.9 (10.8)	7	62.2 (10.6)		4.69%	-0.02[-0.94,0.9]
Rudnitsky 1993	47	310 (100)	52	291 (99)		25.31%	0.19[-0.21,0.58]
Rudnitsky 1993a	35	296 (98)	34	244 (81)		17.02%	0.57[0.09,1.05]
Subtotal ***	**197**		**203**			**100%**	**0.37[0.17,0.57]**
Heterogeneity: Tau^2=0; Chi^2=4.61, df=4(P=0.33); I^2=13.29%							
Test for overall effect: Z=3.61(P=0)							
2.2.2 FEV-1							
Colacone 1990	21	2.5 (1)	21	2.2 (0.9)		16.59%	0.33[-0.28,0.94]
Lin 1993	19	2.4 (0.9)	19	1.8 (0.9)		14.28%	0.7[0.04,1.35]
Reisner 1995	13	50.2 (14.4)	7	53.9 (13.2)		7.23%	-0.25[-1.18,0.67]
Shrestha 1996	38	1.9 (0.7)	42	1.6 (0.6)		31.19%	0.45[0,0.89]
Shrestha 1996a	37	2 (0.9)	40	1.8 (0.7)		30.71%	0.17[-0.28,0.62]
Subtotal ***	**128**		**129**			**100%**	**0.33[0.08,0.58]**
Heterogeneity: Tau^2=0; Chi^2=3.47, df=4(P=0.48); I^2=0%							
Test for overall effect: Z=2.59(P=0.01)							
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%							



Analysis 2.3. Comparison 2 Continuous vs Intermittent PFT time line, Outcome 3 4-6 hours.

Study or subgroup	Continuous N	Continuous Mean(SD)	Intermittent N	Intermittent Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.3.1 PEFR							
Besbes-Ouanes 2000	21	62 (20)	21	58 (20)		69.68%	0.2[-0.41,0.8]
Reisner 1995	13	67.3 (10.8)	7	66.2 (10.6)		30.32%	0.09[-0.83,1.01]
Subtotal ***	**34**		**28**			**100%**	**0.16[-0.34,0.67]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.85); I^2=0%							
Test for overall effect: Z=0.64(P=0.52)							
2.3.2 FEV-1							
Reisner 1995	13	53.6 (14.4)	7	59.2 (13.2)		100%	-0.38[-1.31,0.55]
Subtotal ***	**13**		**7**			**100%**	**-0.38[-1.31,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.8(P=0.42)							
Test for subgroup differences: Chi^2=1.01, df=1 (P=0.31), I^2=1.44%							



WHAT'S NEW

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Date	Event	Description
9 March 2011	New search has been performed	New literature search run. One abstract added to 'studies awaiting classification' (Rose 2010).

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 2003

Date	Event	Description
21 May 2009	Amended	Change of contact details for primary author
17 February 2009	New search has been performed	Literature search run: no new studies identified.
23 July 2008	Amended	Converted to new review format.
1 August 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Camargo CA Jr: Protocol development, study selection, analyses and interpretation of data, and write-up.
Spooner CH: data checking and entry, quality scoring, conversion to RevMan 4.1.
Rowe BH: Study selection, quality scoring, data extraction and entry, editing of manuscript, assigned editor.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest. They are neither involved with the primary studies nor affiliated with any pharmaceutical company that produces any of the continuous nebulizers.

SOURCES OF SUPPORT

Internal sources

- Division of Emergency Medicine, University of Alberta, Edmonton, Canada.

External sources

- National Institute of Health (CAC; NIH HL - 03533), Bethesda, USA.
- Canada Institute of Health Research (BHR), Ottawa, Canada.
- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Inhalation; Adrenergic beta-Agonists [*administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Emergencies; Randomized Controlled Trials as Topic

MeSH check words

Humans

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