Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma (Review)

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[Intervention Review]

Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

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ABSTRACT

Background

In acute asthma inhaled β2-agonists are often administered to relieve bronchospasm by wet nebulisation, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. Nebulisers require a power source and need regular maintenance, and are more expensive in the community setting.

Objectives

To assess the effects of holding chambers (spacers) compared to nebulisers for the delivery of ß2-agonists for acute asthma.

Search methods

We searched the Cochrane Airways Group Trial Register and reference lists of articles. We contacted the authors of studies to identify additional trials. Date of last search: January 2008.

Selection criteria

Randomised trials in adults and children (from two years of age) with asthma, where spacer ß2-agonist delivery was compared with wet nebulisation.

Data collection and analysis

Two reviewers independently applied study inclusion criteria (one reviewer for the first version of the review), extracted the data and assessed trial quality. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CI).

Main results

This review has been updated in January 2008 and two new trials have been added. 2295 children and 614 adults are now included in 27 trials from emergency room and community settings. In addition, six trials on in-patients with acute asthma (213 children and 28 adults) have been reviewed. Method of delivery of ß2-agonist did not appear to affect hospital admission rates. In adults, the relative risk of admission for spacer versus nebuliser was 0.97 (95% CI 0.63 to 1.49). The relative risk for children was 0.72 (95% CI: 0.47 to 1.09). In children, length of stay in the emergency department was significantly shorter when the spacer was used, with a mean

difference of -0.53 hours (95% CI: -0.62 to -0.44 hours). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for spacer in children, mean difference -6.27% baseline (95% CI: -8.29 to -4.25% baseline).

Authors' conclusions

Metered-dose inhalers with spacer produced outcomes that were at least equivalent to nebuliser delivery. Spacers may have some advantages compared to nebulisers for children with acute asthma.

PLAIN LANGUAGE SUMMARY

Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

In acute asthma attacks higher doses of inhaled β2-agonists (reliever inhalers) are used to overcome the narrowing of the passages in the lungs. The medication can be given by wet nebulisation or from an inhaler with a spacer device (holding chamber). This review now includes in-patient studies, as well as those in casualty and community setting, comparing these two delivery methods in acute asthma attacks. In adults, no important differences were found between the two methods, whilst in children those randomised to wet nebulisation spent longer in casualty. Metered-dose inhalers with a spacer can perform at least as well as wet nebulisation in delivering β2-agonists in acute asthma.

BACKGROUND

Acute exacerbations of asthma are common and account for a considerable number of physician encounters, both in hospital and in primary care. In acute exacerbations the airways become narrowed due to mucosal oedema, hyper secretion and bronchospasm. Depending on the severity of the attack, treatment with inhaled ß2-agonists is often required in addition to other agents such as corticosteroids. The use of ß2-agonists is intended to relieve the bronchospasm. This is accomplished most effectively when the drug is delivered to the peripheral airways. This is made more difficult in acute asthma since the narrowed airways and faster respiratory rate result in increased drug deposition in the throat and large airways. Consequently, it is less effective and may cause more side effects.

Two different delivery methods have been employed to overcome this problem: wet nebulisations and metered-dose inhalers with a holding chamber (spacer). Nebulisation creates a mist of ß2-agonist diluted in saline which is inhaled through a mask by tidal breathing. Nebulisation can be accomplished with room air or supplemental oxygen, and requires a supply of compressed gas or a power source. More recently, ß2-agonists delivered via metered-dose inhalers through a spacer have been used in acute asthma. The inhaler is actuated into the spacer that is then emptied by the patient using either tidal breathing or single breaths.

Whilst nebulisers have historically been used in acute exacerbations of asthma, a meta-analysis of trials in adults with asthma or chronic obstructive pulmonary disease (COPD) suggested that metered-dose inhalers with a spacer are as effective (Turner 1997).There has been considerable controversy regarding the merits of each delivery method, but current guidelines have now moved towards the use of spacers in acute asthma, particularly in children (BTS 2003) . In addition, cost and infection control considerations may be important additional determinants of which system is employed. For example, in the community the cost of nebulisers exceeds a spacer and metered-dose inhaler (MDI). In hospital emergency departments, the cost calculations are more complex since disposable nebuliser masks are often driven by piped oxygen; costs may depend on whether or not all patients are sent home with a new spacer. Nebulisers also represent a potential source of cross-infection, and require regular maintenance. As a result of these controversies, this systematic review has been designed to assess all the available evidence from randomised controlled trials comparing the two delivery methods in acute asthma.

OBJECTIVES

The objective of this review was to compare the clinical outcomes following the use of ß2-agonists in acute asthma given by two different delivery methods: a metered-dose inhaler with spacer or a nebuliser.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were considered for this review.

Types of participants

Adults and children (but not infants) with acute asthma presenting for medical assistance in the community setting or hospital emergency department. Studies describing patients who had already been admitted to hospital have been included in this update. Studies on children with a mean age of two years or more were included, as it is difficult to diagnose asthma under this age. Studies on patients with asthma and COPD were included as long as separate results could be obtained for the asthma patients.

Types of interventions

Any ß2-agonist given by any nebuliser versus the same ß2-agonist given by metered-dose inhaler with any spacer. The dose of drug and method of administration must have been recorded. Co-interventions and contamination (cross-over) may have occurred, but these must have been recorded.

Types of outcome measures

Primary outcomes

The primary outcome measures were admission to hospital, or duration of stay for in-patients.

Secondary outcomes

1. Duration in the emergency department
2. Change in respiratory rate
3. Blood gases
4. Pulse rate
5. Tremor
6. Symptom score
7. Lung function
8. Use of steroids
9. Relapse rates

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. All records in the Specialised Register coded as 'asthma' were searched using the following terms: (spacer* OR "holding chamber*" or holding-chamber* OR volumatic OR nebuhaler* OR aerochamber* OR fisonair OR extension* OR "spacing device*" OR inspirease OR babyhaler* or MDI or turbuhaler) AND (nebuli*)
The most recent search of the Register was carried out in January 2008.

Searching other resources

We searched the bibliographies of all included papers and reviews for further references. We contacted authors of included studies for identification of any unpublished or missed trials.

Data collection and analysis

Selection of studies

One reviewer (CJC) originally checked abstracts identified by the above search and obtained the full text of publications of possibly relevant studies, including translation when required. Trials identified for potential inclusion were independently assessed by JAC and CJC for the 2003 and 2006 updates.

Data extraction and management

Data were extracted by CJC and checked by JAC. Authors were sent letters asking for clarification of allocation concealment, devices used, location of the patients and outcomes where these were not clear in the original publication.

Assessment of risk of bias in included studies

We assessed the methodological quality of the included trials with particular emphasis on the allocation concealment, which was ranked using the Cochrane approach:
Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment
Where there was uncertainty we contacted authors for clarification.
We originally assessed the methodological quality of the eligible RCTs with a five point scoring instrument, proposed by Jadad 1996. Two reviewers performed this independently. This instrument evaluates the reported quality of randomisation, blinding, and description of withdrawals and dropouts. One of the reviewers was masked as to authors' names and affiliation, names of journals,

date of publication, sources of financial support for the study and the acknowledgements. The pooled score from this instrument has not been continued for recent updates.

Assessment of heterogeneity

Heterogeneity of the results of individual trials is shown on the MetaView graphical displays. Where the heterogeneity exceeded the expected 95% level, (measured using a chi squared test with appropriate degrees of freedom), sources of heterogeneity were explored and results were either pooled using a random effects model, or not pooled across sub-groups.

Data synthesis

We calculated a weighted treatment effect across trials using the Cochrane statistical package, RevMan (initially version 4.2, now 5.0). The results are expressed as relative risk (RR and 95% CI) for dichotomous outcomes and mean difference (MD) and 95% Confidence Interval (CI) for continuous outcomes. A fixed effect model was used for continuous outcomes, but results using a random effects model were also checked.

The results for adults and children have now been separated in each outcome in view of the significant heterogeneity identified in the pooled analyses. Furthermore it can be argued that adults and children may differ in their ability to use the devices, their degree of airways reversibility and in their sensitivity to side effects from inhaled ß2-agonists.

The single treatment trials have not been pooled due to concern over confounding due to uncertainty over the relative dose delivered and the wide range of dose-ratios used (from 1:1 to 1:13, with the larger doses administered via nebuliser).

Sensitivity analysis

We performed sensitivity analyses on the basis of methodological quality. The results were re-analysed using only studies of the highest quality (scores three to five). Sensitivity analyses have also been performed to check on the effect of estimating standard deviations and the data re-analysed without any estimated results. In addition, we performed a funnel plot of hospital admissions to check for publication bias. In view of the recent discontinuation of Volumatic spacers in some countries, separating the trials that used Volumatic from other types of spacer.

RESULTS

Description of studies

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

Results of the search

112 abstracts were originally identified from the database and 44 were selected for possible inclusion in the review. For the 2006 update seven new abstracts were considered for possible inclusion. One abstract was identified from the references in the included studies (Hodder 1988). The full text of each paper was obtained and translated when necessary (two from Spanish and one from Portuguese). Papers were excluded for the following reasons: studies on non-acute asthma, different drugs delivered and no separate data for asthma patients (see Table of Excluded Studies). A total of 12 papers were initially included for this review and 10 further papers were added up to 2004 (Williams 1996; Batra 1997; Raimondi 1997; Robertson 1998; Rodrigo 1998; Rodriguez 1999; Valencia 1999; Leversha 2000; Ploin 2000; Duarte 2002). The 2006 update includes 5 new trials (Burrows 2004;Chong-Neto 2005; Hussein 2002; Rao 2002; Vivek 2003). The latest search was completed in January 2008, and from the 12 abstracts found, two further trials were included (Jamalvi 2006; Sannier 2007).

Agreement between the two independent assessments of study quality for the original review was as follows:

Randomisation: Kappa = 1

Double-blind: Kappa = 1

Withdrawals/Dropouts: Kappa = 0.8

Method of Randomisation: Kappa = 0.8

Method Blinded: Kappa = 0.5

Included studies

There are now 2295 children and 614 adults included in 27 trials in emergency departments and the community. In addition there are six trials incorporating 213 children and 28 adults studied after hospital admission (Ba 1989; Burrows 2004; Coker 1995; Dewar 1999; Morley 1988; Parkin 1995).

The studies come from all over the world. Only two were carried out in the community (Chong-Neto 2005;Morrone 1990); six trials have been considered in an in-patient setting (Ba 1989; Burrows 2004; Coker 1995; Dewar 1999; Morley 1988; Parkin 1995), and all others were conducted in hospital emergency departments. The single pre-hospital study comparing nebulisation to MDI (Campbell 1995) was excluded, as there was no randomisation. Different ß2-agonists, spacers and nebulisers were represented in the studies. The dosage ratio between delivery methods varied from 1:1 to 1:13, with the larger doses administered via nebuliser. Many recent studies used multiple treatments at 10 to 30 minute intervals(Batra 1997; Chong-Neto 2005; Chou 1995; Colacone 1993; Duarte 2002; Idris 1993; Jamalvi 2006; Leversha 2000; Ploin 2000; Rao 2002; Rodrigo 1993; Rodrigo 1998; Sannier 2007; Valencia 1999; Vivek 2003). Most studies

used commercially available spacers (Aerochamber, Babyhaler, InspirEase, Nebuhaler and Volumatic), but two studies from Brazil (Chong-Neto 2005; Duarte 2002), used home-made spacers in the form of a 500 ml mineral water plastic bottle. Duarte 2002 coated the bottle with detergent to avoid electrostatic charge, whilst Chong-Neto 2005 included 10 children treated with aerochamber and 10 children using a 500 ml water bottle glued onto the MDI with Araldite. The studies using salbutamol all used the racemic form of the drug.

In view of the proposed discontinuation of Volumatic spacers in 2005 an additional table (Table 1) has been added with details of the type of spacer used in each study.

Excluded studies

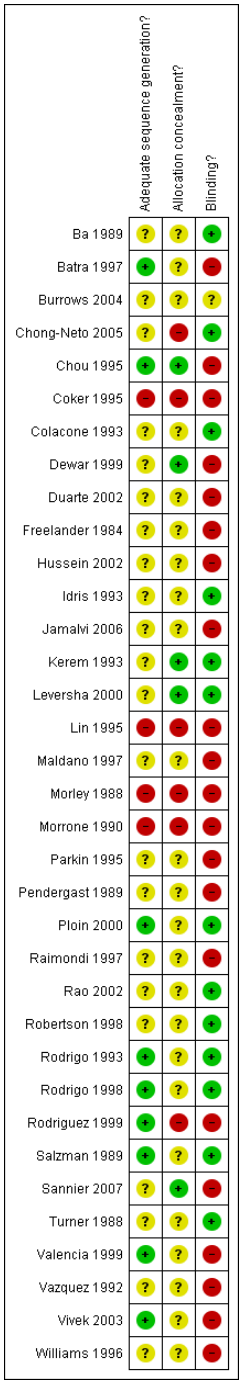
See Characteristics of excluded studies.

Risk of bias in included studies

Overall, the methodological quality of the included studies was variable (see Characteristics of included studies). Only four of the included references commented on the number of participants excluded from the study. Many studies did not comment on withdrawals and dropouts, and also did not report whether intention to treat analysis was employed. The hospital admission rate reported in one study has been amended using an intention to treat analysis (Colacone 1993).

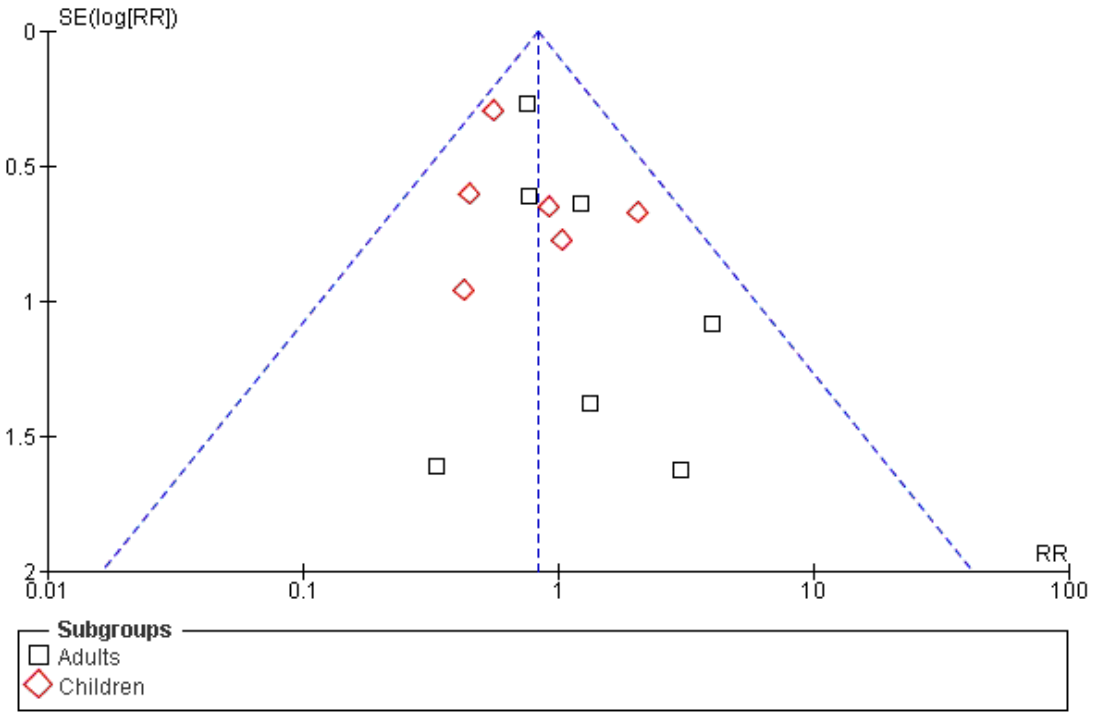
In general the sample size of many individual studies was small, (range 18 to 196 participants in the emergency room studies, and 28 to 61 for in-patients). Whilst seven of the eleven studies in adults used a double blind, double dummy design (Colacone 1993; Idris 1993; Rao 2002; Rodrigo 1993; Rodrigo 1998; Salzman 1989; Turner 1988) only seven of the 22 studies in children were double-blind (Ba 1989; Chong-Neto 2005; Hussein 2002; Kerem 1993; Leversha 2000; Ploin 2000; Robertson 1998), see Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



A funnel plot of hospital admissions did not suggest publication bias since the smaller studies showed spread of results on both sides of the overall relative risk (Figure 2).

Figure 2. Funnel plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.1 Hospital admission.

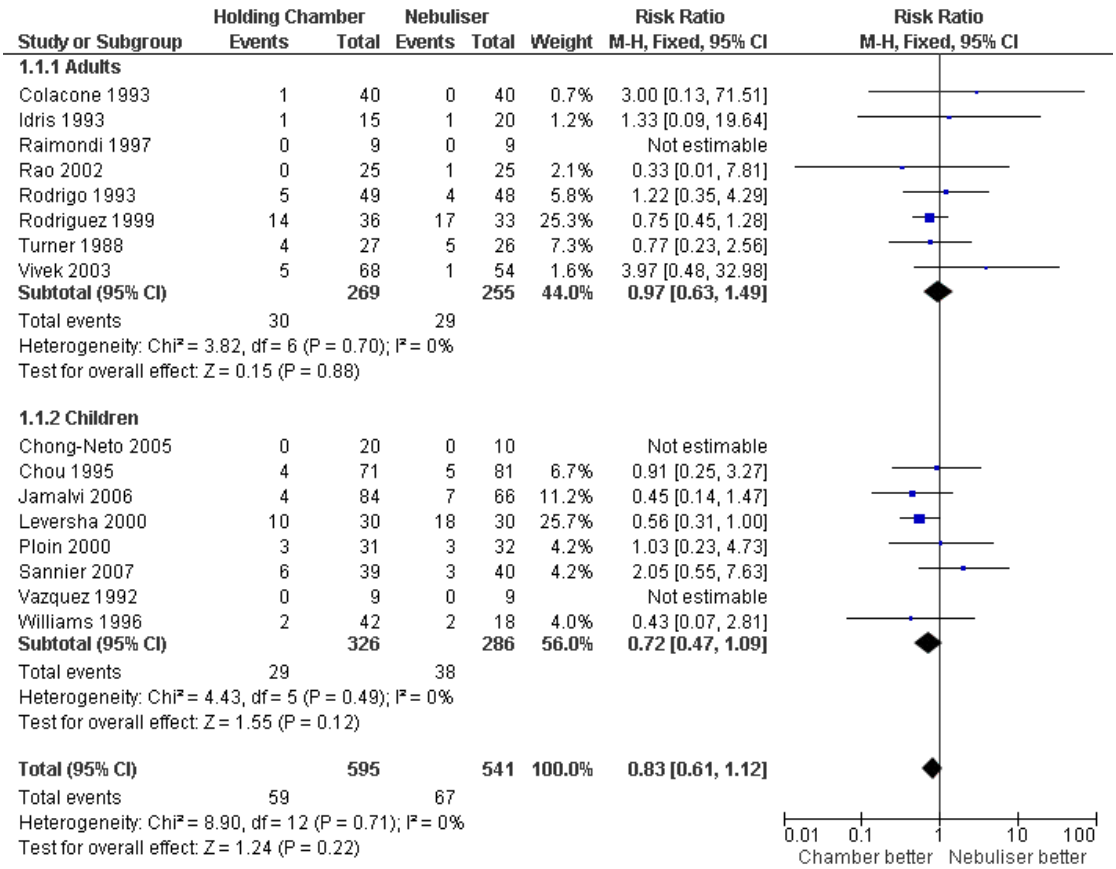


Effects of interventions

SPACER VERSUS NEBULISER MULTIPLE TREATMENTS

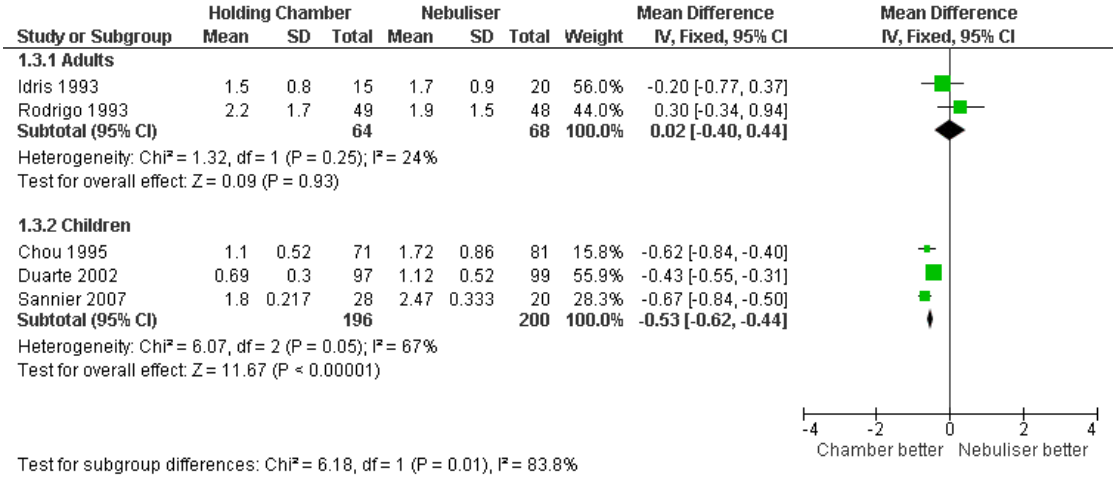
Hospital admission rates did not differ significantly on the basis of delivery method in adults (RR: 0.97; 95% CI: 0.63 to 1.49) or in children (RR: 0.72; 95% CI: 0.47 to 1.09); Figure 3. No significant heterogeneity was observed. These results did not change when studies of lower methodological quality were excluded. Two studies in children did not report admissions but did report data on poor outcomes (Batra 1997; Leversha 2000); when these are included the relative risk in children of admission or poor outcome is not significantly different between spacer and nebuliser (RR: 0.86; 95% CI: 0.60 to 1.23).

Figure 3. Forest plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.1 Hospital admission.



Time spent in the emergency department (ED) originally showed significant heterogeneity when the results from adults and children were pooled, (chi squared = 8.2, df = 2, P < 0.02). This heterogeneity could not be explained on the basis of methodological quality, since the result was based on trials that were all of high methodological quality. However, no significant heterogeneity was demonstrated when adults and children were analysed separately. The results for adults and children have therefore been shown in separate sub-groups in the analyses Figure 4. Duration in the ED in children was significantly shorter with the spacer (MD -0.53 hours; 95% CI: -0.62 to -0.44). This finding is based on three studies (Chou 1995; Duarte 2002; Sannier 2007), containing 427 participants. The fact that these were not double dummy studies may have a bearing on these results as nebulisation is much more time consuming than use of MDI and spacer (Duarte 2002). In adults the duration of the ED visit was similar in both groups (MD 0.02 hours; 95% CI: -0.4 to 0.44). Results in children and adults are based on a fixed-effect model but are very similar when a random-effects model is used.

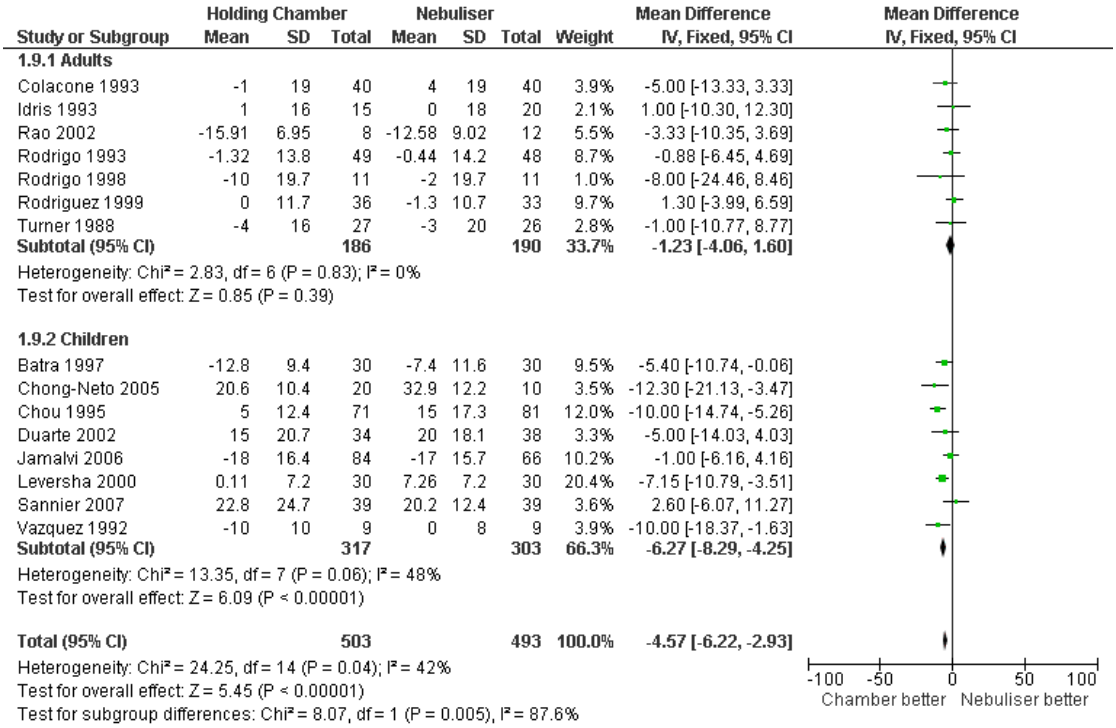
Figure 4. Forest plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.3 Duration in emergency department (hours)..



No significant differences were demonstrated between the two delivery methods in terms of peak flow and forced expiratory volume (FEV_1) at 30 minutes and the end of the study. More specifically, in the four studies in adults that included analysis of changes in lung function in the most severely affected patients (e.g. FEV_1< 30% predicted), there was no statistically significant difference between the two delivery methods (MD -1.6% predicted; 95% CI: -7.69 to 4.49%). The only study (Maldano 1997) which found a significant difference in FEV_1 between the nebuliser and spacer groups used a low dose of Salbutamol via the spacer (200 mcg), and showed a significant decline in FEV_1 in this group three to six hours after the treatment was administered. This trial was not be included in the analysis as no standard deviations were reported and the authors did not respond to requests for further information.

Pulse rate after treatment (expressed as % change from baseline), was significantly lower when a spacer was used in children (MD -6.27% baseline; 95% CI: -8.29 to -4.25%). In adults, no significant difference was found between methods (MD -1.2% baseline; 95% CI: -4.1 to 1.6%). These results were similar for fixed and random effects models. There was a significant difference between the pulse changes in adults and children (Chi squared = 8.07, df = 1, P =0.005), Figure 5.

Figure 5. Forest plot of comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), outcome: 1.9 Rise in pulse rate (% baseline).



Oxygen saturation was not significantly different at the end of the studies with a mean difference of -0.09% between groups (95% CI: -1% to 0.8%). One study (Duarte 2002), however, reported that 25% of children treated with oxygen-driven nebuliser suffered desaturation at some point during treatment compared to 9% of those treated with MDI and spacer (P = 0.006).

No significant differences were demonstrated between the two delivery methods for the other measured outcomes: change in respiratory rate and the number of participants given steroids.
Development of tremor was more common with nebuliser treatment in the two studies that reported this in children, but the test for interaction between adults and children was not significant.
No attempt has been made to combine the findings for symptom score as the scales used were highly variable and the standard deviation of results were rarely reported.
In the light of the decision to temporarily withdraw Volumatic spacers from the UK market in 2005, we carried out a post-hoc sensitivity analysis according to whether Volumatic spacers were used in each study. The type of spacer used is documented in Table 1 and this shows that the majority of adults and children studied used other types of spacer. No significant differences were found between the results from trials using Volumatic (188 adults and 364 children) and those using other types of spacer (433 adults and 907 children). The primary outcome of hospital admission was unaltered in children when Volumatic studies were excluded, but the confidence intervals in adults widened; adult admission using other spacers (RR: 1.45; 95% CI: 0.6 to 3.53) and children's admissions using other spacers was unchanged (RR: 0.65; 95% CI: 0.4 to 1.06). No studies included direct comparison between Volumatic and other types of spacer.

SPACER VERSUS NEBULISER SINGLE TREATMENTS

Results from single treatment studies were not pooled due to concern over confounding by the variable amounts of ß2-agonists delivered to the airways from the different delivery methods.
Blood gas results were reported in two studies (Kerem 1993; Lin 1995). The participant numbers were small but both show less deterioration in gases with a spacer. One study (Lin 1995) also measured lung function 15 minutes after the start of treatment and found a significantly greater rise in peak expiratory flow (PEF) at this time with the spacer (mean difference 10.1% predicted; 95% CI: 15.7 to 4.4%); this study is of low methodological quality,

consequently this information should be interpreted with caution. More recently, Hussein 2002 reported similar changes in oxygen saturation in a single treatment study in 60 children. As yet the author has not responded to a request for further details.

IN-PATIENT SPACER VERSUS NEBULISER STUDIES

The primary outcome of duration of admission was available from three studies (Morley 1988; Parkin 1995; Dewar 1999) but the results in Dewar 1999 were skewed and presented as medians so are not suitable for combination with the other two studies. The duration of admission did not show a significant difference between delivery methods, MD 0.26 hours (95% CI: -0.23 to 0.75).

The results from the individual studies have been outlined below.

Ba 1989 was a single dose comparison in children, and did not measure the primary outcome (time to discharge). The design was double-blind with double dummy. Continuous intravenous aminophylline was given to all children in both groups. There was a significant difference between groups in baseline lung function, spacer baseline FEV_1 38.2 (SD 7.9) % predicted and nebuliser 49.8 (SD 14) % predicted. Results are only presented as change from baseline, and this will favour the spacer group. There was no significant difference in FEV_1 between groups over three hours, and the significant advantage for the spacer in change in FVC is probably due to baseline difference. The paper reported significantly more children treated with spacer increased their pulse rate at 10 minutes compared to the nebuliser group, but this data could not be used as the number of participants with increased pulse reported in the spacer group (17) was greater than the group total (14).

Coker 1995 was a single dose comparison in children, and did not measure the primary outcome (time to discharge). There was no blinding and participants were allocated by alternation. No co-interventions were reported and no significant differences in respiratory score or PEF were found between groups over six hours.

Dewar 1999 compared multiple treatments in children, given up to one hourly by each delivery method. Allocation was concealed with sequential pre sealed envelopes and all children received oral steroids on admission and repeated on subsequent mornings for three to five days according to their recovery. No blinding was reported. Data for duration of stay was noted to be skewed by small numbers of lengthy in-patient stays so medians were used which did not show a significant difference between groups, (36.5 hours for the spacer group and 40 hours for the nebuliser group). Although readmission rates were lower in the spacer group, this group were also given a written asthma plan and this may have confounded the results for readmission and symptoms after discharge. Children requiring immediate intravenous treatment were excluded from the study, and five children were withdrawn due to deterioration requiring intravenous treatment (three in the spacer group and two in the nebuliser group). The authors calculated a significant cost benefit for the spacer group in terms of drug costs, £5.43 per patient in the spacer group and £20.25 in the nebuliser group ($P < 0.001$).

Morley 1988 was the only in-patient study in adults, and used multiple treatments. Allocation was by alternation and no blinding was described. Intravenous aminophylline and methylprednisolone were given at standard doses. Mean duration of hospitalisation was not significantly different between groups, 5.8 days in the spacer group and 6.4 days in the nebuliser group, mean difference of -0.6 days (95% CI: -3.2 to 2.0). No significant differences were found in lung function between groups.

Parkin 1995 compared multiple treatments in younger children (aged one to five years), but gave both salbutamol and ipratropium by spacer or nebuliser. The research nurse only was blinded and all children received intravenous or oral steroids. There was no significant difference in hours to discharge (spacer 53 hours and nebuliser 46 hours), hours to the change of treatments to four hourly intervals or total number of inhaled doses received. Nine participants in the spacer group crossed over to nebuliser treatment, but their results were analysed by original group assignment (intention to treat analysis).

Burrows 2004 studied 29 children aged one to six years old with moderate to severe asthma according to BTS guidelines, who were hospitalised between September 2003 and February 2004. No significant differences were reported in any outcomes except for cost (which was £7.68 per patient in the nebuliser group and £5.96 per patient in the spacer group). The length of stay was 16.5 hours in the nebuliser group and 26.5 hours in the MDI and spacer group, with change in respiratory rate of -5.4 and -6.3, change in pulse of 2.9 and 4.6, and change in oxygen saturation of 0.53 and 1.07 for nebuliser and spacer, respectively. We have been in communication with the author and await details of the standard deviation of these changes to allow computation of between group differences and confidence intervals, and pooling with the other study results.

DISCUSSION

METHODOLOGICAL LIMITATIONS

Several issues restrict the generalisability of the results of this review.

(1) As patients with life threatening asthma exacerbations were excluded from the studies (for example those patients considered for ventilation), the results cannot be assumed to apply to this group.

(2) Only two small studies was carried out in a community setting, (Chong-Neto 2005; Morrone 1990). Although it is reasonable to suppose that the findings would apply in the community setting, further studies are required to confirm that this is the case.

(3) Few authors reported specifically on numbers of patients presenting who were excluded from each study, and intention to treat analysis was not usually reported. Thus it is not entirely clear how these results apply to all patients who present with an exacerbation.
(4) Analysis of the data regarding lung function tests in many papers was complicated by a lack of standardised reporting. In addition, data regarding standard deviation related to the changes that were measured were not always reported. Peak flow and FEV_1 were the most commonly reported measurements and these were both included in the outcome tables.

CLINICAL PRACTICE

Nebulisers are commonly used to deliver ß2-agonists in acute asthma in the community and in hospital emergency departments. Although spacers have also been advocated for use in these circumstances, published guidelines give few details about how they should be used. Overall, this review supports the equivalence of wet nebuliser and MDI with spacer administration of ß2-agonists in the treatment of acute asthma, when treatments are repeated and titrated to the response of the patient. This review also suggests that paediatric patients given ß2-agonists by spacer and MDI may have shorter stays in the ED, less hypoxia, and lower pulse rates, compared to patients receiving the same ß2-agonist via wet nebulisation. No outcomes were worse with the spacer in either adults or children, even in those adults with more severe asthma at presentation. All the studies reviewed excluded patients with life-threatening asthma (for example those patients considered for ventilation), and the results of the review should not be extrapolated to this group. Successful response to ß2-agonists does not diminish the necessity to consider oral steroids in acute attacks of asthma. A previous meta-analysis demonstrated that steroids clearly reduce relapses when given to patients following discharge, and reduce hospitalisation when used early in the course of emergency treatment (Rowe 2007).
In clinical practice the dose of ß2-agonist delivered to the airways varies depending on the type of nebuliser or spacer used and the characteristics of the individual patient's airways at that time (Lipworth 1997). Uncertainty over the dose of ß2-agonists required through any delivery method was overcome in many of the studies (475 adults and 632 children) by repeating treatments at short intervals. For example, one respule (via nebuliser) or four to six puffs (via spacer) every 10 to 30 minutes until the patient responded to treatment (Batra 1997; Chong-Neto 2005; Chou 1995; Colacone 1993; Duarte 2002; Idris 1993; Leversha 2000; Ploin 2000; Rao 2002; Rodrigo 1993; Rodrigo 1998; Valencia 1999; Vivek 2003) were considered equivalent. This approach reduced confounding by different dosages of drug delivered.
In adults, no additional benefit was found using six puffs of Salbutamol (100 mcg each) given at 10 minute intervals through a Volumatic Spacer, when compared with four puffs at 10 minute intervals (Rodrigo 1996). A comparison in children between doses of 0.5 mg/kg and 1.5 mg/kg given at 20 minute intervals via nebuliser showed significantly greater improvement in lung function at the higher dose (Schuh 1989).
The studies included in this review used dosage ratios varying from 1:1 to 1:13 (lower dose in the spacer). One of the included studies plotted a log dose-response curve (Colacone 1993); the equivalent dose ratio found in this study was 1:6 with the lower dose in the spacer.
Experimental evidence suggests that the ß2 agonist should be actuated into the spacer in individual puffs that can be inhaled by tidal breathing or single breaths (Newman 1984; Gleeson 1988). Some of the early studies mentioned difficulty with the valve movement with some spacers; however, this did not appear to be a problem in more recent studies. Some children may co-operate more with either spacer or nebuliser, so this may be an important factor in the choice of delivery method. Two studies compared different types of spacer; Chong-Neto 2005 studied 10 children with aerochamber and 10 with a home-made spacer constructed from a 500 ml mineral water bottle. The study failed to identify differences between the types of spacer, yet did demonstrate significantly lower pulse rates with the Aerochamber than with the home-made spacer. Williams 1996 included 20 children treated with an Aerochamber and 22 children treated with an ACE spacer (both around 150 ml) and found no significant differences between the groups in respiratory rate and lung function.

Overall comparisons between types of spacer is confounded by all the other differences between the designs of each trial. In view of the discontinuation of Volumatic spacers in the UK in 2005, additional details to allow identification of type of spacer used have been added in Table 1. This indicates that the findings of this review for the primary outcome of hospital admission are unchanged in children when trials using Volumatic spacers are excluded, but the confidence intervals widen for adults as less data contributes to the outcome. No significant subgroup differences were found for any outcome between the trials using Volumatic or other spacers.
Cost considerations may dictate which delivery system is used in different settings. In many parts of the world nebulisation is not available in peripheral hospitals and clinics for economic reasons (Rao 2002). Several recent studies have now included a calculation of costs of drug treatment (Burrows 2004; Chong-Neto 2005; Dewar 1999; Duarte 2002) and found a cost advantage for spacer delivery.
Total costs in a hospital setting are more complex to calculate; however, when patients return to the community the cost of a home nebuliser and respules is considerably more than an MDI and spacer (and the nebuliser requires regular maintenance). A recent before-after ED study (Newman 2002) assessed the consequences of changing the acute asthma treatment algorithm from nebulised to MDI/spacer albuterol (salbutamol). Admission rates

did not rise following the change in delivery method and duration of stay in the ED fell significantly from 175 minutes to 164 minutes. There were also reductions in charges that did not reach significance. Lower relapse rates following the change to MDI/spacer delivery were confounded by other changes, such as an asthma bag containing a spacer, peak-flow meter, instructional handout and canister of inhaled corticosteroid given to the patients at discharge. This makes data on relapse rates difficult to interpret, although significant reductions were seen following the combined interventions. As expected, the total dose of albuterol given to patients was lower with MDI/spacer delivery.

IMPLEMENTATION OF CHANGE IN PRACTICE

Implementing research findings is not an easy process, and Powell 2001 found that successfully changing hospital practice from nebulisers to spacers required a structured strategy to overcome the "nebuliser culture" both in hospital medical and nursing staff, as well as parents and families of children with asthma. Osmond 2007 carried out a survey of the use of nebulisers and spacers in Canadian paediatric emergency departments, and found that 21% of emergency physicians used MDI and spacer; the largest perceived barriers amongst non-users included safety and costs, and the lack of a physician champion for change.

AUTHORS' CONCLUSIONS

Implications for practice

(1) For adults seen and assessed for acute asthma, this review found no significant differences between the two delivery methods. Consequently, the choice of delivery method should reflect patient preference, practice situations and formal economic evaluation.

(2) In children, no outcomes were significantly worse with the spacers, and the available evidence suggests that in most cases spacers could be substituted for nebulisers to deliver ß2-agonists in acute asthma. Moreover, other observed benefits (time spent in emergency department, oxygenation and side effects) may favour the groups treated with metered-dose inhaler and spacer.

(3) The experimental method adopted in many of the studies was to give repeated treatments at short intervals (e.g. one respule via a nebuliser or four actuations of a metered-dose inhaler via a spacer every 10 to 15 minutes). The number of treatments required was adjusted to the individual patients response, overcoming the uncertainty of dosage delivery from different devices. This method is therefore recommended for practice until further evidence becomes available.

(4) The studies excluded patients with life-threatening asthma; therefore, the results of this meta-analysis should not be extrapolated to this patient population.

Implications for research

(1) Further studies are required to confirm whether these findings, largely from hospital emergency departments, can be replicated in the community setting.

(2) Further studies in children and adults with more severe asthma are required to confirm whether spacers are as efficacious as nebulisers in this group.

(3) In order to avoid confounding due to differences in the dose of drug delivered to the airways, future studies should use multiple treatments at short intervals titrated against individual patient response.

(4) Implementation of change to overcome the "nebuliser culture" needs further work.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ba 1989

Methods	Randomisation: no details. Blinding: double blinded, double dummy. Excluded:none. Withdrawals: none. Baseline characteristics: Comparable but the Chamber group had significantly lower FEV-1 at baseline (P < 0.02). Intention to treat analysis: not used. Jadad score: 4
Participants	Setting: Hospital inpatients, Canada. 27 children aged 7 to 18 years old (average age 11.9). Inclusion/exclusion criteria: Salbutamol nebulisers and i. v. aminophylline given on admission. 3 hours post if FVC and FEV-1 were still < 65% predicted value then included, if above excluded
Interventions	Beta2-agonist: Salbutamol Spacer: Nebuhaler 750 ml pear shaped. Nebuliser: Hudson, up draft 11 nebu-mist. Driven by continuous flow oxygen output 6L/min. Chamber group: 2mls 0.9% saline (placebo) via nebuliser, immediately followed by continuous tidal breathing of 2 puffs salbutamol every 10 seconds (total 12 puffs= 1.2mg) with MDI + Nebuhaler. Nebuliser group: 1 ml (5mg) salbutamol added to 1 ml of 0.9% saline, immediately followed by tidal breathing with a placebo via MDI + Nebuhaler. Dose ratio 1:4 Co-interventions: All children had continuous i. v. aminophylline
Outcomes	FEV-1 and FVC, pulse, blood pressure, respiratory rate, side effects. Assessed at -11 mins (before) and 10, 30, 60, 90, 120, 180 (after) inhalation from the MDI and spacer. Maximum change in FEV-1 and FVC from baseline
Notes	Lower baseline FEV1 in the spacer group may have contributed to the larger improvement from baseline in this group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	Yes	Double dummy

Batra 1997

Methods	Randomisation: computer generated random numbers. Blinding: none. Excluded: number not stated. Withdrawals: none recorded. Baseline characteristics: comparable. Power analysis: 30 in each group designed to detect a 30% difference in response rate. Jadad score: 2.
Participants	Setting: India. Emergency department. 60 children aged 1 to 12 years (average age 4 years). PEF at presentation was under 40% predicted in the 16 children able to undergo this evaluation. Inclusion criteria: over two previous attacks of wheezing in response to allergens and exercise as well as infection. Exclusion criteria: TB, heart, liver, kidney or lung disease. Skeletal disorders
Interventions	Beta2-agonist: Salbutamol. Spacer: Volumatic (M/s Cipla) 750 ml. Dosage: 2 puffs (200 mcg) given every 5 to 10 minutes for 60 minutes. Nebuliser: no details. Dosage: 0.15 mg/kg in 2.5 ml saline given three times at 20 minute intervals. Co-interventions: all given humidified oxygen and none were given steroids
Outcomes	Further treatment (?admission), PEF in 16 children, blood gases, symptoms score
Notes	This trial was included as the mean age of the children was over 2 years old. No response from authors to requests for further details

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

Burrows 2004

Methods	Randomisation: details awaited Blinding: details awaited Excluded: details awaited Withdrawals: details awaited Baseline characteristics: details awaited Intention to treat analysis: details awaited

Burrows 2004 (*Continued*)

Participants	Southampton General Hospital. 29 children aged 1-6 years admitted to hospital with moderate or severe asthma. Inclusion criteria: moderate or severe asthma according to BTS criteria. Exclusion criteria: details awaited
Interventions	Beta2-agonist: details awaited Spacer: details awaited Nebuliser: details awaited Co-interventions: details awaited
Outcomes	Duration of admission to hospital, oxygen saturation, increase in heart rate, increase in respiratory rate, drug costs
Notes	No SD data provided in abstract.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Infomation not available
Blinding? Hospital admission	Unclear	Information not available

Chong-Neto 2005

Methods	Randomisation: the children drew a slip of paper numbered 1,2,3,4 out of a non-translucent jar. Blinding: double-blind (double dummy design) Excluded: details awaited Withdrawals: none Baseline characteristics: comparable Power calculation:carried out on the basis of a 15% difference in FEV1 between groups
Participants	Critiba, Brazil. 24-hour emergency health unit. 40 children aged 6 to 18 years old. 30 of these were included in this review (10 in each arm as detailed below). Inclusion criteria: Acute asthma attacks. Children were able to use the devices and carry out lung function testing. Exclusion criteria: History of cardiac and pulmonary diseases other than asthma, clinical score < 3, forced expiratory flow in the first second (FEV1) less than 20% and greater than 80% of the predicted value. Smokers (> 10 packs of cigarettes/year), and children treated with short-acting and long-acting beta-2 agonists in the last 24 hours, corticosteroids on the last seven days, and also those receiving xanthines, were also excluded

Chong-Neto 2005 (*Continued*)

Interventions	Beta2-agonist: Salbutamol (Albuterol). Spacer A: Aerochamber, 4 x 100 mcg separate actuations of salbutamol given at 30 second intervals, inhaled using single deep breath per actuation. This was given three times at 20 minute intervals. Home made Spacer: 500 ml plastic water bottle, 4 x 100 mcg separate actuations of salbutamol given at 30 second intervals, inhaled using single deep breath per actuation. This was given three times at 20 minute intervals. Nebuliser: Pari Jet, 0.15 mg/kg salbutamol given every 20 minutes in 3 ml saline driven by Proned ultra compressor (air driven). Dosage ratio: Spacer/Nebuliser = 1/12.5. Co-interventions: not specified. (The further 10 children treated with dry powder inhaler were not included in this review)
Outcomes	FEV1, admission to hospital, change in symptom score, increase in heart rate, tremor, nausea, vomiting, hypokalaemia. Full data provided by authors
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; drawing of lots used but unclear how numbered lots were drawn up
Allocation concealment?	No	Children randomised themselves by drawing lots
Blinding? Hospital admission	Yes	Double dummy design

Chou 1995

Methods	Randomisation: sealed opaque envelopes containing allocation from random number table. Blinding: none. Excluded: none. Withdrawals: none Baseline characteristics: comparable. Intention to treat analysis: not required. Jadad score: 3.
Participants	New York. Urban paediatric emergency department. 152 children aged 2 years or older. Mean PEF at presentation 56% and 53% in the treatment and control group. Inclusion criteria: current wheeze and history of at least 2 episodes of wheezing. Exclusion criteria: no patients were excluded from the study, but exclusion criteria included chronic illness, presenting oxygen saturation less than 90% or symptom score >12

Chou 1995 (*Continued*)

Interventions	Beta2-agonist: Salbutamol (Albuterol). Spacer: Aerochamber, 3x90mcg actuations of salbutamol given every 20 minutes, inhaled using five normal breaths per actuation. (Mean 2.3 treatments given). Nebuliser: Acorn II, 0.15 mg/kg salbutamol given every 20 minutes in 3 ml saline driven by oxygen at 6 L per minute (Mean 2.5 treatments given). Co-interventions: oxygen was given to all patients with an oxygen saturation of less than 94% while breathing room air. Administration of steroids and other medication was at the discretion of the treating physician
Outcomes	Admission to hospital, duration in emergency department, change in symptom score, final Peak Flow (in children old enough to perform test), oxygen saturation, increase in heart rate, administration of steroids
Notes	Standard deviation of results and details of randomisation obtained from author; SD of change in lung function estimated

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers table
Allocation concealment?	Yes	Sealed opaque envelopes
Blinding? Hospital admission	No	Open label study

Coker 1995

Methods	Randomisation: Assigned to each group using alternating numbers. Blinding: None stated. Excluded: None. Withdrawals: None. Baseline characteristics: Comparable. Intention to treat analysis: Not used. Jadad Score: 1.
Participants	Setting: Hospital inpatients, Turkey. 36 children, 12 in each group; 2 groups considered. Mean age 10.33 (SD 1.15) (chamber). 11.75 (SD 1.60) (nebuliser.) Inclusion Criteria: Children over 9 years, admitted with acute asthma crisis. Exclusion criteria: if received any medicine in the last 8 hours
Interventions	Beta2-agonist: Salbutamol Spacer: 750 ml Volumatic spacer using tidal breathing. 200 mcg (given twice with interval of 2 mins in between). Nebuliser: Pari-inhaler boy (ultrasonic) nebuliser driven by compressed air. 0.05-0.1mg/kg (max dose of 2.5mg) nebules.

Coker 1995 (*Continued*)

	Co-interventions: none.
Outcomes	Respiratory score (nasal flaring, cyanosis, retractions, wheezing), PEFR, respiratory rate, heart rate, blood pressure. All measured at 5, 15, 30, 240, and 360 (6 hours) minutes after treatment
Notes	Confirmation of doses, gained from author as well as, method of randomisation (alternation), withdrawals and dropouts and co-interventions. 3rd arm of this trial using MDI only was disregarded.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	Alternate allocation
Allocation concealment?	No	Allocation by alternation at high risk of bias in terms of concealment of allocation
Blinding? Hospital admission	No	Not described as blinded

Colacone 1993

Methods	Randomisation: no details but double blind. Blinding: double blind. Excluded: number not stated. Withdrawals: five. Baseline characteristics: comparable. Intention to treat: not used. Power calculation: performed, estimated 80%. Jadad score: 5.
Participants	Setting: Canada. Hospital emergency department. 80 adults mean age 41(SD18) and 43(SD19) years. Mean FEV1(% predicted) at presentation: Spacer 55%(SD15), nebuliser 54%(SD18). Inclusion criteria: acute asthma, FEV1<70% predicted, over 18 years old, able to perform spirometry. Exclusion criteria: pregnancy, complicating medical illness, already given nebulised or parenteral beta-agonist in emergency department
Interventions	Beta2-agonist: Salbutamol (Albuterol). Spacer: Aerochamber. Dosage: 4x100mcg puffs individually and inhaled by one slow inhalation at one minute intervals. Treatment given every 30 minutes until maximum bronchodilation achieved. Nebuliser: Disposable Updraft nebuliser. Dosage: 2.5mg in 2ml saline driven by oxygen at 5 to 8 L/min. Repeated every 30 mins as above. Dosage ratio: Spacer/Nebuliser = 1/6. Co-interventions: steroids and aminophylline (stratified treatment arms)

Colacone 1993 (*Continued*)

Outcomes	Symptom score, FEV1, heart rate, respiratory rate, presence of tremor
Notes	Cumulative dose response curve showed a relative potency of 1:6 in favour of spacer. One patient was withdrawn from the spacer group due to clinical deterioration; included in review result as a hospital admission on intention to treat basis. Estimated SD for respiratory rate and pulse rate

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? Hospital admission	Yes	Described as blinded

Dewar 1999

Methods	Randomisation: sequential pre sealed envelopes. Blinding: none. Excluded:11 (2 immediately due to needing i. v. therapy, and 9 re-admitted during trial and not re-studied.) Withdrawals: 5 needed i. v. therapy post randomisation (3 chamber group, 2 nebuliser group). 8% did not complete follow up post discharge, but did complete trial in hospital. Baseline characteristics: comparable. Intention to treat: not used. Sample size: estimated from asthma admissions data from previous 2 years. Jadad score: 3.
Participants	Setting: Hospital inpatients, UK. 62 children aged 3 or above: mean age 6.9yr (chamber) 8yr (nebuliser). Inclusion criteria: over 3 years, admitted with acute asthma. Exclusion criteria: Children unable to use chamber mouthpiece effectively. Those requiring i. v. treatment. Those readmitted during 5 month study period
Interventions	Beta2-Agonist: Salbutamol. Spacer: Large volume spacer (Volumatic). Dosage: 100 mcg ,up to 10 puffs one hourly. Children and parents in the spacer group were instructed and supervised on the optimal use of the delivery device. They were also provided with a written treatment plan for managing acute asthma. Nebuliser: jet nebuliser driven by oxygen 6-8 l/min. Dosage: 5mg salbutamol up to 1 hourly. Co-interventions: All children received oral prednisolone at 2 mg/kg (max. dose 60 mg) on admission and repeated on subsequent mornings for 3 to 5 doses according to recovery. Oxygen was administered by face mask or nasal prongs in children who after bronchodilator treatment had Ox. sats of < 93%

Dewar 1999 (*Continued*)

Outcomes	Hospital length of stay, cost, asthma morbidity 2 weeks after discharge, frequency of re admissions during the study period and following 12 months
Notes	All families given same discharge advice re: management of acute attacks, but seems only chamber group received a written treatment plan. No response from author to confirm this. Patients lost to follow up ignored: this can lead to bias.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other details available
Allocation concealment?	Yes	Sequential pre sealed envelopes
Blinding? Hospital admission	No	Open label study

Duarte 2002

Methods	Randomisation: method not stated. Blinding: assessors blinded. Excluded: no details of how many patients were excluded. Withdrawals: none. Baseline characteristics: no significant differences. Intention to treat analysis: not described. Power calculation based on 15L/min difference in PEF. Jadad score: 2.
Participants	Setting: Brazil. Emergency Room. 196 children aged 4 to 15 years. Mean PEF at presentation: Spacer 174 L/min, Nebuliser 173 L/min. Inclusion criteria: two or more previous acute exacerbations, mild to moderate current attack (PEF 50% to 79% of predicted). Exclusion criteria: severe acute asthma (PEF under 50% predicted), patients unable to perform PEF, or use delivery devices, patients who had used controller or rescue medication in the past 2 weeks, and patients with complications (pneumothorax, pneumonia)
Interventions	Beta2-agonist: Salbutamol. Spacer: 500 ml plastic mineral water bottle coated with detergent Dosage: Five separate 100 mcg actuations inhaled by tidal breathing for 20 seconds. Nebuliser: Nevoni (Sao Paulo, Brazil). Driving gas oxygen at 6L/min Dosage: 0.15 mg/kg salbutamol given up to maximum of 5mg Each group had repeated Traitement up to 3 doses. Dosage Ratio: 1 to 4 -10 (Spacer to Nebuliser) Co-interventions: Not specified.

Duarte 2002 (*Continued*)

Outcomes	PEF, Pulse Oximetry, Heart Rate, Respiratory Rate, Clinical Score, Duration in Emergency Room
Notes	Patients were discharged from the study when the PEF rose to 80% predicted or higher. SD given for absolute values imputed for changes in Heart rate and Respiratory rate. PEF data not shown as % predicted so not included

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label, only assessors were blinded

Freelander 1984

Methods	Randomisation: method not stated. Blinding: none. Excluded: not stated. Withdrawals: not stated. Baseline characteristics: comparable, but mean age 9.1 and 6.1 in treatment and control groups. Intention to treat analysis: none. Jadad score: 1.
Participants	Setting: Australia. Accident and Emergency department. 28 children aged 3 to 13 years. Mean PEF(% predicted) at presentation: Spacer 55%, Nebuliser 65%. Inclusion criteria: no details. Exclusion criteria: beta-agonist in previous 2 hours.
Interventions	Beta2-agonist: Terbutaline. Spacer: Nebuhaler. Dosage: 5 puffs (1.25 mg) under 20 kg, 10 puffs (2.5mg) over 20 kg. Details of inhalation technique not given. (single treatment). Nebuliser: Hudson driven by air at 6L/minute. Dosage: 2.5mg in 2ml saline under 20 kg, 5mg in 2ml saline over 20 kg. (single treatment). Dosage Ratio: Spacer/Nebuliser = 1/2. Co-interventions: no details.
Outcomes	Admission to hospital, change in symptom score, change in Peak Flow (in children old enough to perform test)
Notes	Some children had difficulty triggering the Nebuhaler valve. Estimated SD for Peak Flow

Freelander 1984 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

Hussein 2002

Methods	Randomisation: method not stated. Blinding: none recorded Excluded: not stated. Withdrawals: not stated. Baseline characteristics: not stated
Participants	Setting: Alexandria, Egypt. Outpatient department study of children presenting with acute asthma of moderate severity. 60 children aged 2 to 12 years. Inclusion criteria: no details. Exclusion criteria: no details.
Interventions	Beta2-agonist: Salbutamol. Spacer: 'Large volume', up to 10 puffs of salbutamol given as single dose. Nebuliser: No details of nebuliser type, 0.15mg/kg salbutamol given up to maximum of 5mg. Driving gas not specified. Co-interventions: Not specified.
Outcomes	Admission to hospital, change in symptom score, pulmonary function, oxygen saturation, increase in heart rate. 4 admissions in nebuliser group and 3 in holding chamber group. Symptoms, oxygen saturation and lung function reported as similar in both groups, and mean heart rate higher in the nebuliser group
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available

Blinding? Hospital admission	No	No blinding recorded

Idris 1993

Methods	Randomisation: double blind, no other details. Blinding: double blind, double dummy. Excluded: number not stated. Withdrawals: none. Baseline characteristics: comparable. Intention to treat: not applicable. Power calculation: performed, predicted 90% power to detect 12% difference in lung function. Jadad score:5.
Participants	Setting: USA. Hospital emergency rooms. 35 patients aged 10 to 45 years, mean age 23 (spacer) and 25(nebuliser). Mean PEF(% predicted) at presentation: spacer 34(SD14), nebuliser 37(17). Inclusion criteria: acute asthma. Exclusion criteria: angina, respiratory failure, COPD, smoking for 10 pack years or more, unable to perform spirometry
Interventions	Beta2-agonist: Salbutamol (Albuterol). Spacer: InspirEase. Dosage: 4x90mcg puffs one puff every minute, inhaled by one slow inhalation. Treatment repeated every 30 minutes until FEV1 was 80% predicted or patient asymptomatic or 6 treatments given. Nebuliser: T Up-Draft II Nebu-U-Mist. Dosage: 2.5mg in 2ml saline, driven by oxygen at 5 L/min. Treatment repeated every 30 minutes until FEV1 was 80% predicted or patient asymptomatic or 6 treatments given. Dosage ratio: Spacer/Nebuliser = 1/7. Mean dose to max response with spacer 1.11(SD 0.64)mg, nebuliser 7.63(SD 3.9)mg. Co-interventions: parenteral steroids usually given within one hour of discharge
Outcomes	Further treatment (?admission), duration in emergency department, Peak Flow, FEV1,FVC, heart rate, respiratory rate, administration of steroids
Notes	Results include % maximum response (see footnotes). Separate analysis for patients with FEV1 < 30% predicted

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available

Blinding? Hospital admission	Yes	Double dummy

Jamalvi 2006

Methods	Randomisation: Just described as randomised Blinding: none. Excluded: three out of 153 Withdrawals: none Baseline characteristics: significantly higher PEF at baseline in spacer group
Participants	Setting: Emergency Room of the National Institute of Child Health in Karachi from October 2000 to March 2001 150 children (aged 6 months to 15 years). 76% were classified as having as severe asthma attack (24% mild or moderate) Inclusion criteria: acute asthma Exclusion criteria: children requiring intensive care management, PEFR values under 20% or over 70% predicted, oxygen saturation under 90% in room air, or receiving daily systemic corticosteroids for more than two weeks before being seen in the emergency room
Interventions	Beta2-agonist: Salbutamol (Albuterol) Spacer: Babyhaler for younger children and spacer with mouthpiece for older children. Dosage: 2x100 mcg repeated three times at 20 minute intervals Nebuliser: Type 2 Fleam Nuova S.P.A., Bresia, Italy. Dosage: 0.3 mg/kg with 2ml Normal Saline repeated three times at 20 minute intervals Dosage ratio: unknown. Co-interventions: none reported.
Outcomes	Admission to hospital. Pulse, Respiratory Rate, BP, Dyspnoea, Cyanosis, wheeze, PEFR, clinical score, measured at 10 mins, 20 mins and 2 hours after completion of treatment
Notes	No details are given for mean age in each group or how many children were able to perform PEFR. Trial included as mean age is almost certainly over 2 years old

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? Hospital admission	No	Open study

Kerem 1993

Methods	Randomisation: assigned by research pharmacist. Blinding: Double-blind double-dummy study. Excluded: not stated. Withdrawals: not stated. Baseline characteristics: comparable. Intention to treat analysis: not stated. Jadad score:4
Participants	Setting: Canada. Emergency Department. 33 children aged 6 to 14 years old. Mean FEV1(% predicted) at presentation: Spacer 40%, Nebuliser 40% Inclusion criteria: not stated. Exclusion criteria: critically ill, FEV1< 20% or > 70%, oxygen saturation in air < 92%, systemic steroids given for more than 2 weeks
Interventions	Beta2-agonist: Salbutamol (Albuterol) Spacer: VentAHaler. Dosage: 6x100mcg (< 25 kg), 8 x 100 mcg (25 to 35 kg), 10 x 100 mcg (> 35 kg). Total dose discharged into spacer followed by one minute tidal breathing, Single treatment. Nebuliser: Whisper Jet, driven by oxygen at 6 to 10 L/min. Dosage: 0.15 mg/kg to maximum 5mg given in 3 mls saline. Single Treatment. Dosage ratio: Spacer/Nebuliser = 1/5. Co-interventions: none.
Outcomes	Admission to hospital, symptom score, FEV1, oxygen saturation, heart rate, respiratory rate
Notes	Admission to hospital, symptom score, FEV1, oxygen saturation, heart rate, respiratory rate

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Yes	Assigned by research pharmacist.
Blinding? Hospital admission	Yes	Double dummy

Leversha 2000

Methods	Randomisation: pharmacy generated and blinded treatment packets supplied. Blinding: double-blind, double dummy. Excluded: number not stated. Withdrawals: 1 from each group refused both treatments and was admitted. 1 from nebulizer group refused the nebulizer but was treated with spacer and discharged. (All 3 were included in the analysis). Baseline characteristics: comparable for asthma severity. Intention to treat: performed. Power calculation: powered to detect a difference of 1.25 in clinical score between groups. Jadad score: 5.
Participants	Setting: New Zealand. Emergency department in children's hospital. 60 children aged 1 to 4 years; mean age 36 months (spacer) and 32 months. (nebuliser). 66% had received oral steroids in the previous 24 hours in each group. Inclusion criteria: Known history of asthma with a clinical score of greater than 3, presenting to ED with acute asthma. Exclusion criteria: bronchodilator given in the hour before presentation or requiring immediate admission to intensive care unit. Also co-existing medical condition (such as pneumonia)
Interventions	Beta2-agonist: Albuterol (Salbutamol). Spacer: Aerochamber. Dosage: 6x100mcg puffs inhaled separately by tidal breathing. Repeated every 20 minutes for a maximum of 6 treatments. Nebuliser: Marquest bowl with Hudson face mask. Dosage: 2.5mg every 20 mins for a maximum of 6 treatments, driven by wall oxygen. Double dummy methodology so placebo given by the other route to all children. Co-interventions: supplemental oxygen if SaO2 less than 92% and oral prednisone unless child had received oral steroids in past 24 hours. Dosage ratio: Spacer/Nebuliser = 1/4
Outcomes	Admission to hospital. Pulse, Respiratory Rate, SaO2, clinical score, tremor and hyperactivity measured 20 mins after each treatment and 60 mins after final treatment
Notes	Data in the paper is only provided for the results 20 mins after the first treatment. One of the tables of data in the paper was inconsistent and has since been corrected. The data used in the review for heart rate and respiratory rate has been provided by Dr Leversha

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Yes	Pharmacy generated
Blinding? Hospital admission	Yes	Double dummy

Lin 1995

Methods	Randomisation: Alternate weeks. Blinding: none. Excluded: number not stated. Withdrawals: 4 from spacer group, 2 from nebuliser group. Baseline characteristics: comparable. Intention to treat: not performed. Power calculation: not stated. Jadad score:1.
Participants	Setting: Taiwan. Hospital emergency department and paediatric allergy clinic. 111 children aged 5 to 16 years. Mean PEF(% predicted) at presentation: spacer 57(SD20)%, nebuliser 60 (SD21)%. Inclusion criteria: acute asthma or acute exacerbation of chronic asthma. Exclusion criteria: inhaled beta-agonist in previous 6 hours, unable to perform spirometry, pneumonia, congestive heart failure, foreign body aspiration, bronchopulmonary dysplasia
Interventions	Beta2-agonist: Terbutaline. Spacer: Aerochamber. Dosage: 3 x 0.25 mg puffs, each inhaled by three deep breaths. Single treatment. Nebuliser: Pulmo-Aide. Dosage: 2.5mg in 2ml saline, driven by air at 8 L/min. Single treatment. Dosage ratio: Spacer/Nebuliser = 1/3.5. Co-interventions: not stated.
Outcomes	Measured at 15 minutes after the start of treatment: symptom score, Peak, FEV1, FVC, oxygen saturation, heart rate
Notes	Mean fall in SaO2 at 15 minutes was 0.47(SD 1.93)% in the nebuliser group, compared to a mean rise of 0.58(SD 1.72)% in spacer group. Estimated SD for Peak Flow and pulse rate

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	Alternate weeks
Allocation concealment?	No	Investigators had foreknowledge of treatment group assignment
Blinding? Hospital admission	No	Open label study

Maldano 1997

Methods	Randomisation: No data. Blinding: None. Excluded: No data. Withdrawals: All patients completed the study. Baseline characteristics:similar. Power calculation: "approximately 90%". Jadad score: 2.
Participants	Setting: ER Hospital Infantil de Mexico Fredrico Gomez. 42 children aged 6 to 15; baseline FEV1 69% (spacer) and 77% (nebuliser). Inclusion criteria: FEV1 of 60% to 80% of predicted value. Exclusion criteria: use of xanthines, steroids, beta-agonists or anti-histamines. Unable to use spirometer
Interventions	Beta2-agonist: Salbutamol. Spacer: unknown. Dosage: 2x100mcg twice 20 mins apart. Nebuliser: Hudson driven by oxygen, dose 0.15 mg/kg up to maximum of 5mg made up to 5 ml with saline. Given twice 20 minutes apart. Dose ratio up to 1:25.
Outcomes	FEV1 at 1,2,3,4,5,6 hours. Pulse rate rise. Symptoms using Silverman-Anderson scale.
Notes	No standard deviations reported. After 3 hours following treatment the spacer group FEV1 had fallen significantly more than the nebuliser group

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

Morley 1988

Methods	Randomisation: Alternate allocation. Blinding: None (discharge was at the discretion of the attending physician who had no involvement in data acquisition- however this information could be requested if needed!) Excluded: None. Withdrawals: none withdrew however 2 patients data was excluded from daily rates of spirometric improvement as spirometric analysis required was not completed. Baseline Characteristics: Comparable Intention to treat: not used Jadad score: 1
Participants	Setting: Hospital inpatients, New Jersey. 28 adults, admitted with acute status asthmaticus. Mean age of 34.8 (15.9) chamber group, 31.3 (19.0) nebuliser group. Inclusion criteria: acute status asthmaticus, admitted after failing multiple trials of either subcutaneous or nebulised beta-agonists. Exclusion criteria: A smoking history of > 5 packs a year of cigarettes, emphysema, respiratory acidosis on admission, or pregnant. Unstable coronary insufficiency, recent myocardial infarction, or cardiac arrhythmia were also excluded
Interventions	Beta2-agonist: Albuterol (Salbutamol). Spacer: InspirEase, Key Pharmaceutical. Dosage: 3 inhalations (90 micrograms /inhalation) each separated by 5-min intervals. Received every 4 hours. Nebuliser: Acorn 2 nebulizer (Marquest Medical Products Inc, Englewood, CO). Dosage: 0.5 ml (2.5mg) albuterol and 2.0 mls normal saline solution nebulised over 15 min period. Received every 6 hours while awake. Additional therapies: All patients received standard IV dosages of aminophylline. IV methylprednisolone was administered as recommended by Haskell et al. No oral beta-agonists were used. (Group 3 received 15 mg nebulised metaproterenol)
Outcomes	Spirometric improvement (FEV-1 and FVC) 15, 30, 60, 120, 180, 240 mins following the 1st beta-agonist treatment (best of 2 recorded), duration of hospital stay (discharge criteria: free of wheezing on auscultation and no exertional dyspnoea when walking on ground level), daily rates of spirometric improvement during course of hospitalization (performed once in morning and once in afternoon at similar times every day-just prior to treatment). Following 3rd day spirometry was not performed again until discharge (calculations were based on assumption of discharge day at day 6)
Notes	Trial begins from initial beta-agonist dose given once admitted (at least 4 hours after last dose given in A+E.) No data of how much given before trial commenced. 3rd arm of this trial ignored as different beta-agonist used

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Alternate allocation

Morley 1988 (*Continued*)

Allocation concealment?	No	Investigators had foreknowledge of treatment group assignment
Blinding? Hospital admission	No	Open label study

Morrone 1990

Methods	Randomisation: Alternate allocation. Blinding:none. Excluded:not stated. Withdrawals: none. Baseline characteristics: comparable. Intention to treat: not applicable. Jadad score: 2.
Participants	Setting: Brazil. Mobile clinic. 44 adults, 36 female, 8 male. Mean PEF(% predicted) at presentation: 180 L/min (% predicted not stated). Inclusion criteria: PEF 120 to 200 L/min at presentation. Exclusion criteria: not stated.
Interventions	Beta2-agonist: Fenoterol. Spacer: 500 ml (type not stated). Dosage: 1 mg delivered as 200 mcg per minute inhaled by tidal breathing. Single treatment. Nebuliser: type not stated. Dosage: 2.5mg in 3 ml saline driven by oxygen at 6 L/min. Single treatment. Dosage ratio: Spacer/Nebuliser = 1/2.5. Co-interventions: none.
Outcomes	Peak Flow. Actual readings changed to % predicted by assuming expected peak flow of 500 l/min as original data has been lost
Notes	Only the first part of this study compared spacer against nebuliser, the second part of the crossover was not analysed due the high likelihood of contamination. Estimated SD for Peak Flow. Data was measured from graph published in errata. (Rev Paul Med 1990;108:98)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	Alternate allocation
Allocation concealment?	No	Investigators had foreknowledge of treatment group assignment

Morrone 1990 (*Continued*)

Blinding? Hospital admission	No	Open label study

Parkin 1995

Methods	Randomisation: No details. Blinding: Single (nurse measuring outcomes only). Excluded: none. Withdrawals: 4 failures (stopping criteria not given). Baseline characteristics: Clinical asthma score was 5.7 chamber, 4.8 nebuliser (P=0.02) therefore an adjusted mean used. Intention to treat analysis: performed. Power analysis: 30 in each group designed to detect approximately 90% difference in asthma score. Jadad score: 2.
Participants	Setting: Hospital inpatients (after stabilisation in emergency department), Canada. 60 children aged 1-5 years old (2.9 years mean) Inclusion criteria: moderate acute asthma. Exclusion criteria: not stated.
Interventions	Beta2-agonist: Salbutamol and ipratropium bromide. Spacer: Aerochamber 140 ml cylindrical with one way valve and mask. Dosage: Salbutamol 400 mcg for those <12 kg, 500 mcg for 12-16 kg, 600 mcg 16 kg or over. All had 40 mcg ipratropium bromide also. Nebulizer: Driven by compressed air, using a face mask Dosage: Salbutamol 0.15 mg/kg/dose (maximum 5 mg) + ipratropium bromide 125 micrograms, suspended in 3 mls of 0.9% saline over 15 minutes. Drug ratio: Assumed drug ratio of nebuliser : MDI and chamber as 1:4. Co-interventions: All participants received systemic corticosteroids.(i. v. or oral)
Outcomes	Primary outcome: 10 point clinical asthma score measuring: respiratory rate, wheezing, indrawing, observed dyspnoea, and inspiratory to expiratory ratio (Measured up to 60 hrs). Secondary measures: time to discharge, time to 4 hourly dosing interval, total number of inhaled doses required, nurses assessed ease of administration and participants tolerance on a Likert scale, parents reported symptoms at 7 and 14 days post discharge
Notes	Single blinding may have been appropriate due to age of participants i.e. little placebo effect in 1 to 5 year olds. Trial sponsored by Aerochamber and Metered dose inhaler companies. Study included as mean age over 2 years.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Information not available

Parkin 1995 (*Continued*)

Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Single blind (assessor only)

Pendergast 1989

Methods	Randomisation: method not stated. Blinding: none. Excluded: not stated. Withdrawals: 4 from spacer group. Baseline characteristics: compared. Intention to treat: not done. Power calculation: estimated 80%. Jadad score: 2.
Participants	Setting: Australia. Acute presentation at Children's Hospital. 27 children aged 3 to 6.8 years. Mean symptom score at presentation: 2.13(0.49) and 2.30(0.46) in spacer groups, 2.42(0.55) in nebuliser group. Inclusion criteria: not stated. Exclusion criteria: not stated.
Interventions	Beta2-agonist: Terbutaline. Spacer: Nebuhaler. Dosage: Low dose group = one puff (0.25 mg) per 5 kg. High dose group = two puffs (0.5 mg) per 5 kg. Each dose (bursts of 3 or 4 puffs) inhaled with 2 breaths and then a minute of tidal breathing. Nebuliser: Unicorn. Dosage: 0.2 mg per kg weight in 2ml saline (max 5mg) driven by oxygen at 6L/min. Dosage ratio: Spacer/Nebuliser = 4/1 or 2/1. Co-interventions: none.
Outcomes	Admission to hospital, symptom score.
Notes	Withdrawals: 3 from spacer group due to inability to co-operate and 1 from spacer group due to clinical deterioration. Vague descriptions of outcome ("no difference" between number in each group needing a second treatment or admission to hospital). Lower dose spacer group showed a trend to deterioration on score between 30 and 60 minutes after treatment which did not reach significance (P 0.05)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Information not available

Pendergast 1989 (*Continued*)

Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

Ploin 2000

Methods	Randomisation: in blocks of 4. Blinding: Double-blind, double dummy design. Excluded: not stated. Withdrawals: none. Baseline characteristics: SaO2 was significantly lower in the Holding Chamber group. Intention to treat analysis: yes. Power analysis: yes. Jadad score: 5.
Participants	Setting: Paediatric emergency department of 2 teaching hospitals in Lyon (France). 64 children recruited aged 1 to 5 years; mean ages 24.8 months (chamber) and 25.5 months (nebuliser). One child excluded from the analysis due to being randomised twice. Inclusion criteria: Acute wheezing in children with at least 3 episodes of wheezing or 3 episodes with a family history of atopy, eczema or asthma. Exclusion criteria: SaO2 less than 90%, inhaled or systemic steroids within the past 24 hours, or underlying chronic disease
Interventions	Beta2-agonist: Albuterol (Salbutamol). Spacer: Babyhaler. Dosage: 50 mcg/kg (maximum of 10 puffs) each puff followed by 8 breaths over 1 to 2 minutes. Treatment given at 20 minute intervals for 60 mins. Nebuliser: Ultrasonic (ARP 70) used in room air. Dosage: 150 mcg/kg diluted in 4 ml Saline over 8-9 minutes. Repeated at 20 minute intervals. Dose ratio: 1:3 (Spacer:Nebuliser). Duration 60 minutes and double dummy design.
Outcomes	Change in Pulmonary Index, Hospital admission, ease of use, improvement in SaO2
Notes	Clarification of inclusion criteria, and reasons for hospital admission provided by the author. Study included as the mean age was over 2 years and care was taken to exclude children with viral bronchiolitis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Blocks of 4 computer generated
Allocation concealment?	Unclear	o information

Ploin 2000 (*Continued*)

Blinding? Hospital admission	Yes	Double dummy

Raimondi 1997

Methods	Randomisation: no details. Blinding: none. Excluded: number not stated. Withdrawals: none. Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: carried out but in the event the study was underpowered. Jadad score: 2.
Participants	Setting: Argentina, Emergency Department at Hospital Ferrer, Buenos Aires. 27 adults with asthma according to the ATS criteria. Inclusion criteria: severe asthma attack defined as FEV1 < 1 litre or < 30% predicted. Exclusion criteria: smokers, pregnant, pneumothorax, pneumonia or in extremis
Interventions	Beta2-agonist: Albuterol (Salbutamol). Spacer: Aerochamber. Dosage: 400 mcg delivered as four separate actuations, each one inhaled by 3 deep breaths and repeated at 60 second intervals. Repeated every 30 mins for 2 hours and then hourly until the sixth hour. Nebuliser: Puritan-Bennett Raindrop. Dosage: 5mg given over 5 to 10 minutes and repeated as above. Dose Ratio: 1:13 (Spacer:Nebuliser). Co-interventions: all patients received 8 mg Dexamethasone IV and were given oxygen
Outcomes	FEV1, hospital admission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

Rao 2002

Methods	Randomisation: no details Blinding: double blind, double dummy. Excluded: number unknown. Withdrawals:not stated ?none. Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: not stated.
Participants	Setting: Pakistan, Hospital emergency departments in 2 hospitals in Karachi. 50 adults aged 18 to 62, (mean age 40), with acute asthma exacerbation (moderate to severe according to BTS guidelines). Initial mean PEF 27-30% predicted . Inclusion criteria: acute asthma defined by signs, symptoms and peak flow readings. Exclusion criteria: unable to perform spirometry, history of respiratory failure, COPD, IHD or arrhythmias, smoking history of more than 10 pack years or pregnancy
Interventions	Beta2-agonist: Salbutamol. Spacer: Not specified. Dosage: 4x100 mcg one puff every minute for 4 doses repeated at 30 minute intervals until patient improved or FEV1 rose to 70% predicted or 3 doses had been administered. Nebuliser: Not specified. Dosage: 2.5mg in 2.5 ml saline driven by oxygen at 5 L to 6L per minute, given at 30 minute intervals until patient improved or FEV1 rose to 70% predicted or 3 doses had been administered. Dosage ratio: Spacer/Nebuliser 1/6. Co-interventions: not specified.
Outcomes	FEV1, PEF, FVC, and pulse rate at 30 and 60 minutes. Hospital admission. After the first treatment 17 spacer patients and 13 nebuliser patients improved and did not require the second or third treatments
Notes	16% of patients in each group were smokers, and none were taking inhaled therapy at presentation. SD for change in FEV1 based on published absolute SD (conservative estimate)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	Yes	Double dummy

Robertson 1998

Methods	Randomisation: no details. Blinding: Double-blind, double dummy design. Excluded: not stated. Withdrawals: 27 due to inadequate response. Baseline characteristics: comparable. Intention to treat analysis: children requiring additional therapy were excluded from further analysis. Power analysis: none. Jadad score: 4.
Participants	Setting: Australia, multi-centre in Emergency Departments. 155 children recruited aged 4 to 12 years, 147 evaluable. Inclusion criteria:PEF under 70% predicted (aged over 7) or clinical score of > 4 out of 12. Exclusion criteria: critically ill, concurrent cardio-pulmonary disease or given bronchodilator within the last hour
Interventions	Beta2-agonist: Salbutamol. Spacer: Volumatic. Dosage: 600 mcg (under 25 kg) and 1200 mcg (over 25 kg) given in bursts of 3 puffs with 15 seconds of tidal breathing. Nebuliser: AVA-NEB Hudson. Dosage: 2.5mg (> 25 kg) or 5mg (> 25 kg) in 2.5 ml saline driven by oxygen at 8 to 10 L/min. Dose ratio 1:4.2 (Spacer: Nebuliser). Single dose study.
Outcomes	Withdrawal to further treatment, PEF, pulse, Blood pressure, tremor and symptom score
Notes	15 withdrawals in spacer group and 12 in nebuliser group. Both groups showed 1% increase in SaO2

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	Yes	Double dummy

Rodrigo 1993

Methods	Randomisation: random numbers. Blinding: double blind, double dummy. Excluded: number unknown. Withdrawals:not stated ?none. Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: not stated. Jadad score: 4.
Participants	Setting: Uruguay. Hospital emergency room. 97 adults aged 18 to 50. Mean PEF(% predicted) at presentation: 32% in each group. Inclusion criteria: "criteria of the American Thoracic Society". Exclusion criteria: PEF or FEV1 > 50% predicted pregnancy, history of chronic cough, other medical disease
Interventions	Beta2-agonist: Salbutamol. Spacer: Volumatic. Dosage: 4 X 100 mcg every 10 minutes, each puff inhaled with two deep inhalations from the spacer. Nebuliser: Ava-Neb. Dosage: 1.5 mg in 4 ml saline driven by oxygen at 8 L/min at 15 minute intervals. Dosage ratio: Spacer/Nebuliser = 1/2, (mean total dose 5.61 mg/11.8 mg). Co-interventions: oxygen by nasal prongs 4 L/min given to all participants. All participants received oral steroids at discharge
Outcomes	Admission to hospital, duration in emergency department, Peak Flow, FEV1, FVC, heart rate, development of tremor
Notes	Separate analysis was performed on those participants admitted and those with FEV1 < 0.9 L. Estimated SD for final Peak Flow in holding chamber group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random numbers table
Allocation concealment?	Unclear	Infomation not available
Blinding? Hospital admission	Yes	Double dummy

Rodrigo 1998

Methods	Randomisation: random numbers. Blinding: double blind, double dummy. Excluded: number unknown. Withdrawals: no data, ?none. Baseline characteristics: comparable. Intention to treat: no data. Power calculation: powered to detect a 36% difference (0.6 litres) in FEV1. Jadad score: 4.
Participants	Setting: Uruguay, Hospital emergency room in Montevideo. 22 adults aged 18 to 50 with acute asthma exacerbation (all met ATS criteria for asthma). Initial mean PEF 30% predicted and SaO2 95%. Inclusion criteria: PEF and FEV1 both below 50% predicted at presentation. Exclusion criteria: other chronic disease or pregnancy.
Interventions	Beta2-agonist: Salbutamol. Spacer: Volumatic. Dosage: 4x100 mcg every 10 minutes, (2.4 mg per hour) Nebuliser: Hudson T Up-draft flow rate 8 L/min. Dosage: 1.5 mg in 4 ml saline driven by compressed air at 8 L/min at 15 minute intervals. Dosage ratio: Spacer/Nebuliser 1/2.3. Co-interventions: oxygen was allowed in the protocol if SaO2 fell below 90% but was not required in any participant. 500 mg of hydrocortisone was given to all patients with a poor response after 3 hours
Outcomes	FEV1, PEF, QTc interval, SaO2 (arterial oxygen saturation) every 30 minutes. Potassium and Salbutamol blood levels at start and 3 hours
Notes	Neither group showed a deterioration in oxygen saturation and no oxygen was needed in this study. Final plasma salbutamol was 10.1 (SD 1.6 ng/m) in spacer group and 14.4 (SD 2.3 ng. ml) in nebuliser group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random numbers table
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	Yes	Double dummy

Rodriguez 1999

Methods	Randomisation: random number table used but allocation not concealed. Blinding: outcomes evaluated by an observer blinded to the treatment allocated. Excluded: number not stated. Withdrawals: there were none. Baseline characteristics: similar in the two groups. Intention to treat: not required. Power calculation: not stated. Jadad score: 1.
Participants	Setting: Colombia. Hospital emergency department (University Hospital of San Ignatio). 69 adults (56 women) mean age 39 years. Mean PEF at baseline 186 L/min, SD 78 L/min (spacer group) and 179 L/min SD 89 L/min (nebuliser group). Asthma severity: 26 mild asthma attack, 20 moderate and 23 severe. Inclusion criteria: "acute exacerbation of asthma" defined clinically. Exclusion criteria: no details.
Interventions	Beta2-agonist: Salbutamol. Spacer: Volumatic. Dosage: 4x100mcg every 10 minutes for one hour (no details of inhalation method). Nebuliser: type not stated. Dosage: 2.5mg every 20 mins for one hour. Dosage ratio: Spacer/Nebuliser 1/3. Co-interventions: not stated.
Outcomes	Admission to hospital. Heart rate, respiratory rate, PEF, every 20 mins and at 120 mins. Blood gases at baseline and 120 mins
Notes	Unpublished data supplied by authors. Standard deviations provided for each time period, and imputed to the change measurements

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	No	Allocation not concealed
Blinding? Hospital admission	No	Outcomes evaluated by an observer blinded to the treatment allocated

Salzman 1989

Methods	Randomisation: random numbers. Blinding: double blind, double dummy. Excluded: number not stated. Withdrawals: six patients, none for worsening clinical status. Baseline characteristics: comparable, except baseline FEV1 lower in the spacer group. Intention to treat: not done. Power calculation: not stated. Jadad score: 5.
Participants	Setting: USA. Hospital emergency department. 44 adults. Spacer group mean age 32.5 yrs (SD 12.5), nebuliser group mean age 28 yrs (SD 10.3). Mean FEV1(% predicted) at presentation: Spacer 26% (SD 12.1%), nebuliser 33% (SD 16%). Inclusion criteria: acute asthma FEV1< 50% predicted. Exclusion criteria: COPD, pneumothorax, depression, PaCO2 > 40, ventilation required
Interventions	Beta2-agonist: Metaproterenol sulphate. Spacer: Aerochamber. Dosage: 3x0.65 mg puffs each 5 minutes apart. Single treatment. No details of breathing method. Nebuliser: type not stated. Dosage: 15 mg in 2ml saline over 10 minutes. Single treatment. Dosage ratio: Spacer/Nebuliser = 1/8. Co-interventions: none.
Outcomes	Admission to hospital, FEV1, FVC, heart rate, respiratory rate
Notes	Rise in FEV1 (% predicted) calculated from data given in paper

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	Yes	Double dummy

Sannier 2007

Methods	Randomisation: Allocation by numbered envelopes Blinding: none Excluded: 106 of 185 children presenting during working hours were excluded Withdrawals: none for the initial study, six families were lost to longer term follow-up Baseline characteristics: comparable, except imbalance in respiratory rate
Participants	Setting: Pediatric Emergency Department in France . 79 children aged 4 to 15 years (mean age 9 years). 40 patients allocated to nebuliser and 39 allocated to spacer.

Sannier 2007 (*Continued*)

	Inclusion criteria:severe acute exacerbation of asthma (Bishop score >6 or SaO2 less than 92%). The definition of severe asthma was understood as an acute attack developing over more than 24 hours (or nocturnally), non-responsive to beta-agonist therapy (initiated prior to hospital presentation), or occurring in spite of maintenance treatment with inhaled steroids (+/- beta-agonist), or recurring within 1 month of oral steroid treatment and an attack occurring in a child with previous treatment in intensive care for acute asthma**.**
Interventions	Beta2-agonist: Salbutamol or Terbutaline Spacer: Babyhaler/Volumatic or Nespacer/Nebuhaler (according to child's home use). Dosage: 6x100mcg salbutamol or 6x250mcg terbutaline every 20 minutes for six doses (each inhalation was separated by 8 to 10 valve movements). Nebuliser: Mininebuliser AIRVIE, Peters, Bobigny, France. Driven by oxygen at 6 L/min. Dosage: 0.15mg/kg salbutamol in 4 ml saline every 20 mins for six doses (minimum 1.5 mg to maximum 5 mg per dose). Dosage ratio: Spacer/Nebuliser 1/3 to 1/5. Co-interventions: all patients received oral steroids at the start of treatment
Outcomes	Hospitalisation, Pulse Rate, Respiratory Rate, SaO2, PEF
Notes	Baseline imbalance in Respiratory Rate noted, which may have contributed to the larger fall in the nebuliser group

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Yes	"numbered envelopes"
Blinding? Hospital admission	No	open

Turner 1988

Methods	Randomisation: double blind. Blinding: double blind, double dummy. Excluded: 26 out of 101 evaluated. Withdrawals: not stated. Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: not stated. Jadad score: 4.
Participants	Setting: USA. Hospital emergency room. 53 adults with asthma 18 to 75 years old, 22 participants with COPD also in study but excluded from this review. Mean FEV1 at presentation: Spacer 1.2 L (SD 0.1), Nebuliser 1.1 L (SD 0.1)

Turner 1988 (*Continued*)

	Inclusion criteria: onset symptoms < 30 years or < 10 pack years smoking. Exclusion criteria: pregnancy, suspected MI or CCF, intubation required
Interventions	Beta2-agonist: Metaproterenol. Spacer: Inspirease. Dosage: 3 x 0.65 mg puffs at 2 minute intervals inhaled by 2 slow inhalations each. Total of three treatments at 30 minute intervals. Nebuliser: Acorn II. Dosage: 15 mg in 2ml saline given over 10 minutes. Total of three treatments at 30 minute intervals. Dosage ratio: Spacer/Nebuliser = 1/8. Co-interventions: oxygen and intravenous steroids given at the discretion of the emergency room physician who was not involved in the study
Outcomes	Admission to hospital, symptom score, FEV1, oxygen saturation, heart rate, respiratory rate, administration of steroids
Notes	Standard deviations calculated from raw data supplied by the author. Predicted Peak Flow estimated

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	Yes	Double dummy

Valencia 1999

Methods	Randomisation: Random number table, no details of allocation concealment. Blinding: none. Excluded: number not stated. Withdrawals: not stated. Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: not stated. Jadad score:1.
Participants	Setting: Casualty Department of Children's hospital in Columbia. 70 Children with acute asthma aged from 1 to 6 years old mean age 3.2 years (Spacer) and 3.6 years (Nebuliser). Mean Oxygen saturation 92% (Spacer) and 91% (Nebuliser). Inclusion criteria: acute asthma exacerbation. Exclusion criteria: not stated.

Valencia 1999 (*Continued*)

Interventions	Beta2-agonist: Salbutamol. Spacer: Type unspecified (500ml size). Dosage: 2x100mcg given three times at 20 minute intervals. Nebuliser: Breath Neb II. Dosage: 0.15mg/kg diluted in 4 ml of Saline, given three times at 20 minute intervals. Dosage ratio: not stated. Co-interventions: not stated.
Outcomes	Respiratory rate, oxygen saturation, patient rating, clinical response all after 60 minutes
Notes	Paper states that two doses of 100 mg were given via Spacer but this has been assumed to be a misprint for 100 mcg

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

Vazquez 1992

Methods	Randomisation: no details. Blinding: none. Excluded: number not stated. Withdrawals: not stated. Baseline characteristics: comparable. Intention to treat: not stated. Power calculation: not stated. Jadad score: 1.
Participants	Setting: Spain. Hospital Emergency Room. 18 children with asthma. Mean age 9.33 years (Spacer), 8.66 years (Nebuliser). Mean FEV1 (% predicted): Spacer 41.3% (sd 16%), Nebuliser 39.6%(sd 19%) . Inclusion criteria: FEV1 less than 65% predicted and no bets-agonist given in the previous 2 hours
Interventions	Beta2-agonist: Salbutamol. Spacer: Volumatic. Dosage: 5 x 100 mcg together into spacer followed by 30 seconds of tidal breathing. Followed by 10 x 100 mcg every 20 minutes until stable or 1.5 mg/kg maximum dose. Nebuliser: Type not stated. Dosage: 500 mcg diluted in 3 ml driven by oxygen at 7 L/min Dosage ratio: Spacer/Nebuliser = 1.3/1 Total average dose by spacer 3.2 mg(SD1mg) and by nebuliser 2.5mg(SD 0.7 mg).

Vazquez 1992 (*Continued*)

	Co-interventions: not stated.
Outcomes	Admission to hospital, Peak Flow, FEV1, FVC, oxygen saturation, heart rate
Notes	Improvement in lung function expressed as % maximum predicted (see footnote). No significant changes in blood gases in both groups.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Informaion not available
Blinding? Hospital admission	No	Open label study

Vivek 2003

Methods	Randomisation: using a table of random numbers. Concealment of allocation unclear. Blinding: unblinded study Excluded: number not stated. Withdrawals: none Baseline characteristics: "comparable" Power calculation: not stated.
Participants	Setting: South India. Emergency Room. 122 adults and children aged 10 to 50 years. 54 patients allocated to nebuliser and 68 allocated to spacer. Mean PEF at presentation: 200 - 250 L/min Inclusion criteria:acute exacerbation of asthma (PEF 200 - 250 L/min). Exclusion criteria: not stated.
Interventions	Beta2-agonist: Terbutaline Spacer: Astra Spacehaler (750 ml) Dosage: 6 puffs of 0.25 mg. Treatment repeated at 5 and 30 minutes. Each puff inhaled separately. Nebuliser: Aerofamily nebuliser Dosage: 5mg (0.5 ml respirator solution + 1.5 ml normal saline). Treatment repeated at 5 and 30 minutes. Dose ratio: 1:4 (Spacer:Nebuliser). Duration 60 minutes.
Outcomes	Endpoint: Terbutaline doses were administered until: 1. PEFR increased to 250 l/min or 2. Patient becomes asymptomatic 3. Three doses of terbutaline given 4. Side effects/Clinical deterioration occurred

Vivek 2003 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers table
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label

Williams 1996

Methods	Randomisation: no details given. Blinding: none. Excluded: Children under six years old. Impending respiratory failure. Withdrawals: none. Baseline characteristics: comparable. Intention to treat analysis: not required. Jadad score: 2.
Participants	Denver. Urban paediatric emergency department. 60 children aged 6 years or older. Mean PEF at presentation 46% predicted. Inclusion criteria: past history of asthma or current reversibility with albuterol. Exclusion criteria: corticosteroid therapy in the past 7 days, chronic cardiopulmonary disease other than asthma and severe presentation (depressed mental status, cyanosis impending respiratory failure
Interventions	Beta2-agonist: Salbutamol (Albuterol). Spacers: Aerochamber (20 patients) and ACE (22 patients), 4 x 90 mcg actuations of salbutamol given separately every 30 minutes, inhaled using tidal breathing for one minute each. Three treatments given at 30 minute intervals. Nebuliser: PARI-JET II 2.5mg of Albuterol given every 30 minutes in 3 ml saline driven by pressurised air at 6 L per minute. Three treatments given at 30 minute intervals. Co-interventions: oxygen was given to all participants with an oxygen saturation of less than 92% while breathing room air. All participants were given oral prednisolone at a dose of 2 mg/kg (maximum 60 mg) within 30 minutes of enrolment
Outcomes	Admission to hospital, change in % predicted Peak Flow, change in % predicted respiratory rate
Notes	The results for the two spacers were pooled. Four participants required additional treatment in the emergency department with one to three further treatments with nebulised albuterol before they were discharged; these were 1 from the nebuliser group and 3 from the spacer groups

Risk of bias

Williams 1996 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? Hospital admission	No	Open label study

PEF- Peak Flow; FEV1- Forced expiratory volume in one second; %max predicted = (post treatment - basal)/(predicted - basal); puff - actuation of metered-dose inhaler.

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

Study	Reason for exclusion
Beasley 1985	Probably hospitalised patients and no response from authors to request for further information
Benton 1989	Not randomised.
Berenberg 1985	Mixed population of patients, not possible to separate data from asthmatics and no response from authors
Campbell 1995	No randomisation.
Deerojanawong 2005	Mean age of children was under 2 years
Fuglsang 1986	Cross-over design inappropriate for acute asthma.
Hodder 1988	No outcomes presented in this abstract in a form that could be used. No response from author
Jasper 1987	Mixed population of patients, not possible to separate data from asthmatics and no response from authors
Levitt 1995	Mixed population of COPD and asthma; no separate data given for asthmatic patients. No response from author
Madsen 1982	No useable data and no response from authors.
Maguire 1991	Probably hospitalised patients, no response from authors to request for clarification
Mandelberg 1997	Mixed population of COPD and asthma; no separate data given for asthmatic patients. No response from author
Mandelberg 2000	Infants and young children with a median age of 16 months.

(*Continued*)

Morgan 1982	No standard deviation published in paper and no reply from authors. No useable data
Newman 2002	Non randomised (before and after study).
Rubilar 2000	Study in infants of 1 to 24 months.
Shaikh 2001	Not acute asthma.
Shim 1984	Not acute asthma.
Summer 1989	Different beta-2-agonists used.
Tarala 1980	No holding chamber used.
Vilarinho 2003	Not acute asthma. Children using bronchodilators or corticosteroids were excluded
Wildhaber 1999	Not acute asthma.

DATA AND ANALYSES

Comparison 1. Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	16	1136	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.61, 1.12]
1.1 Adults	8	524	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.63, 1.49]
1.2 Children	8	612	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.47, 1.09]
2 Hospital admission or poor response to treatment	18	1266	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.18]
2.1 Adults	8	524	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.63, 1.49]
2.2 Children	10	742	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.60, 1.23]
3 Duration in emergency department (hours).	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Adults	2	132	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.40, 0.44]
3.2 Children	3	396	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.62, -0.44]
4 Final rise in FEV1 (% predicted)	8	355	Mean Difference (IV, Fixed, 95% CI)	1.03 [-1.97, 4.04]
4.1 Adults	6	307	Mean Difference (IV, Fixed, 95% CI)	1.07 [-2.42, 4.57]
4.2 Children	2	48	Mean Difference (IV, Fixed, 95% CI)	0.92 [-4.96, 6.79]
5 30 minute rise in FEV1 (% predicted)	3	200	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.18, 2.78]
5.1 Adults	3	200	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.18, 2.78]
6 Severe asthmatics final rise in FEV1 (% predicted)	4	94	Mean Difference (IV, Fixed, 95% CI)	1.60 [-4.49, 7.69]
6.1 Adults	4	94	Mean Difference (IV, Fixed, 95% CI)	1.60 [-4.49, 7.69]
7 Final rise in peak flow (% predicted)	6	305	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-4.68, 2.07]
7.1 Adults	3	139	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-4.60, 3.63]
7.2 Children	3	166	Mean Difference (IV, Fixed, 95% CI)	-2.99 [-8.88, 2.91]
8 30 minute rise in peak flow (% predicted)	2	147	Mean Difference (IV, Fixed, 95% CI)	0.92 [-2.68, 4.51]
8.1 Adults	2	147	Mean Difference (IV, Fixed, 95% CI)	0.92 [-2.68, 4.51]
9 Rise in pulse rate (% baseline)	15	996	Mean Difference (IV, Fixed, 95% CI)	-4.57 [-6.22, -2.93]
9.1 Adults	7	376	Mean Difference (IV, Fixed, 95% CI)	-1.23 [-4.06, 1.60]
9.2 Children	8	620	Mean Difference (IV, Fixed, 95% CI)	-6.27 [-8.29, -4.25]
10 Number of patients developing tremor	6	343	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.58, 1.10]
10.1 Adults	4	234	Risk Ratio (IV, Fixed, 95% CI)	1.12 [0.66, 1.90]
10.2 Children	2	109	Risk Ratio (IV, Fixed, 95% CI)	0.65 [0.43, 0.98]
11 Number of patients given steroids	3	240	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.81, 1.54]
11.1 Adults	2	88	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.13]
11.2 Children	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.87, 1.67]
12 Rise in respiratory rate (breaths per minute)	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Adults	5	257	Mean Difference (IV, Random, 95% CI)	0.28 [-2.29, 2.84]
12.2 Children	6	491	Mean Difference (IV, Random, 95% CI)	-0.68 [-2.81, 1.44]

13 % Oxygen Saturation (change from baseline)	4	281	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.76, 0.45]
13.1 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.2 Children	4	281	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.76, 0.45]

Comparison 2. Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Children	3		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Final rise in peak flow (% predicted)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.1 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 30 minute rise in FEV1 (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 15 minute rise in FEV1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 30 minute rise in peak flow (% predicted)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.2 Children	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 15 minute rise in peak flow (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Rise in pulse rate (% baseline)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7.2 Children	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Number of patients developing tremor	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Number of patients with deterioration in blood gases	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Children	2		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Rise in respiratory rate	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Adults	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3. Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital admission (days)	2	78	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.23, 0.75]
1.1 Adults	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.23, 2.03]
1.2 Children	1	60	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.21, 0.79]
2 Number of hours until reached 4 hourly dosing regime	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Total number of inhaled doses received	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Number of patients returning to normal PEFR and respiratory score levels (end of study)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Number of symptom-free patients 14 days post discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Readmissions in the subsequent 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Clinical asthma score (end of trial)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Maximum percentage decrease in respiratory score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
8.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Respiratory rate at discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 Heart rate at discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11 Oxygen Saturations at discharge	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Adults	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11.2 Children	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 30 minute rise in FEV1	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.2 Children	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable

13 Final rise in FEV1	2	Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Adults	1	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.2 Children	1	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
14 Final rise in peak flow (% change from baseline)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Adults	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.2 Children	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 4. Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	13	857	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.60, 1.14]
1.1 Adults	5	308	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.60, 3.53]
1.2 Adults with Volumatic	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.38]
1.3 Children	5	365	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.40, 1.06]
1.4 Children with Volumatic	1	18	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Hospital admission or poor response to treatment	15	987	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.22]
2.1 Adults	5	308	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.60, 3.53]
2.2 Adults with Volumatic	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.38]
2.3 Children	6	435	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.23]
2.4 Children with Volumatic	2	78	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.44, 3.06]
3 Duration in emergency department (hours).	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Adults	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.77, 0.37]
3.2 Adults with Volumatic	1	97	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.34, 0.94]
3.3 Children	2	348	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-0.58, -0.37]
4 Final rise in FEV1 (% predicted)	7	335	Mean Difference (IV, Fixed, 95% CI)	0.78 [-2.32, 3.87]
4.1 Adults	3	168	Mean Difference (IV, Fixed, 95% CI)	0.30 [-4.70, 5.30]
4.2 Adults with Volumatic	2	119	Mean Difference (IV, Fixed, 95% CI)	1.20 [-4.13, 6.53]
4.3 Children	1	30	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.4 Children with Volumatic	1	18	Mean Difference (IV, Fixed, 95% CI)	9.8 [-9.41, 29.01]
5 30 minute rise in FEV1 (% predicted)	2	150	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-4.35, 2.21]
5.1 Adults	1	53	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-8.51, 0.91]
5.2 Adults with Volumatic	1	97	Mean Difference (IV, Fixed, 95% CI)	1.5 [-3.07, 6.07]
6 Severe asthmatics final rise in FEV1 (% predicted)	4	94	Mean Difference (IV, Fixed, 95% CI)	1.60 [-4.49, 7.69]
6.1 Adults	3	55	Mean Difference (IV, Fixed, 95% CI)	0.86 [-6.77, 8.48]
6.2 Adults with Volumatic	1	39	Mean Difference (IV, Fixed, 95% CI)	2.90 [-7.21, 13.01]
7 Final rise in peak flow (% predicted)	5	285	Mean Difference (IV, Fixed, 95% CI)	-1.32 [-4.83, 2.20]
7.1 Adults with Volumatic	2	119	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-4.77, 3.98]
7.2 Children	2	148	Mean Difference (IV, Fixed, 95% CI)	-3.75 [-9.95, 2.45]
7.3 Children with Volumatic	1	18	Mean Difference (IV, Fixed, 95% CI)	4.10 [-14.81, 23.01]
8 30 minute rise in peak flow (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

8.1 Adults with Volumatic	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9 Rise in pulse rate (% baseline)	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Adults	3	168	Mean Difference (IV, Fixed, 95% CI)	-2.28 [-7.81, 3.24]
9.2 Adults with Volumatic	3	188	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-3.89, 3.58]
9.3 Children	4	314	Mean Difference (IV, Fixed, 95% CI)	-8.30 [-10.93, -5.67]
9.4 Children with Volumatic	2	78	Mean Difference (IV, Fixed, 95% CI)	-6.73 [-11.24, -2.23]

Analysis 1.1. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 1 Hospital admission.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 1 Hospital admission

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
Colacone 1993	1/40	0/40		3.00 [0.13, 71.51]
Idris 1993	1/15	1/20		1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9		0.0 [0.0, 0.0]
Rao 2002	0/25	1/25		0.33 [0.01, 7.81]
Rodrigo 1993	5/49	4/48		1.22 [0.35, 4.29]
Rodriguez 1999	14/36	17/33		0.75 [0.45, 1.28]
Turner 1988	4/27	5/26		0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		3.97 [0.48, 32.98]
Subtotal (95% CI)	**269**	**255**		**0.97 [0.63, 1.49]**
Total events: 30 (Holding Chamber), 29 (Nebuliser)				
Heterogeneity: Chi² = 3.82, df = 6 (P = 0.70); I² =0.0%				
Test for overall effect: Z = 0.15 (P = 0.88)				
2 Children				
Chong-Neto 2005	0/20	0/10		0.0 [0.0, 0.0]
Chou 1995	4/71	5/81		0.91 [0.25, 3.27]
Jamalvi 2006	4/84	7/66		0.45 [0.14, 1.47]
Leversha 2000	10/30	18/30		0.56 [0.31, 1.00]
Ploin 2000	3/31	3/32		1.03 [0.23, 4.73]
Sannier 2007	6/39	3/40		2.05 [0.55, 7.63]
Vazquez 1992	0/9	0/9		0.0 [0.0, 0.0]

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Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Williams 1996	2/42	2/18		0.43 [0.07, 2.81]
Subtotal (95% CI)	**326**	**286**		**0.72 [0.47, 1.09]**
Total events: 29 (Holding Chamber), 38 (Nebuliser)				
Heterogeneity: Chi^2 = 4.43, df = 5 (P = 0.49); I^2 =0.0%				
Test for overall effect: Z = 1.55 (P = 0.12)				
Total (95% CI)	**595**	**541**		**0.83 [0.61, 1.12]**
Total events: 59 (Holding Chamber), 67 (Nebuliser)				
Heterogeneity: Chi^2 = 8.90, df = 12 (P = 0.71); I^2 =0.0%				
Test for overall effect: Z = 1.24 (P = 0.22)				

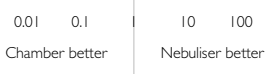
Analysis 1.2. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 2 Hospital admission or poor response to treatment.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 2 Hospital admission or poor response to treatment

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
Colacone 1993	1/40	0/40		3.00 [0.13, 71.51]
Idris 1993	1/15	1/20		1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9		0.0 [0.0, 0.0]
Rao 2002	0/25	1/25		0.33 [0.01, 7.81]
Rodrigo 1993	5/49	4/48		1.22 [0.35, 4.29]
Rodriguez 1999	14/36	17/33		0.75 [0.45, 1.28]
Turner 1988	4/27	5/26		0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		3.97 [0.48, 32.98]



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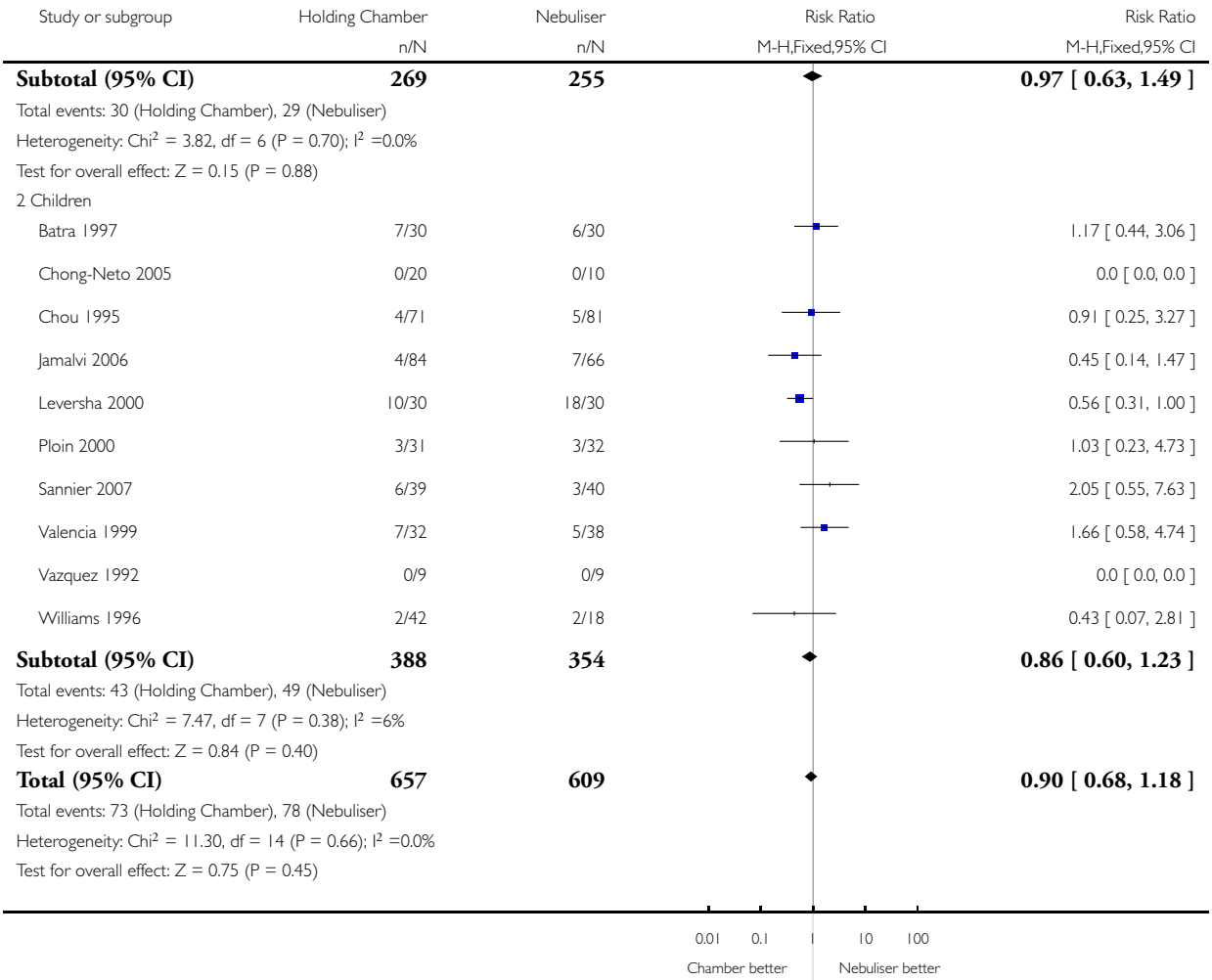


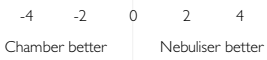
Analysis 1.3. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 3 Duration in emergency department (hours)..

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 3 Duration in emergency department (hours).

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Idris 1993	15	1.5 (0.8)	20	1.7 (0.9)		56.0 %	-0.20 [-0.77, 0.37]
Rodrigo 1993	49	2.2 (1.7)	48	1.9 (1.5)		44.0 %	0.30 [-0.34, 0.94]
Subtotal (95% CI)	**64**		**68**			**100.0 %**	**0.02 [-0.40, 0.44]**
Heterogeneity: Chi^2 = 1.32, df = 1 (P = 0.25); I^2 =24%							
Test for overall effect: Z = 0.09 (P = 0.93)							
2 Children							
Chou 1995	71	1.1 (0.52)	81	1.72 (0.86)		15.8 %	-0.62 [-0.84, -0.40]
Duarte 2002	97	0.69 (0.3)	99	1.12 (0.52)		55.9 %	-0.43 [-0.55, -0.31]
Sannier 2007	28	1.8 (0.217)	20	2.47 (0.333)		28.3 %	-0.67 [-0.84, -0.50]
Subtotal (95% CI)	**196**		**200**			**100.0 %**	**-0.53 [-0.62, -0.44]**
Heterogeneity: Chi^2 = 6.07, df = 2 (P = 0.05); I^2 =67%							
Test for overall effect: Z = 11.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 6.18, df = 1 (P = 0.01), I^2 =84%							



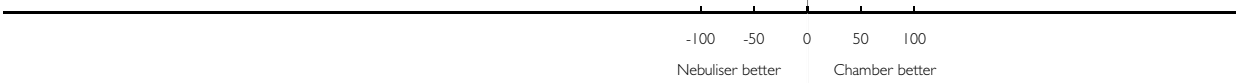
Analysis 1.4. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 4 Final rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 4 Final rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Colacone 1993	40	23 (16)	40	22 (19)		15.2 %	1.00 [-6.70, 8.70]
Idris 1993	15	27.1 (12.7)	20	26.4 (20.4)		7.4 %	0.70 [-10.31, 11.71]
Rao 2002	8	22.7 (14.21)	12	17.58 (13.18)		5.9 %	5.12 [-7.23, 17.47]
Rodrigo 1993	49	25 (15.6)	48	23 (12.7)		28.2 %	2.00 [-3.66, 7.66]
Rodrigo 1998	11	44.3 (16.7)	11	49.4 (21)		3.6 %	-5.10 [-20.96, 10.76]
Turner 1988	27	13.03 (13.88)	26	13.74 (16.41)		13.4 %	-0.71 [-8.91, 7.49]
Subtotal (95% CI)	**150**		**157**			**73.8 %**	**1.07 [-2.42, 4.57]**
Heterogeneity: Chi² = 1.28, df = 5 (P = 0.94); I² =0.0%							
Test for overall effect: Z = 0.60 (P = 0.55)							
2 Children							
Chong-Neto 2005	20	34 (10)	10	34 (7)		23.7 %	0.0 [-6.17, 6.17]
Vazquez 1992	9	29.5 (23.4)	9	19.7 (17.8)		2.4 %	9.80 [-9.41, 29.01]
Subtotal (95% CI)	**29**		**19**			**26.2 %**	**0.92 [-4.96, 6.79]**
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² =0.0%							
Test for overall effect: Z = 0.31 (P = 0.76)							
Total (95% CI)	**179**		**176**			**100.0 %**	**1.03 [-1.97, 4.04]**
Heterogeneity: Chi² = 2.19, df = 7 (P = 0.95); I² =0.0%							
Test for overall effect: Z = 0.67 (P = 0.50)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² =0.0%							



Analysis 1.5. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 5 30 minute rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

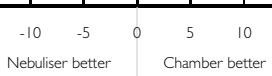
Outcome: 5 30 minute rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Rao 2002	25	19.56 (11.27)	25	15.6 (14.39)		17.3 %	3.96 [-3.20, 11.12]
Rodrigo 1993	49	17 (13.5)	48	15.5 (9.1)		42.6 %	1.50 [-3.07, 6.07]
Turner 1988	27	5.4 (7.5)	26	9.2 (9.8)		40.1 %	-3.80 [-8.51, 0.91]
Total (95% CI)	**101**		**99**			**100.0 %**	**-0.20 [-3.18, 2.78]**

Heterogeneity: Chi^2 = 4.07, df = 2 (P = 0.13); I^2 =51%

Test for overall effect: Z = 0.13 (P = 0.90)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 6 Severe asthmatics final rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

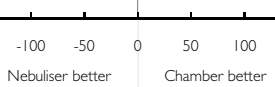
Outcome: 6 Severe asthmatics final rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Idris 1993	6	26 (20)	8	14 (18)		9.0 %	12.00 [-8.29, 32.29]
Raimondi 1997	9	29 (15)	9	27 (15)		19.3 %	2.00 [-11.86, 15.86]
Rodrigo 1993	19	22.6 (17.5)	20	19.7 (14.5)		36.2 %	2.90 [-7.21, 13.01]
Turner 1988	10	9.52 (11.01)	13	12.12 (14.02)		35.4 %	-2.60 [-12.83, 7.63]
Total (95% CI)	**44**		**50**			**100.0 %**	**1.60 [-4.49, 7.69]**

Heterogeneity: Chi^2 = 1.72, df = 3 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable



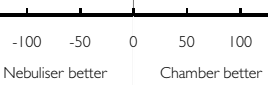
Analysis 1.7. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 7 Final rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 7 Final rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Rao 2002	8	14.24 (15.56)	12	15.43 (9.69)		7.8 %	-1.19 [-13.29, 10.91]
Rodrigo 1993	49	22.1 (13)	48	21.4 (10)		53.6 %	0.70 [-3.91, 5.31]
Rodrigo 1998	11	47.5 (14.4)	11	57.9 (18.7)		5.9 %	-10.40 [-24.35, 3.55]
Subtotal (95% CI)	**68**		**71**			**67.2 %**	**-0.49 [-4.60, 3.63]**
Heterogeneity: Chi² = 2.21, df = 2 (P = 0.33); I² =9%							
Test for overall effect: Z = 0.23 (P = 0.82)							
2 Children							
Chou 1995	39	19 (19.5)	49	25 (19.1)		17.2 %	-6.00 [-14.13, 2.13]
Vazquez 1992	9	29.6 (21.4)	9	25.5 (19.5)		3.2 %	4.10 [-14.81, 23.01]
Williams 1996	42	25 (18.2)	18	25.61 (17)		12.4 %	-0.61 [-10.20, 8.98]
Subtotal (95% CI)	**90**		**76**			**32.8 %**	**-2.99 [-8.88, 2.91]**
Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 0.99 (P = 0.32)							
Total (95% CI)	**158**		**147**			**100.0 %**	**-1.31 [-4.68, 2.07]**
Heterogeneity: Chi² = 3.98, df = 5 (P = 0.55); I² =0.0%							
Test for overall effect: Z = 0.76 (P = 0.45)							
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² =0.0%							



Analysis 1.8. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 8 30 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 8 30 minute rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Rao 2002	25	14.24 (13.94)	25	12.52 (14.24)		21.2 %	1.72 [-6.09, 9.53]
Rodrigo 1993	49	15.4 (11.4)	48	14.7 (8.8)		78.8 %	0.70 [-3.35, 4.75]
Total (95% CI)	**74**		**73**			**100.0 %**	**0.92 [-2.68, 4.51]**

Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%

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

Test for subgroup differences: Not applicable

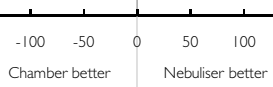
Analysis 1.9. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 9 Rise in pulse rate (% baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 9 Rise in pulse rate (% baseline)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Colacone 1993	40	-1 (19)	40	4 (19)		3.9 %	-5.00 [-13.33, 3.33]
Idris 1993	15	1 (16)	20	0 (18)		2.1 %	1.00 [-10.30, 12.30]
Rao 2002	8	-15.91 (6.95)	12	-12.58 (9.02)		5.5 %	-3.33 [-10.35, 3.69]
Rodrigo 1993	49	-1.32 (13.8)	48	-0.44 (14.2)		8.7 %	-0.88 [-6.45, 4.69]
Rodrigo 1998	11	-10 (19.7)	11	-2 (19.7)		1.0 %	-8.00 [-24.46, 8.46]
Rodriguez 1999	36	0 (11.7)	33	-1.3 (10.7)		9.7 %	1.30 [-3.99, 6.59]
Turner 1988	27	-4 (16)	26	-3 (20)		2.8 %	-1.00 [-10.77, 8.77]
Subtotal (95% CI)	**186**		**190**			**33.7 %**	**-1.23 [-4.06, 1.60]**
Heterogeneity: Chi² = 2.83, df = 6 (P = 0.83); I² =0.0%							
Test for overall effect: Z = 0.85 (P = 0.39)							
2 Children							
Batra 1997	30	-12.8 (9.4)	30	-7.4 (11.6)		9.5 %	-5.40 [-10.74, -0.06]
Chong-Neto 2005	20	20.6 (10.4)	10	32.9 (12.2)		3.5 %	-12.30 [-21.13, -3.47]
Chou 1995	71	5 (12.4)	81	15 (17.3)		12.0 %	-10.00 [-14.74, -5.26]
Duarte 2002	34	15 (20.7)	38	20 (18.1)		3.3 %	-5.00 [-14.03, 4.03]
Jamalvi 2006	84	-18 (16.4)	66	-17 (15.7)		10.2 %	-1.00 [-6.16, 4.16]
Leversha 2000	30	0.11 (7.2)	30	7.26 (7.2)		20.4 %	-7.15 [-10.79, -3.51]
Sannier 2007	39	22.8 (24.7)	39	20.2 (12.4)		3.6 %	2.60 [-6.07, 11.27]
Vazquez 1992	9	-10 (10)	9	0 (8)		3.9 %	-10.00 [-18.37, -1.63]
Subtotal (95% CI)	**317**		**303**			**66.3 %**	**-6.27 [-8.29, -4.25]**
Heterogeneity: Chi² = 13.35, df = 7 (P = 0.06); I² =48%							
Test for overall effect: Z = 6.09 (P < 0.00001)							
Total (95% CI)	**503**		**493**			**100.0 %**	**-4.57 [-6.22, -2.93]**
Heterogeneity: Chi² = 24.25, df = 14 (P = 0.04); I² =42%							
Test for overall effect: Z = 5.45 (P < 0.00001)							
Test for subgroup differences: Chi² = 8.07, df = 1 (P = 0.00), I² =88%							



Analysis 1.10. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 10 Number of patients developing tremor.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 10 Number of patients developing tremor

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
1 Adults				
Colacone 1993	3/40	3/40		1.00 [0.21, 4.66]
Idris 1993	0/15	0/20		0.0 [0.0, 0.0]
Rodrigo 1993	18/49	13/48		1.36 [0.75, 2.45]
Rodrigo 1998	1/11	6/11		0.17 [0.02, 1.17]
Subtotal (95% CI)	**115**	**119**		**1.12 [0.66, 1.90]**
Total events: 22 (Holding Chamber), 22 (Nebuliser)				
Heterogeneity: Chi^2 = 4.11, df = 2 (P = 0.13); I^2 =51%				
Test for overall effect: Z = 0.41 (P = 0.68)				
2 Children				
Chong-Neto 2005	12/20	9/10		0.67 [0.44, 1.01]
Sannier 2007	1/39	3/40		0.34 [0.04, 3.15]
Subtotal (95% CI)	**59**	**50**		**0.65 [0.43, 0.98]**
Total events: 13 (Holding Chamber), 12 (Nebuliser)				
Heterogeneity: Chi^2 = 0.34, df = 1 (P = 0.56); I^2 =0.0%				
Test for overall effect: Z = 2.06 (P = 0.039)				
Total (95% CI)	**174**	**169**		**0.80 [0.58, 1.10]**
Total events: 35 (Holding Chamber), 34 (Nebuliser)				
Heterogeneity: Chi^2 = 6.94, df = 4 (P = 0.14); I^2 =42%				
Test for overall effect: Z = 1.39 (P = 0.16)				
Test for subgroup differences: Chi^2 = 2.50, df = 1 (P = 0.11), I^2 =60%				

Analysis 1.11. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 11 Number of patients given steroids.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 11 Number of patients given steroids

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Adults					
Idris 1993	1/15	6/20		12.6 %	0.22 [0.03, 1.66]
Turner 1988	4/27	2/26		5.0 %	1.93 [0.39, 9.63]
Subtotal (95% CI)	**42**	**46**		**17.6 %**	**0.71 [0.23, 2.13]**
Total events: 5 (Holding Chamber), 8 (Nebuliser)					
Heterogeneity: Chi^2 = 2.77, df = 1 (P = 0.10); I^2 =64%					
Test for overall effect: Z = 0.62 (P = 0.54)					
2 Children					
Chou 1995	38/71	36/81		82.4 %	1.20 [0.87, 1.67]
Subtotal (95% CI)	**71**	**81**		**82.4 %**	**1.20 [0.87, 1.67]**
Total events: 38 (Holding Chamber), 36 (Nebuliser)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
Total (95% CI)	**113**	**127**		**100.0 %**	**1.12 [0.81, 1.54]**
Total events: 43 (Holding Chamber), 44 (Nebuliser)					
Heterogeneity: Chi^2 = 3.13, df = 2 (P = 0.21); I^2 =36%					
Test for overall effect: Z = 0.68 (P = 0.50)					

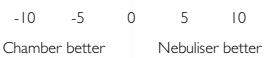
Analysis 1.12. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 12 Rise in respiratory rate (breaths per minute).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 12 Rise in respiratory rate (breaths per minute)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adults							
Colacone 1993	40	-3 (6.3)	40	-3 (7.6)		19.5 %	0.0 [-3.06, 3.06]
Idris 1993	15	-5 (4)	20	-2 (6)		18.4 %	-3.00 [-6.32, 0.32]
Rao 2002	8	-8.62 (3.38)	12	-6.23 (3.39)		19.6 %	-2.39 [-5.42, 0.64]
Rodriguez 1999	36	-3.3 (5.5)	33	-6.5 (5.2)		21.8 %	3.20 [0.68, 5.72]
Turner 1988	27	-3 (5.2)	26	-6 (5.1)		20.7 %	3.00 [0.23, 5.77]
Subtotal (95% CI)	**126**		**131**			**100.0 %**	**0.28 [-2.29, 2.84]**
Heterogeneity: Tau^2 = 6.29; Chi^2 = 15.37, df = 4 (P = 0.004); I^2 =74%							
Test for overall effect: Z = 0.21 (P = 0.83)							
2 Children							
Batra 1997	30	-23.5 (6.7)	30	-20.9 (7.4)		17.9 %	-2.60 [-6.17, 0.97]
Duarte 2002	34	-6 (4.1)	38	-4 (5.9)		23.4 %	-2.00 [-4.33, 0.33]
Jamalvi 2006	84	-22 (9.2)	66	-19 (10.9)		19.1 %	-3.00 [-6.28, 0.28]
Leversha 2000	30	0.13 (8)	30	-1.21 (8)		16.1 %	1.34 [-2.71, 5.39]
Sannier 2007	39	-1.14 (9)	40	-5.05 (9.9)		15.6 %	3.91 [-0.26, 8.08]
Valencia 1999	32	-3.13 (16.4)	38	-4.07 (14.34)		7.8 %	0.94 [-6.35, 8.23]
Subtotal (95% CI)	**249**		**242**			**100.0 %**	**-0.68 [-2.81, 1.44]**
Heterogeneity: Tau^2 = 3.28; Chi^2 = 9.78, df = 5 (P = 0.08); I^2 =49%							
Test for overall effect: Z = 0.63 (P = 0.53)							



Analysis 1.13. Comparison 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies), Outcome 13 % Oxygen Saturation (change from baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 1 Spacer (chamber) versus Nebuliser (Multiple treatment studies)

Outcome: 13 % Oxygen Saturation (change from baseline)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Children							
Duarte 2002	34	1.5 (2.5)	38	1.2 (6.3)		7.8 %	0.30 [-1.87, 2.47]
Leversha 2000	30	0.67 (2.35)	30	1 (2.35)		25.9 %	-0.33 [-1.52, 0.86]
Sannier 2007	39	1.2 (1.5)	40	1.4 (2.1)		56.8 %	-0.20 [-1.00, 0.60]
Valencia 1999	32	1.71 (4.46)	38	1.45 (3.84)		9.5 %	0.26 [-1.71, 2.23]
Subtotal (95% CI)	**135**		**146**			**100.0 %**	**-0.15 [-0.76, 0.45]**
Heterogeneity: Chi^2 = 0.43, df = 3 (P = 0.93); I^2 =0.0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Total (95% CI)	**135**		**146**			**100.0 %**	**-0.15 [-0.76, 0.45]**
Heterogeneity: Chi^2 = 0.43, df = 3 (P = 0.93); I^2 =0.0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Test for subgroup differences: Not applicable							

Analysis 2.1. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 1 Hospital admission.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 1 Hospital admission

Study or subgroup	Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
Salzman 1989	6/24	3/20		1.67 [0.48, 5.83]
2 Children				
Freelander 1984	1/14	3/14		0.33 [0.04, 2.83]
Hussein 2002	3/30	4/30		0.75 [0.18, 3.07]
Kerem 1993	5/17	6/16		0.78 [0.30, 2.07]

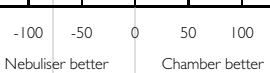
Analysis 2.3. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 3 30 minute rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 3 30 minute rise in FEV1 (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Salzman 1989	24	12.8 (13.2)	20	11 (15.2)		1.80 [-6.70, 10.30]
2 Children						
Kerem 1993	17	8 (10.15)	16	4.93 (9.12)		3.07 [-3.51, 9.65]



Analysis 2.4. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 4 15 minute rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 4 15 minute rise in FEV1 (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Children						
Lin 1995	56	13.06 (13)	55	8.66 (9)		4.40 [0.25, 8.55]

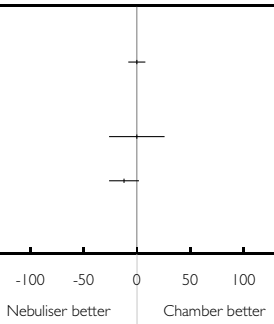
Analysis 2.5. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 5 30 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 5 30 minute rise in peak flow (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Morrone 1990	22	16 (13)	22	16 (13)		0.0 [-7.68, 7.68]
2 Children						
Freelander 1984	11	20 (27)	6	20 (25)		0.0 [-25.59, 25.59]
Robertson 1998	29	9 (22)	30	21 (33)		-12.00 [-26.27, 2.27]



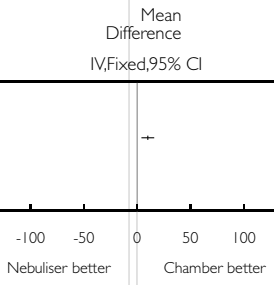
Analysis 2.6. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 6 15 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 6 15 minute rise in peak flow (% predicted)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Children						
Lin 1995	56	12.54 (20)	55	2.49 (8)		10.05 [4.40, 15.70]



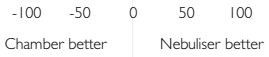
Analysis 2.7. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 7 Rise in pulse rate (% baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 7 Rise in pulse rate (% baseline)

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Salzman 1989	24	-4 (20)	20	-8 (10)		4.00 [-5.12, 13.12]
2 Children						
Kerem 1993	17	-6.8 (14.4)	16	11.8 (27.4)		-18.60 [-33.67, -3.53]
Lin 1995	56	1 (17)	55	2 (19)		-1.00 [-7.71, 5.71]



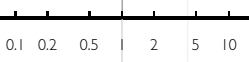
Analysis 2.8. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 8 Number of patients developing tremor.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 8 Number of patients developing tremor

Study or subgroup	Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Children				
Kerem 1993	1/17	4/16		0.24 [0.03, 1.89]



Analysis 2.9. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 9 Number of patients with deterioration in blood gases.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 9 Number of patients with deterioration in blood gases

Study or subgroup	Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Children				
Kerem 1993	2/17	3/16		0.63 [0.12, 3.28]
Lin 1995	13/56	26/55		0.49 [0.28, 0.85]

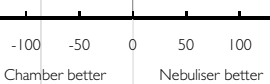
Analysis 2.10. Comparison 2 Spacer (chamber) versus Nebuliser (Single treatment studies), Outcome 10 Rise in respiratory rate.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 2 Spacer (chamber) versus Nebuliser (Single treatment studies)

Outcome: 10 Rise in respiratory rate

Study or subgroup	Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
Salzman 1989	24	-3 (3.9)	20	-4 (4.2)		1.00 [-1.41, 3.41]
2 Children						
Kerem 1993	17	-4.06 (6.38)	16	-4.33 (4.17)		0.27 [-3.39, 3.93]



Analysis 3.1. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 1 Duration of hospital admission (days).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 1 Duration of hospital admission (days)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Morley 1988	10	5.8 (2.1)	8	6.4 (3.3)		3.4 %	-0.60 [-3.23, 2.03]
Subtotal (95% CI)	**10**		**8**			**3.4 %**	**-0.60 [-3.23, 2.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.45 (P = 0.65)							
2 Children							
Parkin 1995	30	2.21 (0.98)	30	1.92 (0.98)		96.6 %	0.29 [-0.21, 0.79]
Subtotal (95% CI)	**30**		**30**			**96.6 %**	**0.29 [-0.21, 0.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.15 (P = 0.25)							
Total (95% CI)	**40**		**38**			**100.0 %**	**0.26 [-0.23, 0.75]**
Heterogeneity: Chi^2 = 0.42, df = 1 (P = 0.51); I^2 =0.0%							
Test for overall effect: Z = 1.04 (P = 0.30)							
Test for subgroup differences: Chi^2 = 0.42, df = 1 (P = 0.51), I^2 =0.0%							

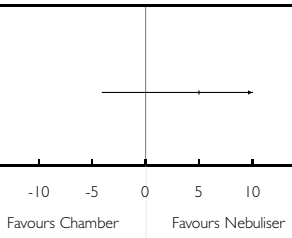
Analysis 3.2. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 2 Number of hours until reached 4 hourly dosing regime.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 2 Number of hours until reached 4 hourly dosing regime

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Parkin 1995	30	24 (18.07)	30	19 (18.07)		5.00 [-4.14, 14.14]



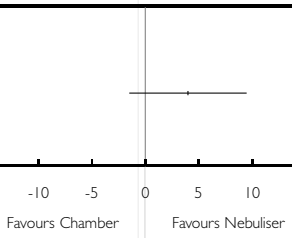
Analysis 3.3. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 3 Total number of inhaled doses received.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 3 Total number of inhaled doses received

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Parkin 1995	30	21 (10.95)	30	17 (10.95)		4.00 [-1.54, 9.54]



Analysis 3.4. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 4 Number of patients returning to normal PEFR and respiratory score levels (end of study).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 4 Number of patients returning to normal PEFR and respiratory score levels (end of study)

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
2 Children				
Coker 1995	7/12	10/12		0.70 [0.41, 1.20]

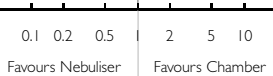
Analysis 3.5. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 5 Number of symptom-free patients 14 days post discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 5 Number of symptom-free patients 14 days post discharge

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
2 Children				
Parkin 1995	19/30	20/30		0.95 [0.66, 1.38]



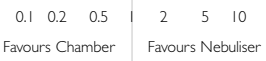
Analysis 3.6. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 6 Readmissions in the subsequent 12 months.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 6 Readmissions in the subsequent 12 months

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
2 Children				
Dewar 1999	4/29	9/33		0.51 [0.17, 1.47]



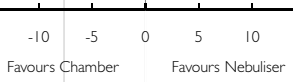
Analysis 3.7. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 7 Clinical asthma score (end of trial).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 7 Clinical asthma score (end of trial)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Parkin 1995	30	2 (1.64)	30	2.2 (1.64)		-0.20 [-1.03, 0.63]



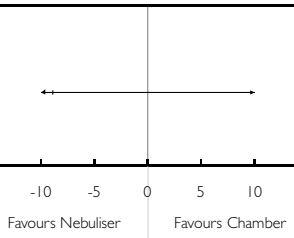
Analysis 3.8. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 8 Maximum percentage decrease in respiratory score.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 8 Maximum percentage decrease in respiratory score

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Coker 1995	12	80.8 (29)	12	89.68 (24.18)		-8.88 [-30.24, 12.48]



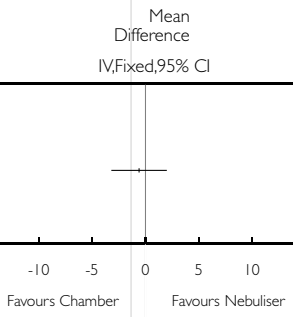
Analysis 3.9. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 9 Respiratory rate at discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 9 Respiratory rate at discharge

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Dewar 1999	29	26.6 (5.25)	33	27.2 (5.17)		-0.60 [-3.20, 2.00]



Analysis 3.10. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 10 Heart rate at discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 10 Heart rate at discharge

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Dewar 1999	29	101.2 (12.39)	33	99.3 (15.08)		1.90 [-4.94, 8.74]

Analysis 3.11. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 11 Oxygen Saturations at discharge.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 11 Oxygen Saturations at discharge

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Dewar 1999	29	96.4 (1.35)	33	96.1 (0.86)		0.30 [-0.27, 0.87]

Analysis 3.12. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 12 30 minute rise in FEV1.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 12 30 minute rise in FEV1

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 Adults						
Morley 1988	10	1.92 (0.78)	8	1.72 (1)		0.22 [-0.72, 1.15]
2 Children						
Ba 1989	14	34.5 (9)	13	23.5 (3.5)		1.54 [0.66, 2.42]

Analysis 3.13. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 13 Final rise in FEV1.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 13 Final rise in FEV1

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 Adults						
Morley 1988	10	1.87 (0.96)	8	1.46 (0.64)		0.47 [-0.48, 1.41]
2 Children						
Ba 1989	14	26 (9)	13	11.5 (5.5)		1.87 [0.94, 2.80]

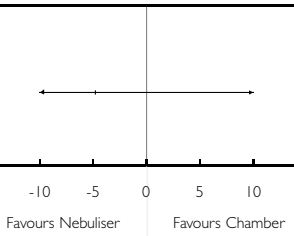
Analysis 3.14. Comparison 3 Spacer (chamber) versus Nebuliser (Inpatient studies), Outcome 14 Final rise in peak flow (% change from baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 3 Spacer (chamber) versus Nebuliser (Inpatient studies)

Outcome: 14 Final rise in peak flow (% change from baseline)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults						
2 Children						
Coker 1995	12	100.62 (79.55)	12	105.43 (53.79)		-4.81 [-59.14, 49.52]



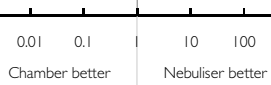
Analysis 4.1. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 1 Hospital admission.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 1 Hospital admission

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
Colacone 1993	1/40	0/40		3.00 [0.13, 71.51]
Idris 1993	1/15	1/20		1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9		0.0 [0.0, 0.0]
Turner 1988	4/27	5/26		0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		3.97 [0.48, 32.98]
Subtotal (95% CI)	**159**	**149**		**1.45 [0.60, 3.53]**
Total events: 11 (Holding Chamber), 7 (Nebuliser)				
Heterogeneity: Chi² = 2.15, df = 3 (P = 0.54); I² =0.0%				
Test for overall effect: Z = 0.83 (P = 0.41)				
2 Adults with Volumatic				
Rodrigo 1993	5/49	4/48		1.22 [0.35, 4.29]
Rodriguez 1999	14/36	17/33		0.75 [0.45, 1.28]
Subtotal (95% CI)	**85**	**81**		**0.84 [0.51, 1.38]**
Total events: 19 (Holding Chamber), 21 (Nebuliser)				
Heterogeneity: Chi² = 0.51, df = 1 (P = 0.48); I² =0.0%				
Test for overall effect: Z = 0.68 (P = 0.49)				
3 Children				
Chong-Neto 2005	0/20	0/10		0.0 [0.0, 0.0]
Chou 1995	4/71	5/81		0.91 [0.25, 3.27]
Leversha 2000	10/30	18/30		0.56 [0.31, 1.00]
Ploin 2000	3/31	3/32		1.03 [0.23, 4.73]
Williams 1996	2/42	2/18		0.43 [0.07, 2.81]
Subtotal (95% CI)	**194**	**171**		**0.65 [0.40, 1.06]**
Total events: 19 (Holding Chamber), 28 (Nebuliser)				
Heterogeneity: Chi² = 1.09, df = 3 (P = 0.78); I² =0.0%				
Test for overall effect: Z = 1.71 (P = 0.087)				
4 Children with Volumatic				
Vazquez 1992	0/9	0/9		0.0 [0.0, 0.0]
Subtotal (95% CI)	**9**	**9**		**0.0 [0.0, 0.0]**



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Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Total events: 0 (Holding Chamber), 0 (Nebuliser)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**447**	**410**		**0.83 [0.60, 1.14]**
Total events: 49 (Holding Chamber), 56 (Nebuliser)				
Heterogeneity: Chi^2 = 5.73, df = 9 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 1.14 (P = 0.25)				

Analysis 4.2. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 2 Hospital admission or poor response to treatment.

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 2 Hospital admission or poor response to treatment

Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Adults				
Colacone 1993	1/40	0/40		3.00 [0.13, 71.51]
Idris 1993	1/15	1/20		1.33 [0.09, 19.64]
Raimondi 1997	0/9	0/9		0.0 [0.0, 0.0]
Turner 1988	4/27	5/26		0.77 [0.23, 2.56]
Vivek 2003	5/68	1/54		3.97 [0.48, 32.98]
Subtotal (95% CI)	**159**	**149**		**1.45 [0.60, 3.53]**
Total events: 11 (Holding Chamber), 7 (Nebuliser)				
Heterogeneity: Chi^2 = 2.15, df = 3 (P = 0.54); I^2 =0.0%				
Test for overall effect: Z = 0.83 (P = 0.41)				
2 Adults with Volumatic				
Rodrigo 1993	5/49	4/48		1.22 [0.35, 4.29]

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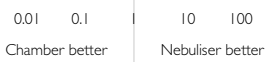
Study or subgroup	Holding Chamber n/N	Nebuliser n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Rodriguez 1999	14/36	17/33		0.75 [0.45, 1.28]
Subtotal (95% CI)	**85**	**81**		**0.84 [0.51, 1.38]**
Total events: 19 (Holding Chamber), 21 (Nebuliser)				
Heterogeneity: Chi² = 0.51, df = 1 (P = 0.48); I² =0.0%				
Test for overall effect: Z = 0.68 (P = 0.49)				
3 Children				
Chong-Neto 2005	0/20	0/10		0.0 [0.0, 0.0]
Chou 1995	4/71	5/81		0.91 [0.25, 3.27]
Leversha 2000	10/30	18/30		0.56 [0.31, 1.00]
Ploin 2000	3/31	3/32		1.03 [0.23, 4.73]
Valencia 1999	7/32	5/38		1.66 [0.58, 4.74]
Williams 1996	2/42	2/18		0.43 [0.07, 2.81]
Subtotal (95% CI)	**226**	**209**		**0.79 [0.51, 1.23]**
Total events: 26 (Holding Chamber), 33 (Nebuliser)				
Heterogeneity: Chi² = 3.91, df = 4 (P = 0.42); I² =0.0%				
Test for overall effect: Z = 1.05 (P = 0.29)				
4 Children with Volumatic				
Batra 1997	7/30	6/30		1.17 [0.44, 3.06]
Vazquez 1992	0/9	0/9		0.0 [0.0, 0.0]
Subtotal (95% CI)	**39**	**39**		**1.17 [0.44, 3.06]**
Total events: 7 (Holding Chamber), 6 (Nebuliser)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.31 (P = 0.75)				
Total (95% CI)	**509**	**478**		**0.91 [0.68, 1.22]**
Total events: 63 (Holding Chamber), 67 (Nebuliser)				
Heterogeneity: Chi² = 8.19, df = 11 (P = 0.70); I² =0.0%				
Test for overall effect: Z = 0.60 (P = 0.55)				



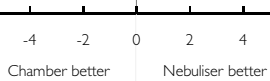
Analysis 4.3. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 3 Duration in emergency department (hours)..

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 3 Duration in emergency department (hours).

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Idris 1993	15	1.5 (0.8)	20	1.7 (0.9)		100.0 %	-0.20 [-0.77, 0.37]
Subtotal (95% CI)	**15**		**20**			**100.0 %**	**-0.20 [-0.77, 0.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
2 Adults with Volumatic							
Rodrigo 1993	49	2.2 (1.7)	48	1.9 (1.5)		100.0 %	0.30 [-0.34, 0.94]
Subtotal (95% CI)	**49**		**48**			**100.0 %**	**0.30 [-0.34, 0.94]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.92 (P = 0.36)							
3 Children							
Chou 1995	71	1.1 (0.52)	81	1.72 (0.86)		22.0 %	-0.62 [-0.84, -0.40]
Duarte 2002	97	0.69 (0.3)	99	1.12 (0.52)		78.0 %	-0.43 [-0.55, -0.31]
Subtotal (95% CI)	**168**		**180**			**100.0 %**	**-0.47 [-0.58, -0.37]**
Heterogeneity: Chi^2 = 2.17, df = 1 (P = 0.14); I^2 =54%							
Test for overall effect: Z = 8.84 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 6.22, df = 2 (P = 0.04), I^2 =68%							



Analysis 4.4. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 4 Final rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 4 Final rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Colacone 1993	40	23 (16)	40	22 (19)		16.2 %	1.00 [-6.70, 8.70]
Idris 1993	15	27.1 (12.7)	20	26.4 (20.4)		7.9 %	0.70 [-10.31, 11.71]
Turner 1988	27	13.03 (13.88)	26	13.74 (16.41)		14.3 %	-0.71 [-8.91, 7.49]
Subtotal (95% CI)	**82**		**86**			**38.4 %**	**0.30 [-4.70, 5.30]**
Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² =0.0%							
Test for overall effect: Z = 0.12 (P = 0.91)							
2 Adults with Volumatic							
Rodrigo 1993	49	25 (15.6)	48	23 (12.7)		30.0 %	2.00 [-3.66, 7.66]
Rodrigo 1998	11	44.3 (16.7)	11	49.4 (21)		3.8 %	-5.10 [-20.96, 10.76]
Subtotal (95% CI)	**60**		**59**			**33.8 %**	**1.20 [-4.13, 6.53]**
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² =0.0%							
Test for overall effect: Z = 0.44 (P = 0.66)							
3 Children							
Chong-Neto 2005	20	34 (10)	10	34 (7)		25.2 %	0.0 [-6.17, 6.17]
Subtotal (95% CI)	**20**		**10**			**25.2 %**	**0.0 [-6.17, 6.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
4 Children with Volumatic							
Vazquez 1992	9	29.5 (23.4)	9	19.7 (17.8)		2.6 %	9.80 [-9.41, 29.01]
Subtotal (95% CI)	**9**		**9**			**2.6 %**	**9.80 [-9.41, 29.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.00 (P = 0.32)							
Total (95% CI)	**171**		**164**			**100.0 %**	**0.78 [-2.32, 3.87]**
Heterogeneity: Chi² = 1.75, df = 6 (P = 0.94); I² =0.0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Test for subgroup differences: Chi² = 0.97, df = 3 (P = 0.81), I² =0.0%							

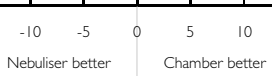
Analysis 4.5. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 5 30 minute rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 5 30 minute rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Turner 1988	27	5.4 (7.5)	26	9.2 (9.8)		48.5 %	-3.80 [-8.51, 0.91]
Subtotal (95% CI)	**27**		**26**			**48.5 %**	**-3.80 [-8.51, 0.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.58 (P = 0.11)							
2 Adults with Volumatic							
Rodrigo 1993	49	17 (13.5)	48	15.5 (9.1)		51.5 %	1.50 [-3.07, 6.07]
Subtotal (95% CI)	**49**		**48**			**51.5 %**	**1.50 [-3.07, 6.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)	**76**		**74**			**100.0 %**	**-1.07 [-4.35, 2.21]**
Heterogeneity: Chi² = 2.50, df = 1 (P = 0.11); I² =60%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Test for subgroup differences: Chi² = 2.50, df = 1 (P = 0.11), I² =60%							



Analysis 4.6. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 6 Severe asthmatics final rise in FEV1 (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 6 Severe asthmatics final rise in FEV1 (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Idris 1993	6	26 (20)	8	14 (18)		9.0 %	12.00 [-8.29, 32.29]
Raimondi 1997	9	29 (15)	9	27 (15)		19.3 %	2.00 [-11.86, 15.86]
Turner 1988	10	9.52 (11.01)	13	12.12 (14.02)		35.4 %	-2.60 [-12.83, 7.63]
Subtotal (95% CI)	**25**		**30**			**63.8 %**	**0.86 [-6.77, 8.48]**
Heterogeneity: Chi^2 = 1.62, df = 2 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 0.22 (P = 0.83)							
2 Adults with Volumatic							
Rodrigo 1993	19	22.6 (17.5)	20	19.7 (14.5)		36.2 %	2.90 [-7.21, 13.01]
Subtotal (95% CI)	**19**		**20**			**36.2 %**	**2.90 [-7.21, 13.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.56 (P = 0.57)							
Total (95% CI)	**44**		**50**			**100.0 %**	**1.60 [-4.49, 7.69]**
Heterogeneity: Chi^2 = 1.72, df = 3 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 =0.0%							

Analysis 4.7. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 7 Final rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 7 Final rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults with Volumatic							
Rodrigo 1993	49	22.1 (13)	48	21.4 (10)		58.1 %	0.70 [-3.91, 5.31]
Rodrigo 1998	11	47.5 (14.4)	11	57.9 (18.7)		6.3 %	-10.40 [-24.35, 3.55]
Subtotal (95% CI)	**60**		**59**			**64.4 %**	**-0.39 [-4.77, 3.98]**
Heterogeneity: Chi² = 2.19, df = 1 (P = 0.14); I² =54%							
Test for overall effect: Z = 0.18 (P = 0.86)							
2 Children							
Chou 1995	39	19 (19.5)	49	25 (19.1)		18.7 %	-6.00 [-14.13, 2.13]
Williams 1996	42	25 (18.2)	18	25.61 (17)		13.4 %	-0.61 [-10.20, 8.98]
Subtotal (95% CI)	**81**		**67**			**32.1 %**	**-3.75 [-9.95, 2.45]**
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² =0.0%							
Test for overall effect: Z = 1.18 (P = 0.24)							
3 Children with Volumatic							
Vazquez 1992	9	29.6 (21.4)	9	25.5 (19.5)		3.5 %	4.10 [-14.81, 23.01]
Subtotal (95% CI)	**9**		**9**			**3.5 %**	**4.10 [-14.81, 23.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.67)							
Total (95% CI)	**150**		**135**			**100.0 %**	**-1.32 [-4.83, 2.20]**
Heterogeneity: Chi² = 3.98, df = 4 (P = 0.41); I² =0.0%							
Test for overall effect: Z = 0.73 (P = 0.46)							
Test for subgroup differences: Chi² = 1.08, df = 2 (P = 0.58), I² =0.0%							

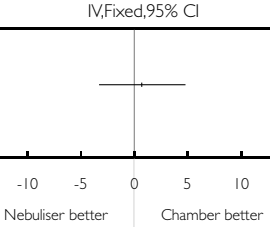
Analysis 4.8. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 8 30 minute rise in peak flow (% predicted).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 8 30 minute rise in peak flow (% predicted)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults with Volumatic						
Rodrigo 1993	49	15.4 (11.4)	48	14.7 (8.8)		0.70 [-3.35, 4.75]



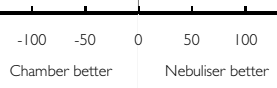
Analysis 4.9. Comparison 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups), Outcome 9 Rise in pulse rate (% baseline).

Review: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma

Comparison: 4 Spacer (chamber) versus Nebuliser (Multiple treatment studies with Volumatic Subgroups)

Outcome: 9 Rise in pulse rate (% baseline)

Study or subgroup	Holding Chamber N	Mean(SD)	Nebuliser N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Adults							
Colacone 1993	40	-1 (19)	40	4 (19)		44.1 %	-5.00 [-13.33, 3.33]
Idris 1993	15	1 (16)	20	0 (18)		23.9 %	1.00 [-10.30, 12.30]
Turner 1988	27	-4 (16)	26	-3 (20)		32.0 %	-1.00 [-10.77, 8.77]
Subtotal (95% CI)	**82**		**86**			**100.0 %**	**-2.28 [-7.81, 3.24]**
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² =0.0%							
Test for overall effect: Z = 0.81 (P = 0.42)							
2 Adults with Volumatic							
Rodrigo 1993	49	-1.32 (13.8)	48	-0.44 (14.2)		44.9 %	-0.88 [-6.45, 4.69]



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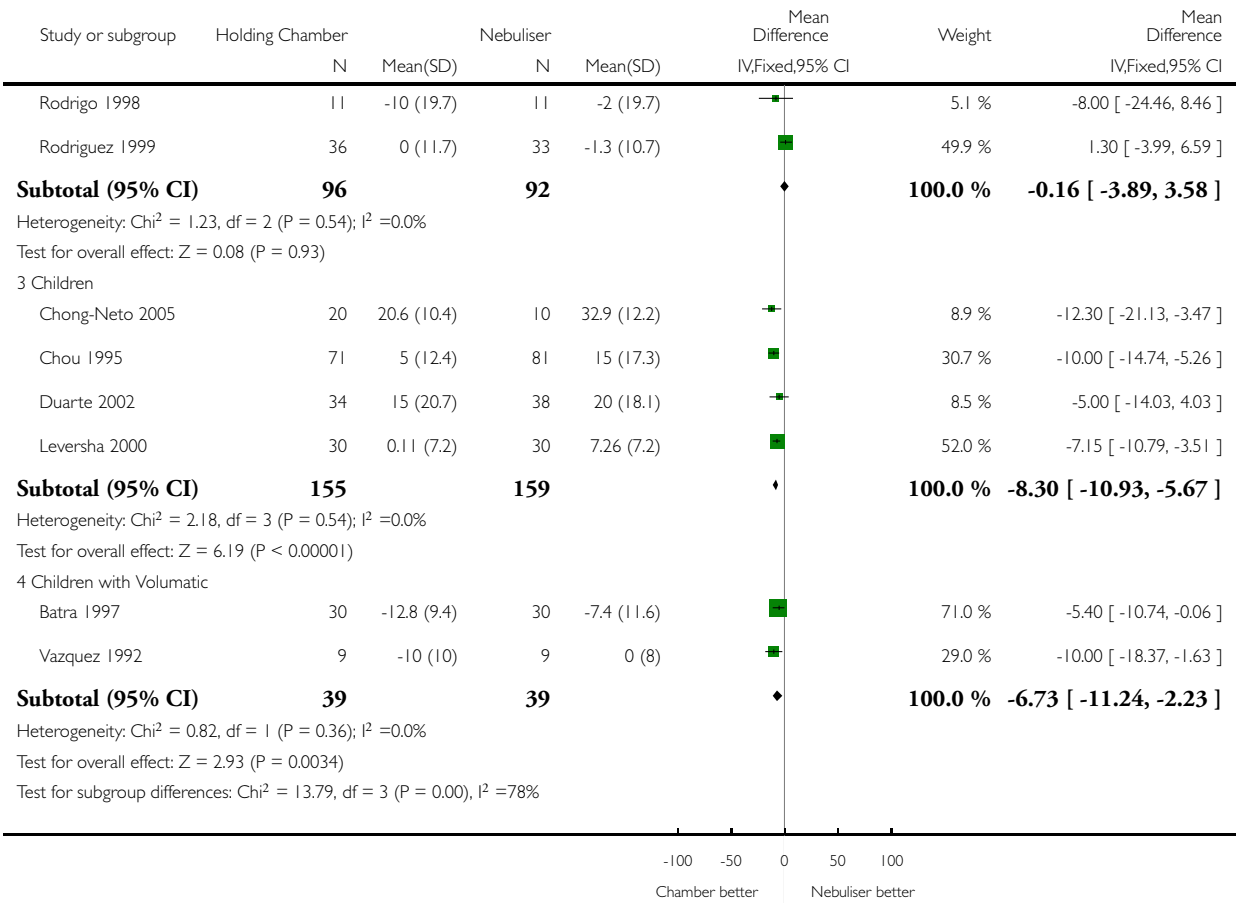

ADDITIONAL TABLES

Table 1. Details of spacers used

Study ID	Spacer Type	Spacer Volume	Adults of Children	Number of subjects	
Ba 1989	Nebuhaler	750	Children	27	
Batra 1997	Volumatic	750	Children	60	
Burrows 2004	unknown		Children	29	
Chong-Neto 2005	Aerochamber and home made	145 or 500	Children	30	

Table 1. Details of spacers used (*Continued*)

Chou 1995	Aerochamber	145	Children	152	
Coker 1995	Volumatic	750	Children	36	
Colacone 1993	Aerochamber	145	Adults	80	
Dewar 1999	Volumatic	750	Children	62	
Duarte 2002	home made	500	Children	196	
Freelander 1984	Nebuhaler	750	Children	28	
Hussein 2002	Large volume		Children	60	
Idris 1993	Inspirease	650	Adults	35	
Kerem 1993	Volumatic	750	Children	33	
Leversha 2000	Aerochamber	145	Children	60	
Lin 1995	Aerochamber	145	Children	111	
Maldano 1997	unknown		Children	42	
Morely 1988	Inspirease	650	Adults	28	
Morrone 1990	unknown	500	Adults	44	
Parkin 1995	Aerochamber	145	Children	60	
Pendergast 1989	Nebuhaler	750	Children	27	
Ploin 2000	Babyhaler	350	Children	64	
Raimondi 1997	Aerochamber	145	Adults	27	
Rao 2002	unknown		Adults	50	
Robertson 1998	Volumatic	750	Children	155	
Rodrigo 1993	Volumatic	750	Adults	97	
Rogrigo 1997	Volumatic	750	Adults	22	
Rodriguez 1999	Volumatic	750	Adults	69	
Salzman 1989	Aerochamber	145	Adults	44	
Turner 1988	Inspirease	650	Adults	53	

Table 1. Details of spacers used (*Continued*)

Valencia 1999	home made	500	Children	70	
Vazquez 1992	Volumatic	750	Children	18	
Vivek 2003	Nebuhaler	750	Adults	122	
Williams 1996	Aerochamber	145	Children	40	

WHAT'S NEW

Last assessed as up-to-date: 21 July 2008.

Date	Event	Description
28 July 2008	New search has been performed	Converted to new review format and two new studies added (Jamalvi 2006 and Sannier 2006). No change in conclusions

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 3, 1996

Date	Event	Description
4 January 2006	New search has been performed	For the 2006 update of this review 4 new trials have been added: Burrows 2005 including 29 paediatric in-patients, Chong-Neto 2005 included 30 children given multiple treatments, Hussein 2002 including 60 children given a single treatment, Rao 2002 including 50 adults given multiple treatments and Vivek 2003 including 120 patients aged 10-50 (and therefore classified as adult) given multiple treatments. An additional table has been added with details of the holding chambers used in each study, and new comparisons added according to type of chamber. This was done because Volumatic spacers were no longer being manufactured (but they have now been reintroduced)
29 July 2003	New search has been performed	Three further trials were added to the review in 1999, but the conclusions of the review remained unchanged. For the 2001 update a further four studies were added and reduced the confidence intervals around the results. One open trial in children has been added for the 2003 update (Duarte 2002) including a further 196 children studied in an emergency room setting in Brazil. In addition the 2003 update has expanded the review to include trials on in-

(*Continued*)

		patients and five new trials have been added including 184 children and 28 adults (Ba 1989, Coker 1995, Dewar 1999, Morley 1988 and Parkin 1995) . The results of the in-patient trials have not been pooled, but are in keeping with the findings in the emergency room and community setting, that holding chambers can be as effective as nebulisers for delivery of beta-agonists in acute asthma

CONTRIBUTIONS OF AUTHORS

CJC had the initial idea for the review and wrote the protocol and review in conjunction with BHR. The data extraction and analysis was performed by CJC and the methodological quality was independently assessed by Robert Chapman for the original papers. Anna Bara independently assessed trials for inclusion, and extracted trial data for the 1997,1999 and 2001 updates. JAC and CJC assessed trials for inclusion and extracted data for the 2003 and 2006 update (to include trials on in-patients). CJC and BHR have updated the review to include further trials in 1997, 1999 and 2001. CJC, JAC and BHR have carried out the 2003, 2006 and 2008 updates.

DECLARATIONS OF INTEREST

The authors have no financial interest in any of the devices used to deliver ß2-agonists in acute asthma and no involvement with the primary studies.

SOURCES OF SUPPORT

Internal sources

- NHS Executive, North Thames, UK.
- NHS Executive Eastern Region, UK.
- Department of Emergency Medicine, University of Alberta, Edmonton, Canada.

External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

*Nebulizers and Vaporizers; Acute Disease; Adrenergic beta-Agonists [*administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Equipment Design; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Child, Preschool; Humans