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Rodriguez-Martinez CE, Sossa M, Lozano JM

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Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children.
Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005536.
DOI: 10.1002/14651858.CD005536.pub2.

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[Intervention Review]

Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

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Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 8, 2017.

Citation: Rodriguez-Martinez CE, Sossa M, Lozano JM. Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD005536. DOI: 10.1002/14651858.CD005536.pub2.

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ABSTRACT

Background

Strong evidence supports the use of metered-dose inhalers combined with a spacer for delivering rapid-acting inhaled beta-2 agonists in the treatment of acute exacerbations of asthma in children. The high cost and lack of availability of commercially produced spacers however, have limited their use in developing countries.

Objectives

The aim of this review was to compare the response to inhaled beta-2 agonists delivered through metered-dose inhaler using home-made spacers, to the use of commercially produced spacers, in children with acute exacerbations of wheezing or asthma.

Search methods

We searched the Cochrane Airwyas Group Register (up to August 2010), Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*, MEDLINE , EMBASE, CINHAL, LILACS and reference lists of included studies. We contacted authors and known experts in the field, and approached pharmaceutical companies that manufacture inhalation spacers to identify additional published or unpublished data. No language restrictions were applied.

Selection criteria

Trials comparing treatment with rapid acting beta 2-agonists delivered through a MDI attached to home-made spacers, versus the same bronchodilator therapy delivered with a MDI and commercially produced spacers, in children under 18 years with acute exacerbations of wheezing or asthma.

Data collection and analysis

Two review authors independently extracted the data and assessed trial quality. Missing data were obtained from the authors or estimated from information available in published reports.

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Main results

Six trials with 658 participants met the inclusion criteria. At the time of this review, five trials were published in full text, and one study was available in abstract form only. No significant differences were demonstrated between the two delivery methods in terms of the need for hospital admission (RR 1.00, 95% CI 0.63 to 1.59), change in oxygen saturation (SMD -0.03, 95% CI -0.39 to 0.33), PEFR (SMD 0.04, 95% CI -0.72 to 0.80), clinical score (WMD 0.00, 95% CI -0.37 to 0.37), in terms of need for additional treatment (RR 1.18, 95% CI 0.84 to 1.65), or regarding change in heart rate per minute (SMD 0.09, 95% CI -0.24 to 0.42).

Authors' conclusions

Overall, this review did not identify a statistically significant difference between these two methods for delivering bronchodilator therapy to children with acute asthma or lower airways obstruction attacks. Care should be taken in the interpretation and applicability of our results because of the small number of RCTs along with few events available meeting the criteria for inclusion in the review, absence of the primary outcome of interest and other clinically important outcomes in the majority of included studies. The possible need for a face-mask in younger children using home-made spacers should also be considered in practice.

PLAIN LANGUAGE SUMMARY

Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

The aim of this review was to compare the response to inhaled beta-2 agonists delivered through a metered-dose inhaler (MDI) attached to home-made spacers, compared with beta-2 agonists delivered through a MDI attached to commercially produced spacers in children with acute exacerbations of wheezing or asthma. Six randomized clinical trials (RCTs) with 658 participants met the inclusion criteria of the review. Overall, this review fails to identify a difference between these two delivery methods for delivering bronchodilator therapy to children with acute asthma or lower airways obstruction attacks. However, given the small total sample and wide confidence intervals, equivalence between the treatments cannot be claimed.

BACKGROUND

Asthma is a major cause of childhood morbidity (Braman 2006) and disability (Newacheck 2000), with acute exacerbations of the disease being a common reason for emergency department (ED) visits and hospital admissions (Akinbami 2002). The main drugs used in the management of acute asthma are rapid-acting beta-agonists and systemic corticosteroids. Ipratropium bromide (Plotnick 2000), inhaled glucocorticosteroids (Edmonds 2000; Edmonds 2003), and intravenous magnesium (Rowe 2000) may also confer benefit in acute asthma. Antibiotics (Graham 2001), inhaled mucolytics (Sethi 1998), aminophylline (Mitra 2005), sedation (Sethi 1998) and antihistamines (Van Ganse 1997), have no established role in the treatment of exacerbations. Although rapid-acting inhaled beta 2-agonists are generally administered by nebulization, equivalent (Cates 2005) or even greater bronchodilatation (Rodríguez 2004), with a more rapid onset, fewer side effects, and less time spent in the ED can be achieved using a metered-dose inhaler (MDI) with spacer.

Effective use of MDI requires synchronization of inhalation with actuation of the device. Since synchronization is difficult in children, spacer devices are used to overcome this poor co-ordination problem. Spacers have further advantages in that they improve efficacy (increase lung deposition and decrease oropharyngeal deposition) and reduce side effects from inhaled drugs (Amirav 1997; Singhal 2001). For this reason, inhaled therapy using an MDI with attached spacer has been increasingly recognized as the optimal method for delivering rapid acting beta 2-agonists for acute exacerbations of wheezing or asthma. A wide variety of commercially produced spacers are available; these differ in shape, size, material out of which they are constructed, and the presence of valves (Zar 2002a). The high cost and lack of availability of commercial produced spacers have limited their use in developing countries (Zar 2002a).

As an alternative, rapid acting beta 2-agonists via MDI have been delivered attached to home-made spacers for treating children with acute exacerbations of wheezing or asthma (Zar 1999; Singhal 2001; Zar 2002a). A wide variety of home-made spacers have been developed, including plastic cold-drink bottles, plastic min-

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eral water bottles, polystyrene cups, plastic zip-up bags, and paper spacers. In spite of the wide use of these home-made spacers in developing countries, there are only a few studies comparing their use for delivery of rapid acting beta 2-agonists via MDI versus the same bronchodilator therapy with commercially produced spacers for treating acute exacerbations of wheezing or asthma in children under 18 years of age.

Although several studies have concluded that rapid acting beta 2-agonists via MDI given attached to home-made spacers produce similar bronchodilation to the same bronchodilator therapy delivered with commercially produced spacers for treating acute exacerbations of wheezing or asthma in children (Panicker 2001; Singhal 2001; Quetulio 2002; Obgaidze 2005), some of these studies were not powered sufficiently to detect differences between the two devices. We therefore aimed to review the literature to determine if the existing evidence allows concluding that the bronchodilatory response to beta 2-agonists, delivered through metered-dose inhaler (MDI) attached to home-made spacers, is equivalent to the bronchodilatory response to beta 2-agonists delivered through MDI attached to commercially produced spacers, in children with acute exacerbations of wheezing or asthma.

OBJECTIVES

The aim of this review was to compare the response to inhaled beta-2 agonists delivered through metered-dose inhaler (MDI) attached to home-made spacers, to beta-2 agonists delivered through MDI attached to commercially produced spacers, in children with acute exacerbations of wheezing or asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCT) including open and blinded study designs.

Types of participants

Children under 18 years with acute exacerbations of wheezing or asthma presenting to an ED or equivalent care setting.

Types of interventions

Intervention: Rapid acting beta 2-agonists via MDI given attached to home-made spacers. Combination treatment with anti-cholinergic agents was permitted. Controls: The same bronchodilator therapy delivered with commercially produced spacers. Combination treatment with anti-cholinergic agents was permitted.

Types of outcome measures

Primary outcomes

The primary outcome measure was the need for hospital admission.

Secondary outcomes

Secondary outcomes measures were changes from baseline in peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), oxygen saturation (SaO_2), respiratory rate (RR), clinical scores, and physical signs, such as dyspnea, accessory muscle use, and wheezing. Other secondary outcomes measures were intensive care unit (ICU) admission rates, emergency department length of stay, need for additional treatment upon completion of the intervention protocol, and adverse effects such as heart rate (HR), dysrhythmia, tremor, and nausea.

Search methods for identification of studies

For the original version of this review potentially relevant trials relevant trials were identified through searches of the electronic databases MEDLINE (From 1966 to August 2009), EMBASE (From 1974 to August 2009), CINHAL (From 1982 to August 2009), Cochrane Central Register of Controlled Trials (CENTRAL) - Issue 3/2009, and LILACS (From 1982 to August 2009). The full strategies are in Appendix 1. Controlled trials were identified by using the Cochrane highly sensitive search filter (Robinson 2002). A search of the Cochrane Airways Group Register was also conducted with the following search strategy:
(spacer* or MDI or bronchodilat* or nebuli* or vapori* or aerosol* or inhal* or "holding chamber" or holding-chamber) and (bottle* or home-made* or "home made" or homemade or alternative* or improvi* or cup or plastic or paper or polystyrene)
For the latest update of this review (2010), the Airways Register has been searched up to August 2010.The Airways Group Register 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.
We included citations in any language. We also reviewed the bibliographies of the randomized trials identified, contacted the authors of included trials and known experts in the field, and approached pharmaceutical companies that manufacture inhalation spacers to identify additional published or unpublished data.

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Data collection and analysis

I. Trial selection

Two review authors (CRM, MPS) scanned the abstracts and titles of articles retrieved by the electronic and handsearches for eligibility, according to the inclusion criteria above. One of the review authors retrieved full copies of all those deemed potentially eligible for closer examination. Two review authors determined whether or not they met eligibility criteria; if necessary we sought advice from other authors. Disagreement was resolved by consensus.

II. Data extraction and management

We developed our data abstraction forms a priori to capture specific items of data needed for this review. We pilot-tested the data extraction form with a sample of three included studies to ensure clarity, completeness and ease of use. We extracted data on study design, details on participants (including age, gender, number in each group), description of the interventions (including process), and description of outcomes, including timing of assessment, and adverse effects. Two review authors (CRM, MPS) independently extracted data from trials to the specially designed form, one review author (CRM) then entered into RevMan, and this was checked by a second using the double data entry facility. If data were not reported in abstractable form, we contacted one of the authors of the included study for additional information. For binary outcome measures we calculated a pooled estimate of the relative risk (RR) of the treatment effect for each outcome. For continuous outcomes, we recorded either mean change from baseline for each group or mean values after intervention, and their respective standard deviations or standard errors, and calculated mean differences. If standard deviations or standard errors were missing, we tried to extract them from other relevant information reported in the paper (P-values, confidence intervals, etc). If the authors could not be contacted or if the information was no longer available, this was reported.

III. Trial quality assessment

Two review authors (CRM, MPS) independently assessed the methodological quality using two methods. Firstly, all included trials were scored using the Cochrane approach to assessment of allocation concealment, using the following principles (Schulz 1995):
Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment
Secondly, the methodological quality of the eligible RCTs was also assessed with a modified version of a 5-point scoring instrument, proposed by Jadad (Jadad 1996), and summarized as follows:
1. Was the trial described as randomized (1 = yes; 0 = no)?;
2. Was the trial described as double-blind (1 = yes; 0 = no)?;
3. Was there a description of withdrawals and dropouts (1 = yes; 0 = no)?;
4. Was the method of randomisation well described and appropriate (1 = yes;0 = no);
5. Was the method of blinding well described and appropriate (1 = yes; 0 = no)?;
6. One point was deducted if methods for randomization or blinding were inappropriate.
The modification of the original Jadad scoring instrument consisted of giving one additional point for each of the two items of (1) description and appropriateness of the method of generating the sequence of randomization and (2) description and appropriateness of the method of double blinding, as opposed to the original Jadad scale, which would only award one point even if both items were fulfilled.
Inter-rater reliability was measured by using simple agreement and kappa weighted statistics.

IV. Data analysis

Cochrane Review Manager software (RevMan 2008) was used to compile and analyze the data. For binary outcomes, we calculated relative risks (RR) and their 95% confidence intervals (CI) for each study. For continuous outcomes, we calculated the weighted mean difference (WMD) (for variables measured using the same scale), or the standardised mean differences (SMD) (for variables measured using different scales) and 95% CI. We measured heterogeneity among trials using I^2 statistic (Higgins 2002), heterogeneity test Q and by comparing the fixed-effect model (where only within-study variation is considered to influence the uncertainty of the weighted mean results) and random-effects model results (in which both within-study and between-study variations are included in the assessment of the uncertainty of the overall mean results). If statistical heterogeneity was not found, a fixed-effect model was used with 95% confidence interval (CI). If significant heterogeneity was detected, we devoted further research to identify possible causes of heterogeneity for the following characteristics: methodological quality of included studies, severity of asthma attack at presentation, age, presence of valves in commercially produced spacers, material of home-made spacer, and dose of bronchodilator. We explored the impact of these characteristics on heterogeneity and the effectiveness of the intervention by means of subgroup analyses.
In the sensitivity analysis we evaluated the impact of the study quality by separating studies according to low risk of bias (characteristic = "adequate") or medium/high risk of bias (characteristic = "unclear/inadequate") for allocation concealment. We also performed sensitivity analysis with respect to the modified version of the Jadad scale.
We intended to assess publication bias with funnel plots (Egger 1997).

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RESULTS

Description of studies

Results of the search

The computerised search has yielded a total of 1789 citations (see Appendix 2 for the search history). A total of 31 studies were examined in full text for possible inclusion. One paper was translated from Russian into English. This left six trials and data for 658 children and adolescents available for meta-analysis. There was total agreement between the two independent reviewers on inclusion of studies. At the time of this report, five trials were published in full text (Zar 1999; Panicker 2001; Singhal 2001; Chong Neto 2005; Zar 2007), and one study was available in abstract form only (Quetulio 2002). Confirmation of methods and data extraction was obtained from the authors of two trials, including voluntary disclosure of data for one unpublished study.

Included studies

Most studies were relatively small randomized controlled trials, and were relatively homogeneous in the age and sex of the participants. Four trials enrolled children older than four years of age (Zar 1999; Singhal 2001; Quetulio 2002; Chong Neto 2005), and two enrolled children younger than four (Panicker 2001; Zar 2007). The oldest included study was published in 1999 (Zar 1999) and the most recent in 2007 (Zar 2007). Studies that were included were conducted mainly in developing countries: two were from India (Panicker 2001; Singhal 2001), two from South Africa (Zar 1999; Zar 2007), one from Brazil (Chong Neto 2005), and one from the Philippines (Quetulio 2002). The exact method of randomization was described in only four of the seven studies (Zar 1999; Panicker 2001; Chong Neto 2005; Zar 2007), and the investigators performing the clinical assessment were blind as to which delivery system patients were randomized to in five studies (Zar 1999; Singhal 2001; Quetulio 2002; Chong Neto 2005; Zar 2007). In one study it was not possible to determine whether those assessing the outcomes of interest were blind to the delivery system allocation (Panicker 2001). Two studies included patients with mild-to-moderate acute exacerbations of wheezing or asthma (Singhal 2001; Chong Neto 2005), one study with mild-to-severe exacerbations (Zar 1999), one with moderate-to-severe exacerbations (Panicker 2001), and two studies failed to report wheezing or asthma exacerbations severity (Quetulio 2002; Zar 2007).

Five studies tested 500-750 ml plastic drink bottles (Zar 1999; Singhal 2001; Panicker 2001; Chong Neto 2005; Zar 2007), and one study tested a cardboard cone as home-made spacers (Quetulio 2002). One study tested three types of home-made spacers (sealed 500 ml plastic drink bottle, unsealed 500 ml plastic drink bottle, and 200 ml polystyrene cup). (Zar 1999). Commercial spacers were Cipla (750 ml) in two studies (Singhal 2001; Panicker 2001), Aerochamber (145-165 ml) in three studies (Zar 1999; Chong Neto 2005; Zar 2007), and NebuChamber (250 ml) in one study (Quetulio 2002). All commercial spacers were valved devices. Salbutamol was the rapid acting beta 2-agonist used in four studies (Singhal 2001; Panicker 2001; Chong Neto 2005; Zar 2007), terbutaline in one (Quetulio 2002), and fenoterol in one (Zar 1999). There was a wide range of doses of beta-2 agonist used in the included studies. For salbutamol: single doses of 100 mcg to cumulative doses up to 2400 µg. Fenoterol: single doses of 100 µg to cumulative doses up to 600 µg. One study was available in abstract form only, so the cumulative doses of terbutaline could not be established (Quetulio 2002).

There was complete short-term follow up of all randomized children in the included studies. No long-term follow-up data were presented in any of the studies. The most frequently reported outcomes were change in PEFR (four studies) (Zar 1999; Singhal 2001; Panicker 2001; Quetulio 2002), and need for additional treatment (three studies) (Zar 1999; Panicker 2001; Zar 2007). Hospitalization rate was used in only one study (Zar 2007), and the reporting of adverse effects was variable. One study included patients with acute lower airway obstruction, without a diagnosis of asthma (Zar 2007). One of the studies included in the review was reported as an abstract and we wrote to one of the authors in an attempt to obtain complete data from the study, but the authors did not respond to requests for further information (Quetulio 2002).

Excluded studies

A total of 25 studies were excluded due to the following reasons: not acute asthma (N = 6) (Becker 1985; Vichyanond 1992; Kerac 1998; Schleufe 1998; Lipworth 2002; Rajkumar 2002), no commercial spacer involved in study comparison (N = 4) (Henry 1983; Carson 1985; Teo 1988; Duarte 2002), absence of outcomes of interest (N = 5) (Zar 1998a; Zar 1998b; Fowler 2001; Kissoon 2001; Lipworth 2002), review article (N = 4) (Mazur 2000a; Motala 2000; Zar 2002a; Zar 2002b), study included adult patients (N = 5) (El-Kassimi 1987; Samaranayake 1998; Schleufe 1998; Fowler 2001; Willemse 2003), duplicate study (N = 2) (Mazur 2000b; Mazur 2000c), non-randomized trial (Obgaidze 2005) and no outcomes presented in a usable form, and no response from authors (N = 1) (Quetulio 2004).

Risk of bias in included studies

The methodological quality of the included studies was variable (*see* table 'Characteristics of included studies'). In general the sample size of the majority of studies was small (range 30 to 400 participants).

One study was given a modified Jadad score of four (Chong Neto 2005), two studies were given a modified Jadad score of three

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(Zar 1999; Zar 2007), and three studies were given a score of two (Singhal 2001; Panicker 2001; Quetulio 2002). One study was reported in abstract and was therefore devoid of substantial details for critical appraisal (Quetulio 2002). Only one study was described as double-blind (Chong Neto 2005). Only one study of the included studies reported that intention to treat analysis was employed (Zar 2007).

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

- Randomisation: Kappa = 1
- Double-blind: Kappa = 1
- Withdrawals/Dropouts: Kappa = 0.8
- Method of Randomisation: Kappa = 0.8
- Method Blinded: Kappa = 0.8

There was total agreement between two independent assessments of study quality using the Cochrane approach. Five studies were graded A according to the Cochrane approach to concealment of allocation (Zar 1999; Singhal 2001; Quetulio 2002; Chong Neto 2005; Zar 2007). One study were graded B since the method of concealment of allocation was not described, and details were not able to be obtained from the authors (Panicker 2001).

Effects of interventions

Primary outcome: admission to hospital

The primary outcome of hospital admission was available only from one study (Zar 2007). In this study the proportion of admitted patients was identical in the home-made and commercial spacer groups (15% in each group), so no significant differences were demonstrated between the two spacers in terms of this outcome (RR 1.0, CI 95% 0.63 to 1.59, Analysis 1.1).

Oxygen saturation

Two studies (Panicker 2001; Singhal 2001) (120 patients) had complete data on measurements of change in SaO_2. When comparing home-made spacers and commercial spacers, no significant differences were demonstrated between the two delivery methods in terms of change in SaO_2 (SMD -0.03, 95% CI -0.39 to 0.33, Analysis 1.2). Two additional trials could not be pooled owing to skewness of the data and lack of report of mean and standard deviation for this outcome (Zar 1999; Zar 2007). These studies showed that the median change in SaO_2 was not significantly different between the two spacers (P = 0.52 and P = 0.53, respectively).

Pulmonary function tests

Two studies involving 90 patients reported change in PEFR (Panicker 2001; Quetulio 2002). No significant differences were demonstrated between the two spacers in terms of this outcome based on a random effects model (SMD 0.04, 95% CI -0.72 to 0.80, Analysis 1.3). These results should be interpreted with caution because significantly heterogeneity (X^2 = 2.99, df =1, I^2 = 66.6%, P = 0.08) was identified among trials. Two additional studies could not be pooled owing to skewness of the data and lack of report of mean and standard deviation for this outcome (Zar 1999; Singhal 2001). These studies did not show significant differences in the median change in PEFR between home-made and commercial spacer groups (P = 0.95 and P = 0.4, respectively).

Clinical score

No significant differences were demonstrated between the two delivery methods in terms of change in clinical score (WMD 0.0, 95% CI -0.37 to 0.37, Analysis 1.4). This finding is based on one study containing 20 participants (Chong Neto 2005). Two additional studies could not be pooled owing to skewness of the data and lack of report of mean and standard deviation for this outcome (Zar 1999; Zar 2007). These studies did not show significant differences in the median number of change in clinical score between home-made and commercial spacer groups (P = 0.60 and P = 0.53, respectively).

Vital signs

Three studies totaling 140 patients reported change in HR (Singhal 2001; Panicker 2001; Chong Neto 2005). No significant differences were demonstrated between the two spacers in terms of this outcome (SMD 0.09, 95% CI -0.24 to 0.42, Analysis 1.5).

Clinical outcomes

Three studies involving 552 patients had complete data on the proportion of children who needed additional treatment (Zar 1999; Panicker 2001; Zar 2007). When comparing home-made spacers and commercial spacers, no significant differences were demonstrated between groups in terms of this outcome (RR 1.18, 95% CI 0.84 to 1.65, Analysis 1.6).

These results did not change significantly when studies of lower methodological quality or studies that included patients without asthma diagnosis were excluded. Heterogeneity was found among trials pooled for change in PEFR (X^2 = 2.99, df = 1, I^2 = 66.6%, P = 0.08) but not for other outcomes.

There was insufficient information to pool outcomes such as change in RR, in accessory muscle use, in grading of dyspnea, and in breath sounds due to the insufficient number of trials reporting these outcomes. Analysis of the only trial which tested these outcomes did not show significant differences between patients

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treated with home-made spacers when comparing with patients treated with commercial devices (P > 0.05) (Panicker 2001). One additional trial could not be pooled owing to skewness of the data and lack of report of mean and standard deviation for change in RR. (Singhal 2001). This study showed a significantly greater decline in RR with the commercial spacer compared with the home-made device (P = 0.003).

No data were available for the following outcome measures in any study: emergency department length of stay, dysrhythmia and ICU admission.

We wrote to five authors of the six included studies for further information and received three replies. Any replies or data received from authors after publication of this review will be incorporated into future updates of the review.

DISCUSSION

This systematic review constitutes an effort to incorporate the best evidence available up to August 2010 on the role of home-made spacers compared to commercial spacers in delivering bronchodilator therapy to children with acute asthma or lower airway obstruction attacks. Overall, this review fails to identify a difference between these two delivery methods for delivering bronchodilator therapy to children with acute asthma or lower airways obstruction attacks. When comparing home-made spacers and commercial spacers, no significant differences were demonstrated between the two delivery methods in terms of hospital admission, change in SaO_2, clinical score, change in PEFR, and need for additional treatment. Moreover, sensitivity analysis did not show any significant influences of quality of methods in the efficacy of the commercially produced spacers compared to home-made devices in delivering bronchodilator therapy to children with acute exacerbations of wheezing or asthma.

In our meta-analysis we also looked at adverse effects but these were difficult to analyse because there was insufficient information to be pooled. The only one of these measurements that could be pooled was change in HR. When comparing home-made spacers and commercial spacers, no significant differences were demonstrated between groups in terms of this outcome.

These are very relevant findings since acute exacerbations of asthma account for the largest part of direct health costs for asthma in most countries, and the fact that inhaled therapy using a MDI with attached spacer has been increasingly recognized as the optimal method for delivering rapid acting beta 2-agonists for acute exacerbations of wheezing or asthma, and that high cost and lack of availability of commercially produced spacers have limited their use in developing countries.

The following outcome measures did not show any heterogeneity when data from different trials were combined: change in SaO_2, change in HR, and need for additional treatment. Statistical heterogeneity was found among trials pooled for change in PEFR (X^2 = 2.99, df = 1, I^2 = 66.6%, P = 0.08). The statistical heterogeneity for this outcome is difficult to explain due to the limited number of trials reporting this outcome in a way that could be pooled (only two trials). No significant differences were demonstrated between the two spacers in terms of this outcome based on a random effects model (SMD 0.04, 95% CI -0.72 to 0.80). However, these results should be interpreted with caution because of this statistical heterogeneity among trials, and because there are very few studies, and very few events for this outcome.

Interpretation and applicability of our results needs to be cautious for several reasons: (1) The small number of RCTs along with few events available meeting the criteria for inclusion in the review, (2) absence of the primary outcome of interest (hospital admission, available from only one study) and other clinically important outcomes in the majority of included studies, (3) only limited analysis of outcomes such as change in SaO_2, change in clinical score, and change in PEFR was possible due to data being presented as medians, and (4) the careful preparation and use of delivery devices in some studies (Zar 2007 used a facemask with the home-made spacer in younger children and took measures to reduce static in both spacers and bottles). Valved commercial spacers contain a one-way, low resistance valve that allows the aerosol to remain within the device until the patient's inhalation effort opens the valve. The theoretical advantages of these valved holding spacers compared to non-valved devices consist in that the former improve coordination with inspiratory flow, and eliminate the cold-Freon effect (Rubin 2005). Moreover, if the child exhales through non-valved spacers, whether home-made or not, any remaining drug which would have been inhaled on the second inspiration may be lost. However, it's important to take into account that it also has been described advantages of the non-valved spacers over valved holding chambers: the former devices may increase pulmonary aerosol deposition, especially in young children or those with airway obstruction (since overcoming the resistance of the valve on inspiration may be difficult for such patients), and may also minimize the amount of dead space in the spacer (Zar 2002b).

A possible weakness of this review is the inaccessibility of data on outcomes known to have been measured (but unreported), and data not presented in a form that can be combined in the meta-analysis. This may be a confounding factor in the results and thus the conclusions. However, outcomes that could not be entirely pooled owing to skewness of the data and lack of report of mean and standard deviation in some studies (change in SaO_2, change in clinical score, and change in PEFR), were not significantly different between the two spacer devices in these studies.

In summary, this review has demonstrated that all of the analyzed outcomes were not significantly different when home-made spacers were compared with commercial devices in delivering bronchodilator therapy to children with acute exacerbations of wheez-

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ing or asthma. However, further studies are needed in order to support or to refute the use of home-made spacers in delivering bronchodilator therapy to these children. These additional studies should include assessment of clinically important outcomes such as rate of hospitalization or rate of ICU admission, and should be designed and adequately powered to test equivalence (null hypothesis that one device is superior to the other), and also should be designed to compare the two spacers, using lower doses of bronchodilators. Additionally, cost-effectiveness analysis and patient preferences are important considerations that require still further assessment, and must be considered in these additional studies.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, this review did not identify a difference between these two delivery methods for delivering bronchodilator therapy to children with acute asthma or lower airways obstruction attacks. However, because of the small number of RCTs along with few events available meeting the criteria for inclusion in the review, absence of the primary outcome of interest and other clinically important outcomes in the majority of included studies, we consider that the results of this review should be interpreted with caution and need confirmation through further, larger trials. In the meanwhile, selection of the spacer device for an individual patient should begin with a commercial spacer with home-made spacers being used if commercial device is not available. The possible need for a facemask in younger children using home-made spacers should be considered.

Implications for research

Further studies are needed before we can confidently draw conclusions about the efficacy of home-made spacers in delivering bronchodilator therapy to children with acute exacerbations of wheezing or asthma. These additional studies should include assessment of clinically important outcomes such as rate of hospitalization or rate of ICU admission, and should be designed and adequately powered to test equivalence (null hypothesis that one device is superior to the other), in order to evaluate whether the theoretical advantages of commercial spacers over non-valved devices (including home-made devices) are so important as to influence the bronchodilator response in evaluating clinically important outcomes. The use of a mask with home-made spacers in small children also needs further clarification. Additionally, cost-effectiveness and patient preferences are important considerations that require further assessment, and should be considered in these additional studies.

ACKNOWLEDGEMENTS

The reviewers would like to acknowledge the assistance provided by the Review Group Coordinator (Toby Lasserson) for his continued encouragement, by the Trials Search Coordinator (Elizabeth Arnold) for her help in identifying the trials and obtaining copies of the papers, Dr Tatiana Kit and Dr Jesus Agreda for their assistance in translation of a paper from Russian, and Georgia Salanti (MRC Biostatistics Unit, Cambridge, UK) for her helpful guidance and comments. We would like to acknowledge Dr Heather Zar for providing the data from of her last study for inclusion into the review prior to publication. We would also like to thank Dr SK Kabra, Dr Herberto Chong Neto, Dr Heather Zar, Dr Shamim Qazi, Glaxo Wellcome (UK), Boehringer-Ingelheim (Colombia), and Trudell Medical International (Colombia) who responded enthusiastically to our enquiries and requests for data.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Chong Neto 2005

Methods	Design: Randomized, placebo-controlled study (four arms). Randomisation: Children were asked to draw a slip of paper that determined which group they were in. Blinding: double-blind. Excluded: described. Withdrawals: none. Baseline characteristics: comparable. Power calculation: calculation of sample size necessary to establish significant differences (P < 0.05) between groups for a 15% increase in FEV1 with a power of 80%. Modified Jadad score: 4
Participants	Setting: Emergency health unit affiliated with the City Hall of Curitiba. 40 children (10 in each arm) aged 6 to 18 years (average age 11.01 years). Inclusion criteria: patients with acute asthma attacks who sought medical care. Exclusion criteria: history of cardiac and pulmonary diseases other than asthma, clinical score < 3, FEV1 < 20% and greater than 80% of the predicted value, smokers, children treated with short-acting and long-acting beta-2 agonists in the last 24 hours, corticosteroids in the last 7 days, and those receiving xanthines
Interventions	Beta-agonist: salbutamol (albuterol). Home-made spacer: sealed 500 ml mineral water bottle. Dosage: 4 puffs (400 µg) given every 20 minutes during one hour (total dosage: 1200). Co-interventions: not stated Beta-agonist: salbutamol (albuterol). Commercial spacer: Aerochamber 145 ml. Dosage: 4 puffs (400 µg) given every 20 minutes during one hour (total dosage: 1200). Co-interventions: not stated
Outcomes	Primary outcomes: Change in clinical score, FEV1, and heart rate per minute. Secondary outcomes (adverse effects): tremor, nausea and/or vomiting, and hypokalaemia
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details on how randomised sequence was generated were not available
Allocation concealment (selection bias)	High risk	Children drew slips of paper to determine which group they were allocated to

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Panicker 2001

Methods	Design: Parallel group study. Randomisation: computer generated random numbers. Blinding: no details. Excluded: described. Withdrawals: none. Baseline characteristics: comparable. Power calculation: not given. Modified Jadad score: 2
Participants	Setting: India. Emergency room department. 60 children (30 in each group) aged 1 to 12 years (average age 4.8 years). Inclusion criteria: over two previous attacks of asthma exacerbation, and children seeking treatment for an acute exacerbation of bronchial asthma. Exclusion criteria: pulmonary tuberculosis, emphysema, other cardiac, hepatic, pulmonary, or skeletal disease involving the spine, any neuromuscular disorder involving intercostal muscle or diaphragm, or children who had already received steroids before going to hospital
Interventions	Beta-agonist: salbutamol (albuterol). Home-made spacer: 750 ml (final volume) plastic water bottle. Dosage: 2 puffs (200 µg) given every 5 - 10 minutes during one hour (total dosage: 1200 - 2400 µg). Co-interventions: humidified oxygen was given to all patients. Cases with incomplete or poor response at 60 minutes were given further treatment. Beta-agonist: salbutamol (albuterol). Commercial spacer: Cipla 750 ml. Dosage: 2 puffs (200 µg) given every 5 - 10 minutes during one hour (total dosage: 1200 - 2400 µg). Co-interventions: humidified oxygen was given to all patients. Cases with incomplete or poor response at 60 minutes were given further treatment
Outcomes	Primary outcomes: Change in grading of dyspnoea, ability to speak, heart rate per minute, respiratory rate, cyanosis, accessory muscle use, breath sounds, rhonchi, PEFR, pulsus paradoxus, arterial blood gas, and oxygen saturation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers sequence
Allocation concealment (selection bias)	Unclear risk	Not reported

Quetulio 2002

Methods	Design: Parallel group study. Randomisation: method not given. Blinding: single blind. Excluded: not described. Withdrawals: not described. Baseline characteristics: not described. Power calculation: not given. Modified Jadad score: 2
Participants	Setting: Philippines. Pediatric out-patient department and children′ s asthma unit. 30 children aged 5 to 18 years. Inclusion criteria: acute exacerbation of bronchial asthma. Exclusion criteria: not given

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Quetulio 2002 (*Continued*)

Interventions	Beta-agonist: terbutaline. Home-made spacer: cardboard cone. Dosage: not stated. Co-interventions: not stated. Beta-agonist: terbutaline. Comercial Spacer: NebuChamber 250 ml. Dosage: not stated. Co-interventions: not stated
Outcomes	Primary outcomes: Change in respiratory rate, subcostal and intercostal retractions, air exchange, wheezes and PEFR
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Singhal 2001

Methods	Design: Parallel group study. Randomisation: method not given. Blinding: single blind. Excluded: described. Withdrawals: none. Baseline characteristics: comparable. Power calculation: 27 for each spacer was calculated to ensure detection of a 15% change in PEFR between the two spacers at a significance level 0.05 with a power of 95%. Modified Jadad score: 2
Participants	Setting: India. Pediatric Chest Clinics of all India Institute of Medical Sciences. 60 children (31 in home-made spacer, and 29 in commercial spacer group) aged 5 to 15 years (average age 9.6 years). Inclusion criteria: asthmatic who presented with an acute exacerbation. Exclusion criteria: severe or life threatening attack characterized by either inability to speak, severe recessions, very poor air entry, PEFR < 20% of predicted, and oxygen saturation < 92%
Interventions	Beta-agonist: salbutamol (albuterol). Home-made spacer: 700ml (final volume) plastic mineral water. Dosage: 10 puffs (1000 µg) given at a rate of 1 puff every 30-60 seconds. Co-interventions: not stated. Beta-agonist: salbutamol (albuterol). Spacer: Aerochamber 150 ml. Dosage: 10 puffs (1000 µg) given at a rate of 1 puff every 30-60 seconds. Co-interventions: not stated
Outcomes	Primary outcome: change in PEFR. Secondary outcomes: change in oxygen saturation, heart rate per minute and respiratory rate
Notes	

Risk of bias

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Singhal 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Zar 1999

Methods	Design: Parallel group study (four arms). Randomisation: block randomisation. Blinding: single blind. Excluded: described. Withdrawals: none. Baseline characteristics: comparable. Power calculation: 22 for each spacer to ensure detection of a 15% change in PEFR at a significance level of 0.05 with a power of 90% for each type of spacer. Modified Jadad score: 3
Participants	Setting: South Africa. Red Cross Children´ s Hospital. 88 children (22 in each arm) aged 5 to 13 years. Inclusion criteria: children with a known history of asthma who presented to the Hospital with an acute asthma attack. Exclusion criteria: inability to use an MDI and spacer or to reliably undergo pulmonary function tests, PEFR < 20% of the predicted normal, arterial oxygen saturation < 92% in air, underlying cardiac or other chronic chronic pulmonary disease, treatment with oral corticosteroids for more than 5 days before presentation, and use of beta-agonists within 4hours of presentation
Interventions	Beta-agonist: fenoterol hydrobromide. Home-made spacers: sealed 500 ml plastic cold-drink bottle, unsealed 500 ml plastic cold-drink bottle, and 200 ml polystyrene cup. Dosage: 4 puffs (400 µg) for children who weighed 25 kg or less, and 6 puffs (600 µg) for children who weighed more than 25 kg, given at a rate of 1 puff every 10 seconds. Co-interventions: fenoterol 1000 µg in 2 ml normal saline via a jet nebuliser, and oxygen at a flow rate of 5 L per min in children who after bronchodilator treatment had PEFR < 70% of the predicted value. Beta-agonist: fenoterol hydrobromide. Commercial spacer: Aerochamber 145 ml. Dosage: 4 puffs (400 µg) for children who weighed 25 kg or less, and 6 puffs (600 µg) for children who weighed more than 25 kg, given at a rate of 1 puff every 10 seconds. Co-interventions: fenoterol 1000 µg in 2 ml normal saline via a jet nebuliser, and oxygen at a flow rate of 5 L per min in children who after bronchodilator treatment had PEFR < 70% of the predicted value
Outcomes	Primary outcomes: changes in clinical score and pulmonary function, and need for and response to nebulisation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Zar 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method to generate randomised sequence not reported; investigators employed block randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported

Zar 2007

Methods	Design: Parallel group study. Randomisation: computer-generated. Blinding: single blind. Excluded: described. Withdrawals: none. Baseline characteristics: comparable. Power calculation: 198 children were required in each group to demonstrate that hospitalisation with bottle spacer was not more than 10% higher, 80% power and a one-tailed significance level of 0.05. Modified Jadad score: 3
Participants	Setting: South Africa. Red Cross Children´ s Hospital. 400 children (200 in each group) aged 2 months to 5 years. Inclusion criteria: children with history of cough or difficulty breathing within the prior 5 days and clinical signs of acute lower airways obstruction (expiratory wheeze on auscultation or hyperinflation of the chest). Exclusion criteria: use of bronchodilator within the preceding 4 hours, known underlying cardiac or chronic pulmonary disease (other than asthma), presence of stridor or daily treatment with oral corticosteroids for more than 2 days prior
Interventions	Beta-agonist: salbutamol (albuterol). Home-made spacer: modified 500 ml plastic bottle. Dosage: 5 puffs (500 µg) given at a rate of 1 puff every 10 seconds, and given until three times at 15 minute intervals. Co-interventions: oral corticosteroids were prescribed for children who required hospitalisation or who required 2 or more bronchodilator treatments. If additional treatments were required after third inhalation, patients were nebulised (5 mg salbutamol in 2.5 mls normal saline) using a jet nebuliser. Anti-cholinergic agents were not used. Beta-agonist: salbutamol (albuterol). Commercial spacer: Aerochamber 150 ml. Dosage: 5 puffs (500 µg) given at a rate of 1 puff every 10 seconds, and given until three times at 15 minute intervals. Co-interventions: oral corticosteroids were prescribed for children with recurrent wheeze who required hospitalisation or who required 2 or more bronchodilator treatments. If additional treatments were required after third inhalation, patients were nebulised (5 mg salbutamol in 2.5 ml normal saline) using a jet nebuliser. Anti-cholinergic agents were not used
Outcomes	Primary outcome: hospitalization. Secondary outcomes: change in clinical score, oximetry, number of bronchodilator treatments required prior to discharge (if not hospitalised) , and need for systemic corticosteroids
Notes	

Risk of bias

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

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Zar 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Not reported

FEV1: forced expiratory volume in one second
PEFR: peak expiratory flow rate

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

Study	Reason for exclusion
Becker 1985	Not acute asthma.
Carson 1985	Study comparison was a home-made spacer vs. oxygen-driven nebulizer, no commercial spacer involved
Duarte 2002	Study comparison was a home-made spacer vs. oxygen-driven nebulizer, no commercial spacer involved
El-Kassimi 1987	Study included adult patients
Fowler 2001	Study included adult patients, and did not include outcomes of interest
Henry 1983	Study comparison was salbutamol versus placebo via a home-made spacer, no commercial spacer involved
Kerac 1998	Not acute asthma
Kissoon 2001	No outcomes of interest in this study.
Lipworth 2002	Not a randomised controlled trial, not acute asthma, and absence of outcomes of interest
Mazur 2000a	Not a randomised controlled trial, but a review and commentary of a previous published paper
Mazur 2000b	Same study as Zar 1999.
Mazur 2000c	Same study as Zar 1999.
Motala 2000	Review article.
Obgaidze 2005	Non-randomized trial
Quetulio 2004	Probably some patients included in Quetulio 2002, no outcomes presented in this abstract in a usable form, and no response from authors to request for clarification

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(*Continued*)

Rajkumar 2002	Not acute asthma.
Samaranayake 1998	Mixed population of patients (pediatric and adult participants), not possible to separate data from pediatric patients and no response from authors
Schleufe 1998	Not a randomised controlled trial, design more suitable to before and after study. Not acute asthma. Probably adult patients, no response from authors to request for clarification
Teo 1988	Study comparison was salbutamol versus placebo via a home-made spacer, no commercial spacer involved
Vichyanond 1992	Not acute asthma.
Willemse 2003	Study included adult patients. Not acute asthma.
Zar 1998a	Absence of outcomes of interest.
Zar 1998b	Absence of outcomes of interest.
Zar 2002a	Review article.
Zar 2002b	Review article.

vs: versus

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DATA AND ANALYSES

Comparison 1. Home-made spacers versus commercial spacers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 O2 saturation (SaO2)	2	120	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.39, 0.33]
3 Peak expiratory flow rate (PEFR)	2	90	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.72, 0.80]
4 Clinical score	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.37, 0.37]
5 Heart rate per minute (HR)	3	140	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.24, 0.42]
6 Need for additional treatment	3	552	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.84, 1.65]

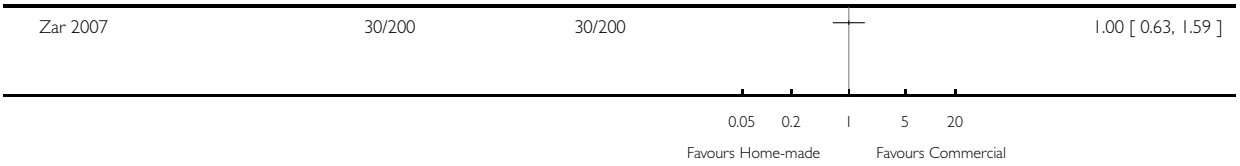
Analysis 1.1. Comparison 1 Home-made spacers versus commercial spacers, Outcome 1 Hospital admission.

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 1 Home-made spacers versus commercial spacers

Outcome: 1 Hospital admission

Study or subgroup	Home-made Spacer n/N	Commercial n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Zar 2007	30/200	30/200		1.00 [0.63, 1.59]



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Analysis 1.2. Comparison 1 Home-made spacers versus commercial spacers, Outcome 2 O2 saturation (SaO2).

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 1 Home-made spacers versus commercial spacers

Outcome: 2 O2 saturation (SaO2)

Study or subgroup	Home-made N	Mean(SD)	Commercial N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Panicker 2001	30	94.57 (1.9)	30	94.49 (3.58)		50.1 %	0.03 [-0.48, 0.53]
Singhal 2001	31	1.7 (1.9)	29	1.9 (2.36)		49.9 %	-0.09 [-0.60, 0.41]
Total (95% CI)	**61**		**59**			**100.0 %**	**-0.03 [-0.39, 0.33]**

Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Home-made spacers versus commercial spacers, Outcome 3 Peak expiratory flow rate (PEFR).

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 1 Home-made spacers versus commercial spacers

Outcome: 3 Peak expiratory flow rate (PEFR)

Study or subgroup	Home-made N	Mean(SD)	Commercial N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Panicker 2001	30	69.6 (11.1)	30	73 (10.7)		55.7 %	-0.31 [-0.82, 0.20]
Quetulio 2002	15	16.6 (6.14)	15	13.6 (6.14)		44.3 %	0.48 [-0.25, 1.20]
Total (95% CI)	**45**		**45**			**100.0 %**	**0.04 [-0.72, 0.80]**

Heterogeneity: Tau^2 = 0.20; Chi^2 = 2.99, df = 1 (P = 0.08); I^2 =67%

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Not applicable



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Analysis 1.4. Comparison 1 Home-made spacers versus commercial spacers, Outcome 4 Clinical score.

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 1 Home-made spacers versus commercial spacers

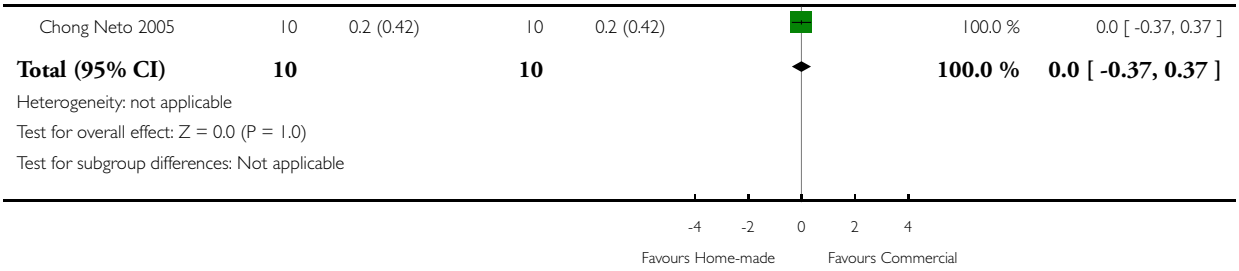
Outcome: 4 Clinical score

Study or subgroup	Home-made N	Mean(SD)	Commercial N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Chong Neto 2005	10	0.2 (0.42)	10	0.2 (0.42)		100.0 %	0.0 [-0.37, 0.37]
Total (95% CI)	**10**		**10**			**100.0 %**	**0.0 [-0.37, 0.37]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



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Analysis 1.5. Comparison 1 Home-made spacers versus commercial spacers, Outcome 5 Heart rate per minute (HR).

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 1 Home-made spacers versus commercial spacers

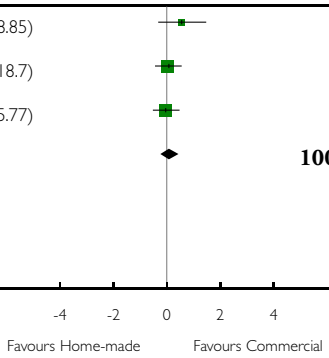
Outcome: 5 Heart rate per minute (HR)

Study or subgroup	Home-made N	Mean(SD)	Commercial N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Chong Neto 2005	10	130.1 (16.2)	10	119.8 (18.85)		13.7 %	0.56 [-0.34, 1.46]
Panicker 2001	30	127 (20.6)	30	125.7 (18.7)		43.2 %	0.07 [-0.44, 0.57]
Singhal 2001	31	8.4 (17.44)	29	8.9 (15.77)		43.1 %	-0.03 [-0.54, 0.48]
Total (95% CI)	**71**		**69**			**100.0 %**	**0.09 [-0.24, 0.42]**

Heterogeneity: Chi^2 = 1.28, df = 2 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable



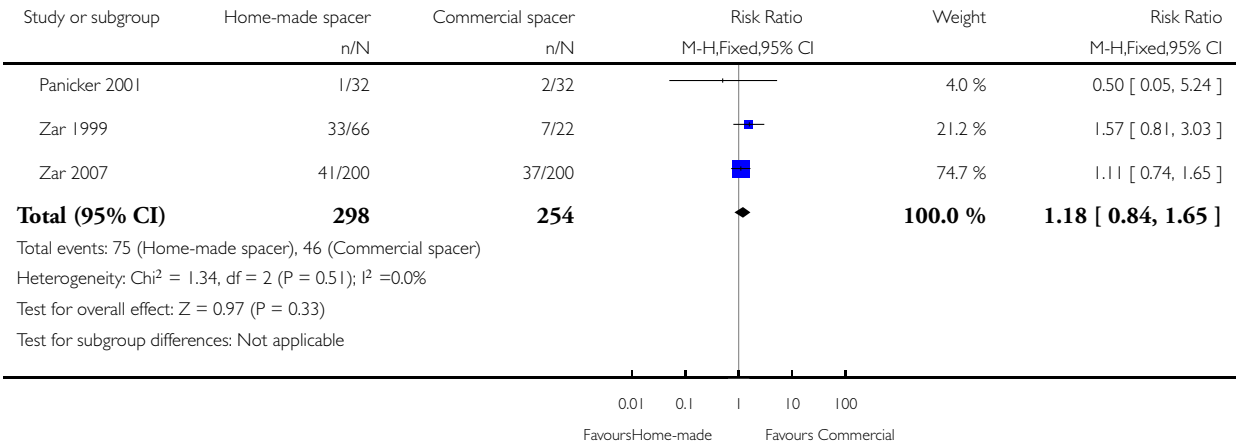
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Analysis 1.6. Comparison 1 Home-made spacers versus commercial spacers, Outcome 6 Need for additional treatment.

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 1 Home-made spacers versus commercial spacers

Outcome: 6 Need for additional treatment



APPENDICES

Appendix 1. Search strategies

CENTRAL	MEDLINE/CINAHL	EMBASE
#1. ASTHMA explode tree 1 (MeSH) #2. BRONCHIAL SPASM single term (MeSH) #3. asthma* #4. wheez* #5. (bronch* near spas*) #6. bronchospas* #7. bronchoconstrict* #8. (#1 or #2 or #3 or #4 or #5 or #6 or #7) #9. NEBULIZERS AND VAPORIZERS explode all trees (MeSH) #10. spacer*	1. exp asthma/ 2. bronchial spasm/ 3. asthma$.mp. 4. wheez$.mp. 5. (bronch$ adj3 spas$).mp. 6. bronchospas$.mp. 7. bronchoconstrict$.mp. 8. or/1-7 9. exp nebulizers/ and vaporizers/ 10. spacer$.mp. 11. MDI.mp. 12. nebuli$.mp.	1. exp asthma/ 2. Bronchospasm/ 3. asthma$.mp. 4. wheez$.mp. 5. (bronch$ adj3 spas$).mp. 6. bronchospas$.mp. 7. bronchoconstrict$.mp. 8. or/1-7 9. exp nebulizer/ 10. spacer$.mp. 11. MDI.mp. 12. nebuli$.mp.

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(*Continued*)

#11. mdi #12. nebuli* #13. vapori* #14. aerosol* #15. inhal* #16. bronchodilat* #17. (#9 or #10 or #11 or #12 or #13 or # 14 or #15 or #16) #18. (#8 and #17) #19. home-made* #20. (home next made*) #21. alternative* #22. improvi* #23. bottle* #24. ((plastic or paper) and cup*) #25. polystyrene #26. (#19 or #20 or #21 or #22 or #23 or #24 or #25) #27. (#26 and #18)	13. vapori$.mp. 14. aerosol$.mp. 15. inhal$.mp. 16. bronchodilat$.mp. 17. or/9-16 18. "home made".mp. 19. alternative$.mp. 20. improvi$.mp. 21. bottle$.mp. 22. ((plastic$ or paper$) adj3 cup).mp. 23. polystyrene.mp. 24. or/18-23 25. 8 and 17 and 24	13. vapori$.mp. 14. aerosol$.mp. 15. inhal$.mp. 16. bronchodilat$.mp. 17. or/9-16 18. "home made".mp. 19. alternative$.mp. 20. (improvis$ or improviz$).mp. 21. bottle$.mp. 22. ((plastic$ or paper$) adj3 cup).mp. 23. polystyrene.mp. 24. or/18-23 25. 8 and 17 and 24

Appendix 2. Search history

1) **Original search 2006/2007**: 1531 references
2) **2008 search update**: 81 references
3) **2009-2010 search update**: 81 references

WHAT'S NEW

Last assessed as up-to-date: 18 August 2010.

Date	Event	Description
21 August 2017	Amended	New literature search run to assess the need to update this review. Seven potentially eligible studies added to Studies awaiting classification.

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HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 2, 2008

Date	Event	Description
18 August 2010	New search has been performed	Literature search run, no new studies found.
13 August 2008	New search has been performed	Literature search re-run; no new studies were identified.
17 April 2008	Amended	Converted to new review format.
3 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

CM: initiation and development of the review; study assessment, data extraction, data entry, write-up

MS: Study assessment, data extraction, write-up

JL: Write-up

DECLARATIONS OF INTEREST

The authors have no financial interest in any of the devices used to deliver beta-2-agonists in acute asthma and no involvement with the primary studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Adrenergic beta-2 Receptor Agonists; * Nebulizers and Vaporizers; Administration, Inhalation; Asthma [* drug therapy]; Bronchodilator Agents [*administration & dosage]; Equipment Design; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Humans

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