ORIGINAL ARTICLE

Randomised controlled trial of the efficacy of a metered dose inhaler with bottle spacer for bronchodilator treatment in acute lower airway obstruction

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Background: Inhaled bronchodilator treatment given via a metered dose inhaler (MDI) and spacer is optimal for relief of bronchoconstriction. Conventional spacers are expensive or unavailable in developing countries, but there is little information on the efficacy of low-cost spacers in young children.

Objective: To compare the response to bronchodilator treatment given via a conventional or a low-cost bottle spacer

Methods: A randomised controlled trial of the efficacy of a conventional spacer compared with a bottle spacer for bronchodilator treatment in young children with acute lower airway obstruction. Bronchodilator treatment was given from an MDI via an Aerochamber or a bottle spacer. Clinical score and oximetry recording were carried out before and after 15 min of treatment. MDI-spacer treatment was repeated up to three times, depending on clinical response, after which nebulisation was used. The primary outcome was hospitalisation.

Results: 400 children, aged (median (25th–75th centile)) 12 (6–25) months, were enrolled. The number of children hospitalised ($n = 60$, 15%) was identical in the conventional and bottle spacer groups ($n = 30$, 15% in each). Secondary outcomes including change in clinical score (-2 (-3 to -1)), oxygen saturation (0 (-1 to 1)) and number of bronchodilator treatments (2 (1 to 3)) were similar in both groups. Oral corticosteroids, prescribed for 78 (19.5%) children, were given to a similar number in the conventional (37 (18.5%)) and bottle spacer groups (41 (20.5%)).

Conclusion: A low-cost bottle spacer is as effective as a conventional spacer for bronchodilator treatment in young children with acute obstruction of the lower airways.

Acute obstruction of the lower airway is common in young children. Inhaled bronchodilator treatment is recommended for relief of airway obstruction. In children, a pressurised metered dose inhaler (MDI) with spacer produces bronchodilation equivalent or superior to nebulised treatment even in the case of severe airway obstruction.^{1–3} An MDI-spacer delivery system has many advantages over nebulisation, including shorter and easier administration of drug, transportability, no need for a power source and lower risk of nosocomial infection.⁴ Moreover, use of an MDI-spacer has been reported to be cost effective; the cost and time for MDI-spacer treatment has been calculated as 40–60% that for nebulised treatment.⁵ However, a spacer is essential to minimise dependence on the child's inhalation technique and to optimise drug delivery.^{1,4}

Various commercially produced spacers have been developed, but expense and unavailability have limited their use in developing countries. The development of low-cost spacers has received relatively little attention; however, a modified plastic bottle spacer has been shown to have clinical efficacy in children >5 years.^{6,7} A randomised trial of a plastic bottle compared with a conventional spacer in children >5 years with acute asthma found that bottle and conventional spacers produced similar bronchodilation as measured by improvements in clinical score and pulmonary function.⁷ Another study of children aged 5–15 years with acute asthma reported similar improvements in peak expiratory flow rates and clinical parameters in patients who used a bottle spacer compared with those using a commercially produced spacer.⁸ However, the clinical efficacy of a bottle spacer has not been tested in infants or young children.

The potential efficacy of a modified plastic bottle as a spacer for young children has been suggested by aerosol deposition studies in which lung deposition of nebulised technetium 99m DTPA given via a bottle or a conventional spacer was measured.⁹ In children <5 years, lung deposition from a bottle was found to be twice that obtained with a conventional small-volume spacer.⁹ The amount of lung deposition was dependent on age, with a marked reduction occurring at around 50 months; this pattern occurred with both conventional and bottle spacers.

The aim of this study was to compare the response to bronchodilator given via an MDI with bottle or conventional spacer in young children with acute lower airway obstruction (LAO).

METHODS

A randomised controlled trial of the efficacy of two delivery systems (MDI-conventional spacer or MDI-bottle spacer) for treatment of LAO in young children was performed. Children with acute LAO were randomly assigned to receive bronchodilator treatment from a conventional or a bottle spacer. Written informed consent was obtained from a parent or guardian. The study was approved by the Ethics Committee of the University of Cape Town, South Africa.

Study population

Children aged 2 months to 5 years, presenting with acute LAO, were sequentially enrolled during working hours at Red Cross Children's Hospital, Cape Town, South Africa from April 2003

Abbreviations: LAO, lower airway obstruction; MDI, metered dose inhaler

to November 2005 inclusive. Children were eligible if they had a history of cough or difficulty breathing within 5 days prior to treatment and clinical signs of LAO (defined as an expiratory wheeze on auscultation or hyperinflation of the chest). Exclusion criteria were use of a bronchodilator within the preceding 4 h, known underlying cardiac or chronic pulmonary disease (other than asthma), presence of stridor or daily treatment with oral corticosteroids for >2 days prior.

A history and clinical examination was carried out and baseline clinical score and oximetry in room air recorded. A clinical scoring system using an Asthma Severity Scale that has been evaluated in children aged 6 months to 17 years and has been reported to have moderate interobserver agreement and moderate agreement with clinical judgement was used.¹⁰ The Asthma Severity Scale clinical score¹⁰ assigned was based on three clinical characteristics (heart rate, accessory muscle use and wheeze) in which each is graded on a 4-point scale with a maximum severity score of 9 (table 1). Arterial oxygen saturation in room air was measured with a pulse oximeter (Ohmeda Biox 3760, BOC Health Care, Louisville, Kentucky, USA).

Patients received a β_2 agonist (500 μ g, 5 puffs salbutamol, GlaxoSmithKline, Ventolin) from an MDI given at one puff every 10 s. Children were reassessed, and clinical score and oximetry recorded 15 min after bronchodilator administration. If no improvement occurred by way of a reduction in clinical score or increase in arterial oxygen saturation in room air or if symptoms were still present, a repeat inhalation using the same MDI-spacer combination was given. Clinical score and oximetry were then recorded 15 min after the second inhalation. If no improvement occurred, a third inhalation using the same MDI-spacer combination was given, and clinical score and oximetry recorded 15 min after this inhalation. If additional treatments were required thereafter, patients were nebulised (5 mg salbutamol in 2.5 ml normal saline, Ventolin, Nebules, GlaxoSmithKline) using a jet nebuliser, as is routine practice. Clinical score and oximetry were then recorded 15 min thereafter. Anticholinergic agents were not used.

The investigators performing the clinical assessment were blinded as to which delivery system the patients were randomised. Criteria for admission to hospital were room air oxygen saturation of <92% after completion of three bronchodilator treatments, persistent subcostal retractions, cyanosis or poor social circumstances that did not allow safe home care of the acute episode. Oral corticosteroids were prescribed for children with recurrent wheeze who required hospitalisation or who required two or more bronchodilator treatments. Administration of additional treatment was at the discretion of the treating doctor who was blinded to the randomisation.

Delivery systems

Two delivery systems were compared:

1. Conventional spacer with MDI—a small-volume (150 ml) valved spacer (Aerochamber, Trudell Medical, London, Ontario, Canada). For children <3 years a mask was

Figure 1 Child using a bottle spacer with attached facemask. Parental consent was obtained for publication of this figure.

attached, whereas for those >3 years a mouthpiece was used

2. Modified 500-ml plastic bottle with MDI—this was constructed as described previously.¹¹ The end of the bottle was held in the mouth simulating a mouthpiece. For children <3 years a small, flexible and well-fitting facemask (Cipla Medpro, India) was used (fig 1).

Each patient was randomly assigned to one of the delivery systems. The randomisation sequence was computer-generated and known only to one author (GS) who played no part in the enrolment of participants. Allocation was concealed until after the intervention had been assigned, using sequentially numbered sealed envelopes that contained tin foil to make them opaque to bright light. Bottle spacers were primed by washing in detergent and left to dry. The electrostatic charge on the side walls of spacers was further reduced by precoating with 10 puffs of aerosol from an MDI.

Outcome measures

The primary outcome measure was hospitalisation. Secondary outcome measures were change in clinical score, oximetry, number of bronchodilator treatments required before discharge (if not hospitalised) and need for systemic corticosteroids. Change in clinical score was measured as the difference between the clinical score at presentation and the clinical score recorded after the final bronchodilator treatment before discharge or hospitalisation. Change in oximetry was measured as the difference between oximetry recorded at presentation in room air and that recorded after the final bronchodilator treatment before discharge or hospitalisation. A bronchodilator treatment was regarded as five puffs of salbutamol or a salbutamol nebulisation.

Table 1 Clinical Asthma Severity Scale score¹⁰

Scale	Wheeze	Accessory muscle use	Heart rate (beats/min)
0	None	None	≤80
1	Expiratory	Subcostal	81–110
2	Inspiratory and expiratory	Subcostal and intercostals	111–140
3	Audible without stethoscope or no wheeze owing to minimal air entry	Subcostal, intercostal, suprasternal	>140

Figure 2 Participant flow.

Sample size and statistics

This was an equivalence study; equivalence was regarded as not more than an absolute 10% increase in hospitalisation with the bottle spacer. Assuming that hospitalisation with the conventional spacer would occur in 20% of children and that the spacers were equally effective, 198 children were required in each group (total sample of 400 children) to demonstrate that hospitalisation with the bottle spacer was not >10% higher, with 80% power and a one-tailed α of 0.05.

The primary outcome was expressed as an absolute difference in hospitalisation. The effect size for primary and other categorical outcomes was expressed as an absolute difference, with an upper 90% confidence limit for any difference favouring the conventional spacer. For continuous outcomes, differences in medians or means were reported, with an upper 90% confidence limit for any difference favouring the conventional spacer. No other comparisons were planned or performed. Analysis was by intention to treat. An interim analysis of the primary outcome was performed on 200 patients.

RESULTS

A total of 452 children were screened, 400 of whom (157, 39.3% boys) were enrolled (fig 2). The median (25th–75th centile) age of participants was 12 (6–25) months. Baseline characteristics were similar in the conventional and bottle spacer groups (table 2). Most children (322, 80.5%) had experienced a prior wheezing episode, with a median of three prior episodes; this was similar in both groups (table 2). More than a quarter (104 (26%)) had been hospitalised for a prior wheezing attack; the incidence of prior hospitalisation was similar in the conventional and bottle spacer groups (58 (29%) v 46 (23%), $p = 0.17$).

However, only 60 (15%) children were using inhaled corticosteroid treatment (table 2).

Overall, 60 (15%) children were hospitalised; the number of children hospitalised in the conventional and homemade spacer groups (30, 15% in each) was identical. The upper 90% confidence limit for a difference—that is, the largest benefit of a conventional spacer that could reasonably be expected—was 5.9%, less than the pre-specified 10% for equivalence. At this maximal difference of 5.9%, one additional child would be hospitalised for every 17 children treated with a bottle spacer.

We found no significant differences in the secondary outcomes in the two groups (table 3). The median (25th–75th centile) change in clinical score (–2 (–3 to –1)), oxygen saturation (0 (–1 to 1)) and number of bronchodilator treatments given (2 (1 to 3)) were similar in both groups (table 3). Overall, 78 (19.5%) children were given oral corticosteroids (41 (20.5%) in the bottle group versus 37 (18.5%) in the conventional group). This represented a 2% lower risk for use of oral corticosteroids in the bottle group, with the “worst case” 90% confidence limit being a difference of 8.5%. The point estimate of the difference (2%) implied that, in this setting, one additional child would receive systemic steroids for every 50 treated with the bottle, whereas in the worst case (8.5%) one additional child would receive steroids for every 12 treated with the bottle.

DISCUSSION

This study has shown that a low-cost bottle spacer and a conventional Aerochamber spacer produced equivalent clinical responses when used to deliver bronchodilator treatment in young children with acute airway obstruction. To our knowl-

Table 2 Baseline characteristics of children

Characteristic	All		Bottle spacer		Conventional	
	n		n		n	
Age in months (median, IQR)	400	12 (6–25)	200	12 (7–25)	200	12 (6–24)
Clinical score (median, IQR)	399	6 (4–7)	199	6 (4–8)	200	6 (4–7)
Male (n, %)	400	157 (39.3)	200	80 (40)	200	77 (38.5)
First attack (n, %)	400	78 (19.5)	200	36 (18)	200	42 (21)
Prior episodes (median, IQR)	309	3 (2–7)	159	3 (2–6)	150	3 (2–7)
Use of inhaled steroid (n, %)	400	60 (15)	200	28 (14)	200	32 (16)
Use of oral steroid (n, %)	400	34 (8.5)	200	19 (9.5)	200	15 (7.5)
Currently using metered dose inhaler (n, %)	400	85 (21.3)	200	41 (21.5)	200	44 (22)
Prior hospitalisation (n, %)	400	104 (26)	200	58 (29)	200	46 (23)
Number of prior hospitalisations (median, range)	395	0 (0–6)	198	0 (0–5)	197	0 (0–6)
Oxygen saturation (median %, IQR)	399	96 (95–97)	199	96 (95–97)	200	96 (94–97)

edge, this is the first study of the efficacy of a bottle spacer in young children and infants. Wheezing in young children is common, particularly with acute asthma or viral lower respiratory tract infections.¹² The prevalence of asthma has been reported to be rising in developing countries in association with urbanisation, exposure to allergens, and changing dietary and behavioural patterns.¹³ As a result, increasing numbers of young children can be expected to require treatment for wheezing in these geographical areas. The characteristics of children enrolled in this study indicate that recurrent wheezy illness is common in this population, and that inhaled corticosteroids are under-prescribed, given the frequency and severity of prior wheezy episodes that care givers reported.

Inhaled bronchodilators, particularly short-acting β_2 agonists, are the treatment of choice for reversal of airway obstruction in acute asthma and wheezing disorders. Although the response to bronchodilators in children <2 years of age with wheezing may be variable, this is currently the primary treatment for acute wheezy illness.¹⁴ Further, the children in both groups of our study responded to bronchodilators, as measured by an improvement in clinical score. In young children, bronchodilators are best given using an MDI with spacer.^{1–2} Besides efficacy and reduced side effects, an MDI has important advantages relevant to developing countries compared with nebulised treatment—an MDI delivery system does not require a power source, is relatively quick to administer and is more affordable.^{4–5} However, a spacer must be used with an MDI as children are unable to synchronise inspiration with actuation of the MDI.^{1–2}

Although inhaled β_2 agonists in MDI form are widely available and are on the World Health Organization essential drug list, their use in children is limited by the cost and unavailability of spacers, particularly in developing countries. A spacer functions as a reservoir from which aerosol can be inhaled, allows MDI propellant to evaporate, and acts as a surface for impaction of high-inertia aerosol droplets.⁴ Evaporation of MDI propellant promotes the formation of smaller particles to be carried into the small airways. Large,

high-inertia particles moving rapidly from the MDI affect the oropharynx in the absence of a spacer. The ability to briefly hold suspended aerosol before inhalation helps to minimise the detrimental effects of poor timing between MDI actuation and inhalation.⁴ This benefit may be especially important for young children and during an acute asthma attack, when correct use of an MDI may be extremely difficult.

A plastic bottle spacer has been reported to be as effective as a conventional spacer for bronchodilator treatment in children >5 years with acute wheezing.^{7–8} However, there are few data on the efficacy of a bottle spacer in young children and infants. Aerosol deposition studies reported lung deposition from a plastic bottle spacer in young children to be twice that from a conventional valved small-volume spacer, suggesting the potential efficacy of a bottle spacer.⁹ Absence of a valve in a bottle spacer may possibly increase aerosol lung deposition, particularly in young children or in those with airway obstruction, as overcoming the resistance of a valve on inspiration may be difficult in such patients. As evidence of this, a valveless spacer has been reported to enhance the delivery of aerosol to the lungs of infants with chronic lung disease compared with the delivery obtained from the same spacer with a valve.¹⁵

Given the resource constraints in developing countries, it is essential that a low-cost, effective spacer be available for effective bronchodilator treatment of wheezing. The efficacy of a bottle spacer in this study suggests that it can be recommended for use in infants and young children for bronchodilator treatment of acute wheezing. This applies to the delivery of β_2 agents; caution must be exercised in extrapolating to other agents such as inhaled corticosteroids where there may be differences in drug properties and drug-spacer interactions. The efficacy of a bottle spacer may be due to careful attention to its construction and use. Although a bottle spacer seems simple to make and use, modification and use should be according to methods shown to be effective.¹⁶ Bottle spacers used in this study were made using a standard technique by a single person, as has been described.¹¹

Table 3 Secondary outcomes by spacer group

Outcome	Bottle	Conventional	p Value
Need for systemic corticosteroids (n, %)	41 (20.5%)	37 (18.5%)	0.61
Change in clinical score (median, IQR)	−2 (−3 to −1)	−2 (−3 to −1)	0.53
Change in oxygen saturation (median, IQR)	0 (−1 to 1)	0 (−1 to 1)	0.53
Number of bronchodilator treatments (median, IQR)	2 (1 to 3)	2 (1 to 3)	0.67

What is already known on this topic

- Inhaled bronchodilator treatment given through a metered dose inhaler with attached spacer provides optimal treatment in acute airway obstruction.
- In many developing countries the use of inhaled treatment is limited by the cost and unavailability of commercially produced spacers.
- A low-cost plastic bottle spacer has been shown to be effective in children >5 years, but its efficacy in infants or young children is unknown.

What this study adds

- The study shows that a low-cost bottle spacer is as effective as a conventional spacer for delivery of bronchodilator treatment in young children with acute airway obstruction.
- A low-cost bottle spacer can be recommended for use in young children, allowing more widespread use of inhaled bronchodilator treatment.

Attention to priming and use are necessary, as for a conventional spacer. In this study, bottle spacers were washed with detergent and allowed to air dry to reduce electrostatic charge on the side walls.^{17 18} In addition, bottle spacers were primed with aerosol from the MDI at first use.¹⁸ Obtaining a good seal between the spacer mask and face is important to minimise aerosol loss into the environment. Although commercial spacers should be used when available, a bottle spacer may be recommended in situations where commercial spacers are inaccessible or unaffordable. Patients, care givers and health-care professionals must be educated as to the optimal way in which an MDI-bottle spacer should be made and used if this is to be effective.

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