

Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma

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Objective: To compare the costs and effectiveness of albuterol by metered dose inhaler (MDI) and spacer versus nebulizer in young children with moderate and severe acute asthma.

Design: Randomized, double-blind, placebo-controlled trial in an emergency department at a children's hospital. The participants were children 1 to 4 years of age with moderate to severe acute asthma. Patients assigned to the spacer group received albuterol (600 µg) by MDI by spacer (AeroChamber) followed by placebo by nebulizer (n = 30). The nebulizer group received placebo MDI by spacer followed by 2.5 mg albuterol by nebulizer (n = 30). Treatments were repeated at 20-minute intervals until the patient was judged to need no further doses of bronchodilator, or a total of 6 treatments.

Results: Clinical score, heart rate, respiratory rate, auscultatory findings, and oxygen saturation were recorded at baseline, after each treatment, and 60 minutes after the last treatment. Baseline characteristics and asthma severity were similar for the treatment groups. The spacer was as effective as the nebulizer for clinical score, respiratory rate, and oxygen saturation but produced a greater reduction in wheezing ($P = .03$). Heart rate increased to a greater degree in the nebulizer group (11.0/min vs 0.17/min for spacer, $P < .01$). Fewer children in the spacer group required admission (33% vs 60% in the nebulizer group, $P = .04$, adjusted for sex). No differences were seen in rates of tremor or hyperactivity. The mean cost of each emergency department presentation was NZ\$825 for the spacer group and NZ\$1282 for the nebulizer group ($P = .03$); 86% of children and 85% of parents preferred the spacer.

Conclusion: The MDI and spacer combination was a cost-effective alternative to a nebulizer in the delivery of albuterol to young children with moderate and severe acute asthma. (J Pediatr 2000;136:497-502)

Inhaled bronchodilator, typically albuterol, is the standard management for acute exacerbations of asthma.¹ Whereas a spacer and metered dose inhaler combination is commonly used

for mild exacerbations of asthma among young children, for more severe asthma and in the emergency department setting, the bronchodilator is typically administered by nebulizer.

The spacer/MDI combination has been evaluated in all ranges of severity in acute asthma among adults and is at least as effective as the nebulizer in outpatient, inpatient, ED, and inten-

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sive care settings.²⁻¹¹ In adults with acute severe asthma, the spacer appears to be more effective than the nebulizer, resulting in more rapid reso-

ED	Emergency department
MDI	Metered dose inhaler
SaO ₂	Oxygen saturation

lution of bronchospasm and a greater increase in forced expiratory volume after the first dose.⁵ In addition to clin-

Table I. Clinical score

Scale	Wheeze	Accessory muscle use	Pulse rate (beats/min)
0	None	None	<80
1	Expiratory	+	81-110
2	Inspiratory and expiratory	++	111-140
3	Audible without stethoscope or No wheeze due to minimal air entry	+++	≥140

Each component graded on a scale of 0 to 3 and a summary clinical severity score assigned (maximum 9).^{4,20}

ical benefit, there is a cost benefit, with some U.S. hospitals documenting a 30% to 50% savings of the annual cost of asthma therapy with substitution of spacers for nebulizers.^{2,6,9,12}

Studies among children comparing the spacer with the nebulizer have been limited.¹³ Although inhalation of β_2 -agonist by spacer is often prescribed in children for maintenance therapy in an ambulatory setting, this delivery method has not been widely accepted for managing acute asthma in the ED. Whereas the spacer has been shown to be equivalent to a nebulizer for children with mild and moderate asthma,¹⁴⁻¹⁸ most studies exclude children with severe asthma.¹⁴⁻¹⁶ In addition, although several studies suggest the spacer and MDI combination may be cost-effective in pediatric populations, no direct cost comparisons have been performed.^{14,16,17} Because asthma is one of the most common reasons young children are seen in the ED, it is important to assess whether the clinical and economic advantages observed in adults with severe asthma are also observed in children. Therefore the aim of this study was to evaluate the costs and effectiveness of albuterol delivered by MDI and spacer versus nebulizer in young children seen in the ED with moderate and severe acute asthma.

METHODS

Children were eligible if they were 1 to 4 years of age and presented with an acute exacerbation of asthma to the ED

of the Starship Children's Hospital in Auckland, New Zealand. Baseline observations included heart rate, respiratory rate, chest findings on auscultation, and room air oxygen saturation (saturation measured noninvasively with Nellcor pulse oximeter). Wheezing, heart rate, and accessory muscle use were graded on a scale of 0 to 3 (Table I) and a summary asthma clinical severity score assigned with a maximum score of 9.^{19,20} Only children with a known history of asthma and a clinical score >3 (moderate and severe exacerbation) were eligible for inclusion. Note was made of their asthma history and the therapy received before presentation to the ED. Children were excluded if they received inhaled bronchodilator in the hour before presentation or required immediate admission to the intensive care unit, or if examination confirmed a coexisting medical condition such as pneumonia. The study was approved by the hospital ethics committee, and children were enrolled after informed consent was obtained from their parent or caregiver.

Patients were randomized to receive 1 of 2 treatments administered in a double-blind, double-dummy fashion. The spacer group received 600 μ g albuterol by MDI (100 μ g/actuation Ventolin, Glaxo) by spacer followed by normal saline solution by nebulizer over a 10-minute period. The nebulizer group received 6 actuations of placebo MDI by spacer followed by 2.5 mg albuterol by nebulizer over a 10-minute period (1 mg/mL Ventolin, Glaxo). To optimize

delivery the MDI was shaken before each actuation, and medication was administered one actuation at a time into the child AeroChamber with a face-mask (150 mL, Trudell Medical). Each actuation was administered just before inhalation and cleared from the spacer by 5 tidal breaths. Because "new" (previously unused) spacers have an electrostatic charge that reduces the available dose to the patient by 66% compared with "used" spacers,²¹⁻²⁵ the spacers were primed with 10 actuations from the MDI before use. Wherever possible the medication was administered when the child was quiet and cooperative. Nebulizer therapy was delivered with a Marquest bowl and Hudson facemask, and normal saline solution was added for a 4-mL fill volume. This combination with wall oxygen as driving gas flow at 8 L/min for 10 minutes produces an output of 0.36 mL/min and a mass median aerodynamic diameter particle of 3.41 μ m. The ratio of 600 μ g albuterol by spacer to 2.5 mg by the nebulizer was estimated to be an equivalent dose from previous studies among both children and adults. The hospital pharmacy generated the randomization schedule with random numbers and supplied blinded treatment packets.

Treatments were repeated at 20-minute intervals, until the patient was judged by the attending clinician (A.L., S.C.) to need no further doses of bronchodilator, up to a maximum of 6 treatments. A single dose of oral steroid (prednisone) was administered according to standard ED protocol (2 mg/kg as a single dose in the first 30 minutes of the ED stay). No oral steroid was administered to children who had received an appropriate dose in the 24 hours before assessment. Patients with sustained room air oxygen saturation <92% received supplemental oxygen. No other concurrent medications were given during the study period. Patients reverted to the standard ED protocol if they refused medication, required more than 6 treatments, or their clinical condition deteriorated.

Observations including heart rate, respiratory rate, oxygen saturation, and the clinical severity score were recorded at baseline, 20 minutes after each treatment, and 60 minutes after the final study treatment. Additional outcome measures included an assessment of wheezing (0 = nil, 1 = end expiratory, 2 = expiratory, 3 = inspiratory and expiratory, 4 = silent chest) and side effects. Side effects included a clinical assessment of tremor (0 to 3, 0 = nil, 3 = severe), a parental assessment of hyperactivity (0 to 3, 0 = nil, 3 = severe), and change in heart rate. Record was made of the time required to administer each treatment, the number of treatments required, and whether the child was discharged home from the ED or required admission to hospital. Children were admitted to the hospital if they had ongoing hypoxia or wheezing 60 minutes after the final study treatment. Children discharged from ED were prescribed 4-hourly inhaled bronchodilator, completed a course of oral steroids (prednisone 2 mg/kg for 5 days), and continued taking their usual asthma prophylaxis. Families were advised to return to the ED if the prescribed asthma treatment did not result in improvement of asthma symptoms. Re-presentation to the ED in the 48 hours after discharge was noted. The child and his or her parent were asked which treatment option they preferred.

Costs were calculated with the cost of the medication, equipment (spacer, masks, and nebulizer bowl), the ED presentation, and for those requiring admission, the cost of the resulting hospital admission. The Children's Hospital Management Unit provided cost estimates that included the fixed costs, human resources, and investigation and treatment costs. Benchmark estimates in 1996 were NZ\$190 for each ED presentation and NZ\$1814 for each hospital admission for asthma.

Data were analyzed with the SPSS statistical package (SPSS, Inc) with an intention-to-treat analysis. Baseline characteristics and response to treat-

Table II. Baseline characteristics

	Spacer (n = 30)	Nebulizer (n = 30)
Mean age (mo) ± SD	36.0 ± 11.5	32.3 ± 13.5
Inhaled corticosteroid prophylaxis (%)	46.4	33.3
Mean No. of hospital admissions in previous year	1.1	0.62
Mean No. of ED attendances in previous year	1.82	1.42
Oral steroids in previous 24 h (%)	66.7	66.7
Median No. of doses of inhaled bronchodilator in previous 24 h	2.0	2.0
Median No. of hours since last bronchodilator before ED presentation	2.0	2.25

Table III. Baseline recordings

	Spacer (n = 30)	Nebulizer (n = 30)	Mean difference	95% CI
Wheeze	2.5	2.2	0.33	-0.05, 0.72
HR (beats/min)	150.1	149.0	1.43	-5.6, 8.4
RR (breaths/min)	45.2	46.9	-1.7	-7.9, 4.6
SaO ₂ saturation (%)	93.7	93.9	-0.13	-1.2, 0.93
Accessory muscle use	2.3	2.4	-0.13	-0.45, 0.18
Clinical score	7.5	7.8	-0.30	-1.0, 0.41

Mean values presented for each group, 95% CI around the mean difference.
HR, Heart rate; RR, respiratory rate.

ments were compared with *t* tests, Wilcoxon rank sum tests for continuous variables, and chi-squared tests for categorical variables. Multiple regression was used to adjust for covariates. To assess both clinical and statistical equivalence, we report the mean difference between the treatment groups and the 95% confidence interval around the difference. The proportion of children admitted to the hospital from the ED after each treatment was compared with the log-rank statistic and displayed with Kaplan-Meier survival curves. A sample size of 30 per group provided 80% power to detect a difference of 1.25 in clinical score with an SD of 1.5 and an α of .05.

RESULTS

Sixty children entered the study: 30 in each treatment group. The treat-

ment groups were similar with respect to age, but a higher proportion of the nebulizer group was male (80.0% vs 47%, $P = .02$). The groups were similar for measures of asthma severity in history, usual asthma therapy, and medication received in the 24 hours before presentation to ED (Table II); 78% of the spacer group had received inhaled bronchodilator in the previous 24 hours compared with 80% of the nebulizer group. In the preceding 24 hours, 82% of both groups had used a spacer at home, whereas 22% of the spacer group and 15% of the nebulizer group received bronchodilator therapy by a nebulizer. No clinically or statistically significant differences were seen in the baseline assessment of asthma severity on presentation to the ED (Table III).

A significantly greater reduction occurred in wheezing with the first treatment for the spacer group compared with the nebulizer group ($P = .03$)

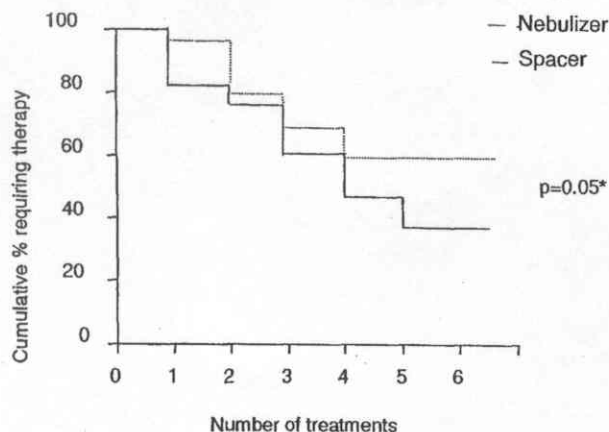


Figure. Proportion of children requiring ongoing medical therapy (hospital or ED). *Adjusted for sex.

Table IV. Response to first treatment

Change in measure	Spacer (n = 30)*	Nebulizer (n = 30)*	Mean difference	95% CI
Wheeze	-0.93	-0.48	0.45	0.07, 0.9
HR (beats/min)	2.4	10.5	10.8	5.3, 16.4
RR (breaths/min)	0.3	-0.9	1.3	-2.9, 5.3
SaO ₂ saturation (%)	0.7	1.0	-0.33	-1.4, 1.0
Accessory muscle use	-0.43	-0.55	-0.12	-0.41, 0.16
Clinical score	-1.67	-1.45	0.12	-0.3, 0.8
Tremor	0.20	0.31	-0.11	-0.3, 0.2
Hyperactivity	0.57	0.28	0.09	-0.2, 0.4

*Negative values decreased with the first treatment; positive values increased with the first treatment.
95% CI around the mean difference.
HR, Heart rate; RR, respiratory rate; SaO₂, oxygen saturation.

(Table IV). Children in the nebulizer group had a significantly greater increase in heart rate with the first treatment than those in the spacer group ($P < .01$) and continued to have a significantly higher heart rate throughout the remainder of the study period ($P = .03$). No other differences were seen between groups in the response to the first treatment. The median number of treatments required was 4 in the spacer group and 4.5 in the nebulizer group. Over the whole study period, the absolute change in clinical score was similar (-2.9 spacer vs -2.7 nebulizer, $P = .55$).

Of the children in the spacer group, 33% required admission to hospital compared with 60% in the nebulizer

group ($P = .04$ adjusted for sex). Children in the spacer group improved with each treatment and were discharged home from the ED with fewer treatments overall (Figure: the survival curve for requirement for ongoing medical therapy, log-rank test, $P = .05$). In contrast, little clinical improvement occurred in the children in the nebulizer group after the fourth treatment. Two of 20 children discharged home from the ED after treatment with the spacer re-presented within 48 hours: one with a viral pneumonia, the other with a repeat exacerbation of asthma. None of the 12 children discharged home from the ED after nebulizer therapy re-presented within the follow-up period ($P = .58$).

The mean cost of the medication and equipment required during the ED stay was NZ\$30.60 for the spacer group and NZ\$3.52 for the nebulizer group. The mean total cost was NZ\$825 for the spacer group and NZ\$1282 for the nebulizer group ($P = .03$) (includes the cost of the ED stay, medication and equipment, and subsequent hospital admission, if required). The time required to deliver each treatment was approximately 1.5 minutes by spacer compared with 10 minutes for the nebulizer. Eighty-six percent of children and 85% of parents preferred the spacer to the nebulizer.

Three patients were withdrawn from the study but were included in the study sample and analysis. Two children refused both the spacer and nebulizer (one in each treatment group) and were admitted to hospital. One child in the nebulizer group refused the nebulizer but was successfully treated with bronchodilator by the spacer and was subsequently discharged.

DISCUSSION

Comparisons between spacer and nebulizer treatment suggest they are equivalent methods of delivery of bronchodilator to children with mild or moderate asthma.¹³⁻¹⁸ However, most studies specifically exclude children with severe asthma,¹⁴⁻¹⁶ and few include children <5 years of age.^{14,26-28} Studies including young children with moderate and severe asthma have reported difficulties with valve movement in the spacer²⁶ and a modest withdrawal rate because of lack of tolerance with the spacer.²⁸ Parkin et al²⁷ specifically compared the 2 methods in severe asthma in young children but randomized children to spacer or nebulizer treatment after ED stabilization with standard nebulizer therapy. Other studies have methodologic limitations including lack of blinding, no control group, and lack of adjustment for concomitant medications.¹³

We documented that albuterol delivered by spacer and MDI was an effective alternative to a nebulizer, was well tolerated, was quicker to deliver, and had fewer side effects. In addition to being a more efficient means of drug delivery, for this population of children with severe asthma, the spacer and MDI combination was cost-effective. Although the delivery system itself was more expensive, there were fewer hospital admissions with the spacer and thus lower costs overall per child presenting with an acute exacerbation of asthma. For each NZ\$1200 hospital admission avoided, the marginal cost of the spacer/MDI combination was NZ\$87. Although the cost benefit would be less in populations of children with less severe asthma, this degree of cost savings is consistent with other studies examining the spacer and MDI in the treatment of hospitalized adults with asthma.^{2,6,9,12} A large component of the cost savings in U.S. studies is in respiratory therapist time. This is not applicable to the New Zealand situation, because nursing staff deliver both therapies. Cost savings are even greater if the downstream costs of using the 2 treatments at home are considered.

The equivalent dose of spacer to nebulizer albuterol has yet to be agreed on. In our study the average cumulative dose of albuterol delivered by the spacer (2.3 mg) was more effective than the 10.8 mg delivered by the nebulizer (a ratio of 1:4.7). The wide range reported in the literature (1:1 to 1:12.5)^{2,5,6,9,12-16,18,26,27,29-32} is a reflection of the differing study designs and the variability in dose delivered to the lungs by the different delivery systems. Although the nebulizer is the gold standard by which other aerosolized therapies are compared, output from a nebulizer system is greatly influenced by the type and brand of nebulizer used and how it is operated.³³⁻³⁸

The way the medication is delivered with the spacer/MDI combination and the choice of spacer have important in-

fluences on the amount of drug delivered to the lungs.³⁹ We chose to use a small-volume spacer despite the evidence the output may be higher from large-volume spacers.⁴⁰ Because the higher concentration of aerosol in a small chamber tends to enhance drug delivery at low tidal volumes and low inspiratory flows,⁴¹ the small volume spacer was more appropriate in our population of young children with severe asthma. We did not observe difficulties with valve movement resulting from low flow rates with severe asthma found in other studies.²⁶ Possible reasons for this include the close application of the mask to the face producing an effective seal and the use of a pediatric spacer with a lightweight valve.

The spacer was the preferred treatment option for both parents and children and was well tolerated by almost all of the children. The spacer is an accepted alternative to the nebulizer in outpatient settings in New Zealand, and this is likely to have played a major part in the acceptance in the ED setting. In populations where the spacer is less widely used and the nebulizer is the standard of care, initial parental and child acceptance and tolerance may not be as high.

Although nebulizers have been the standard of care for acute asthma in the ED, several features detract from their use. Nebulizers are noisy, require the child to sit still for 10 minutes, and are relatively inefficient, delivering at best 10% of the prescribed drug to the lungs.³³ Moreover, nebulizer units require regular maintenance, and some do not deliver a good respirable output.³⁵ Compared with a nebulizer, a spacer and MDI is a more efficient means of drug delivery; less total dose is required for the same degree of bronchodilation, and the time to deliver a complete dose is shorter.^{11,42} There appear to be fewer side effects as manifest by the lower heart rate response to treatment in the spacer group. The higher heart rate in the nebulizer group reflects unresolved

asthma and the poorer therapeutic index of bronchodilator with a nebulizer. Delivery by nebulizer results in greater facial and oropharyngeal deposition of medication, with consequent systemic absorption and side effects (particularly tachycardia). Delivery with spacer improves targeting of medication to the lung and reduces the dose delivered elsewhere, thus reducing the amount of medication available for systemic absorption. In addition, a spacer and MDI is compact, relatively cheap, and because it requires no external power source, it can be used in most settings.

Our study has shown that an MDI and spacer combination is at least as effective as a nebulizer in the delivery of albuterol to young children with moderate and severe acute asthma. In our population the MDI/spacer combination resulted in lower rates of hospital admission and lower costs per ED presentation and was the preferred treatment option for parents and children. The spacer provides an effective alternative to the routine use of the nebulizer in the acute setting.

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