AEROSOL DELIVERY IN RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS: HOOD OR FACE MASK?

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Objectives To compare the utility of the hood versus the face mask for delivery of inhaled medications to infants hospitalized with viral bronchiolitis.

Study design Randomized, double-blinded, controlled trial; 49 hospitalized infants with viral bronchiolitis, age 2.75 ± 2.2 months (mean ± SD), were grouped to either the hood (n = 25) or the mask (n = 24). Each subject received inhalation treatments with the use of both devices. Half of the Hood Group received the active drug treatment (1.5 mg epinephrine in 4 mL saline [3%]) via hood followed immediately by placebo treatment (normal saline) via mask, whereas the other half received the opposite order. Half of the Mask Group received the active drug treatment via mask followed immediately by placebo treatment via hood, whereas the other half received the opposite order. Therapy was repeated 3 times daily until discharge. Outcome measures included clinical scores and parental preference.

Results Percent improvement in clinical severity scores after inhalation was significant in both groups on days 1, 2, and 3 after admission (Hood Group: 15%, 15.4%, and 16.4%, respectively; Mask Group: 17.5%, 12.1%, and 12.7%, respectively; $P < .001$). No significant difference in clinical scores improvement between groups was observed. Eighty percent (39/49) of parents favored the hood over the mask; 18% (9/49) preferred the mask and 2% (1/49) were indifferent.

Conclusions In infants hospitalized with viral bronchiolitis and in whom aerosol treatment is considered, aerosol delivery by hood is as effective as by mask. However, according to parents, the tolerability of the hood is significantly better than that of a mask. *(J Pediatr 2005;147:627-31)*

Bronchiolitis is the most common respiratory illness resulting in hospital admission in infants and is associated with considerable morbidity.[1] Despite increasing skepticism and conflicting results, many centers still attempt to deliver various therapeutic agents (mostly bronchodilators) by aerosol to patients with respiratory syncytial virus (RSV) bronchiolitis. Difficulties in aerosol delivery may be the major cause of poor therapeutic response in RSV bronchiolitis.[2]

Most devices currently used for delivering aerosol medications to infants (eg, nebulizers) are adaptations of devices developed for use in adults without empiric data to support their effectiveness in infants.[3] Generally, these devices were modified for infants primarily by attaching a small face mask. The face mask covers the mouth and nose and provides the interface between the aerosol generator and the patient. For optimal therapy, the edge of the mask must fit tightly on the infant's face. However, achieving a good mask-to-face seal may be difficult in many infants because of squirming and crying.[4,5] It has been shown that even a 1-cm gap between the mask and the face reduces delivery of the dose by 50%.[6] Furthermore, nebulizer treatments take up to 15 minutes to administer, which is longer than most infants will tolerate. They become impatient and agitated, and the efficiency of drug delivery to their lungs is greatly reduced. Clearly, there is a need to develop a more acceptable, patient-friendly interface for improving aerosol delivery to infants.

BA	Baby Air	INH	Inhalation
CS	Clinical scores	RSV	Respiratory syncytial virus

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Figure 1. Aeroneb nebulizer attached at the top of the Baby Air device. Figure available in color online at www.jpeds.com.

It has been recently demonstrated scintigraphically in infants that inhalation via hood achieves a lung deposition of salbutamol comparable to that delivered by a conventional face mask.[7] Infants tolerated the hood better than the mask, and there was a significant positive correlation between poor acceptance and upper airways and stomach deposition for both treatment modalities. In addition, parents unequivocally preferred the hood treatment. The present double-blinded placebo control trial was designed to compare the efficacy, safety, and tolerance of hood versus the face mask interface in delivering aerosol medications to infants hospitalized with RSV bronchiolitis and in whom aerosol treatment is considered.

METHODS

Study Design

A prospective, single-center, randomized, parallel group, double-blinded, controlled clinical trial to compare efficacy, safety, and tolerance of a hood (Baby Air) as compared with face mask for the delivery of inhaled bronchodilators.

Patients

Inclusion criteria were age between 1 and 24 months, clinical presentation of viral bronchiolitis leading to hospitalization, saturation of ≥85% and ≤96% on room air, and first episode of respiratory disease. Signed informed consent was obtained from parents/guardians. Patients' parents/guardians were required to be able to comply with the study procedures and follow-up. Exclusion criteria included cardiac disease, chronic respiratory disease or previous wheezing episode, obtunded consciousness, progressive respiratory failure requiring mechanical ventilation, and saturation <85% on room air.

Sex, age, and medical history (including previous treatments, concurrent diseases, and concomitant medications) of each infant and physical examination (weight, height, body temperature, pulse rate, and respiration rate) were recorded.

Devices and Medications

Aerosol generated by an Aeroneb Go Nebulizer (Aerogen, Inc, Mountain View, CA) was delivered either via a Baby Air device (Baby's Breath, Yozmot-Granot, Israel) (Figure 1, available in color online at www.jpeds.com) or via a conventional face mask (Cranehouse Molly, Berkshire, England). This nebulizer has an output of 0.3 to 0.35 mL/min, an aerodynamic diameter mass medium of 2.6 μm, and a geometric SD of 1.9 to 2.1 μm for all inhalation solutions nebulized. Based on recent suggestions that inhaled epinephrine delivered with hypertonic saline is significantly more efficient than inhaled epinephrine delivered with traditional normal saline,[8,9] we have chosen the former combination (inhalation of 1.5 mg epinephrine in 4.mL hypertonic saline 3%) as our active treatment drug. Normal saline inhalation was used as placebo.

The Baby Air device was cleaned and sterilized between patients by brushing and washing with Chlorhexidine gluconate 4.5% solution (Septal Scrub, Teva, Ashdod, Israel) followed by water rinsing and air drying.

Protocol

Eligible patients judged by the attending physician to require frequent inhaled bronchodilator treatments were randomly assigned (computer generated) in a double-blinded fashion either to the Hood Group (treatment drug administered via Baby Air) or the Mask Group (treatment drug administered via face mask). Half of the Hood Group received the active drug treatment via hood followed immediately by placebo treatment via mask; the other half received the opposite order. Half of the Mask Group received the active drug treatment via mask followed immediately by placebo treatment via hood; the other half received the opposite order. Both groups received the active treatment. Each patient received 3 treatments delivered at intervals of 8 hours per hospitalization day until discharge. Additional inhalations of epinephrine in 3% saline were given via mask as needed. These treatments were recorded and calculated as add-on therapy. The investigators and medical personnel were blinded to the combination of the therapeutic package (active versus placebo) used, and there was no detectable difference in color, smell, or other physical properties of the solutions. The code was deposited with the statistician. The decision to discharge a baby was made during morning rounds by the attending physician, based on clinical grounds only. The attending physician was blinded to the combination of the therapeutic package.

Outcome Measures

Primary outcome was the change in clinical severity score (CS) (Table I; available online at www.jpeds.com), as described by Wang et al[10] after inhalations. This scoring system assigns a number from 0 to 3 to each variable, with increased severity receiving a higher score. Daily follow-up sessions were conducted by the investigator on enrollment and then each morning at treatment time and 30 minutes

after the beginning of each inhalation session. Comparisons of the difference between the pretreatment and posttreatment CS for each patient on days 1, 2, and 3 of treatment and comparing daily posttreatment values (ie, day 1 posttreatment value versus day 2 posttreatment value) determined the primary outcome.

Secondary outcome was parental assessment at the end of the study of tolerability. Parents graded their opinion of their child's tolerance to treatment, by using subjective response to a simple question after each study treatment: "In your opinion, which device was better tolerated by your child?"

In addition, number of hospitalization days, number of add-on treatments, pulse rate, and oxygen saturation on room air were also recorded and compared. Also, one investigator observed the babies' behavior regarding crying or fussing. Crying or fussing was considered positive when a baby cried or fussed more than half of the time while receiving treatment inhalation (using hood or mask).

Virology Studies

Antigen detection using a commercial immunochromatographic assay (ImmunoCard STAT! RSV; Meridian Diagnostics Europe, Catalog No. 750930) was used. The sensitivity of the test is 80% to 90%.[1]

Staistical Methods

Each variable was visually scanned for normalcy of distribution. Variables demonstrating a distribution significantly different from normal were tested by nonparametric methods. Continuous normally distributed variables were examined by using the paired or unpaired *t* test as appropriate. Noncontinuous variables were examined by using the χ^2 test. Mann-Whitney *U* test was also used to examine differences in nonnormally distributed variables measured by using hood versus mask. The mean ± SD value expresses the central tendency of the data. The mean ± SEM value was used in graphs. To examine the change in CS after inhalations, paired *t* tests were carried out in each treatment group separately for each day. For this analysis, a *P* value of <.006 for a 2-tailed *t* test was considered significant due to multiple comparisons. Otherwise, $P < .05$ was considered statistically significant.

Sample Size

Using a similar score, it was previously shown[11] that a difference of 2 points clearly differentiated patients who were admitted to the hospital from those who were sent home, making this difference clinically significant. Thus, with a total sample size of 45 subjects, the current study was designed to have 90% power to detect a true, by-treatment difference in CS of 2 ± 2 points using the *t* test for independent samples, assuming a 2-sided α of 0.05.

RESULTS

Forty-nine infants with viral bronchiolitis were enrolled in this study between December 2002 and March 2003. Mean age was 2.7 ± 2.2 (range, 1 to 7.5) months. Twenty-five received inhalations of 1.5 mL (1.5 mg) epinephrine in 4 mL of 3% saline (treatment drug) via hood (Hood Group) and 24 received inhalations of the same treatment drug via mask (Mask Group). The groups had similar clinical characteristics and variables at baseline (Table II). Using immunochromatographic assays, 43 of 49 (88%) infants were found to be RSV positive. The positive rate for RSV in the Hood Group was 88% (22/25) and in the Mask Group was 87% (21/24, *P* = NS).

Table II. Baseline clinical characteristics

	Hood group (n = 25)	Mask group (n = 24)	*P* value
Age (mo)	2.7 ± 2.2	2.8 ± 2.3	NS
Female/male	8/17	7/17	NS
Baseline clinical severity scores	7.12 ± 1.16	6.8 ± 1.21	NS
Days of illness at admission	5.7 ± 3.7	4.5 ± 3.4	NS ($P = .4$)
Baseline saturation (%)	93 ± 4.2	93 ± 3.7	NS

CS at baseline were 7.12 ± 1.16 in the Hood Group and 6.8 ± 1.25 in the Mask Group (*P* = NS). The decrease (improvement) in CS after the active drug treatment was significant in the Hood Group on the first (1.1 ± 0.86), second, and third days after admission (15%, 15.4%, and 16.4%, respectively, compared with pretreatment). In the Mask Group, significant improvement in CS after the active drug treatment was also observed on the first (1.2 ± 0.83), second, and third days after admission (17.5%, 17.1%, and 12.7%, respectively, $P < .001$) (Figure 2). However, the improvement in CS did not differ significantly between the two groups (*P* = NS).

With a total sample size of n = 49 subjects, the current study actually has 80% power to detect a true by-treatment group difference of 0.7 ± 0.8 in CS, assuming a 2-sided α of 0.05, using the *t* test for independent samples. (The post hoc power of these data to detect a clinically significant difference between the groups was >90%).

The mean duration of hospitalization (in days) was 3.2 ± 1.7 for the whole population, with no significant difference between the groups.

Thirty-nine of 49 (80%) of the parents responded that the hood was better tolerated than the mask; 18% (9/49) preferred the mask and 1/49 (2%) was indifferent for the two modalities used. Significantly more infants cried and/or fussed while being treated with the mask than with the hood; 71% (35/49) and 29% (14/49) of the babies in the Mask Group and in the Hood Group cried or fussed, respectively. No adverse effects were observed. Pulse rate, add-on inhalation therapy, and room air oxygen saturation did not differ between the two groups at any time.

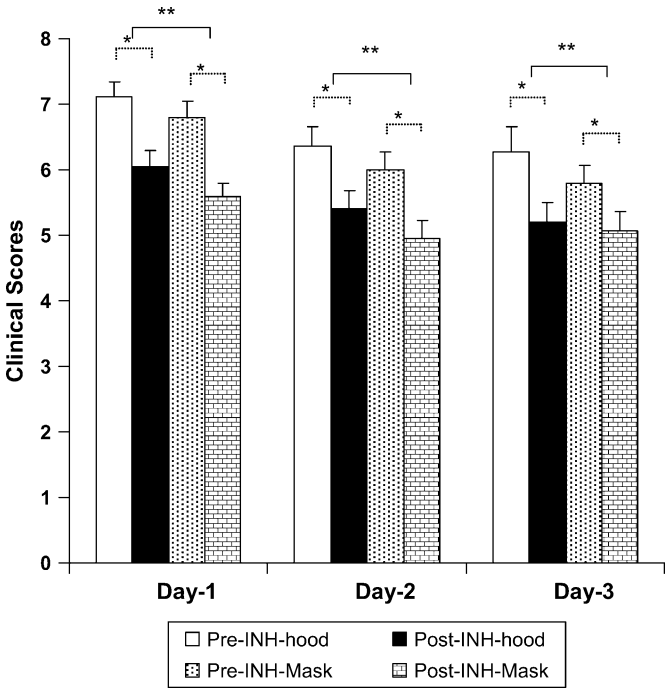

Figure 2. Clinical severity scores in hood and mask groups. Decrease in the clinical score after the inhalation therapy was significant (*P < .001) in both groups on the first, second, and third days after hospital admission. There was no significant difference between the two groups on any day (**P = NS). INH, inhalation.

DISCUSSION

The results of this double-blinded study indicate that when young, wheezy infants with bronchiolitis are treated with inhaled medications, the Baby Air device combined with the Aeroneb nebulizer is as effective and as safe as the conventional face mask with the same nebulizer. The Baby Air was easier to use, more tolerated by infants, and preferred by the parents, thus making it the superior option for delivering inhaled medications to these infants.

Difficulties in aerosol delivery may be a major cause of poor therapeutic response in RSV bronchiolitis. It has recently been shown that with the use of the conventional nebulizer and traditional face masks, only 1% to 2% of the nebulized aerosol will reach the lungs of infants with RSV bronchiolitis.[2] Most current devices used for delivering aerosol medications to infants require a tight fit on the infant's face,[12,13] and achieving a good mask-to-face seal may be difficult in many infants because of the squirming and crying.[4,14,15] Given the results of recent studies[7,16-18] it is time to dispel the myth that aerosol delivery to the lungs of crying children is enhanced as a result of a deep inspiratory breath. This is probably related to the fact that crying or screaming infants adopt abnormal breathing patterns such as a greatly prolonged expiration followed by short, high inspiratory flow velocity gasps leading to greater aerosol impaction in the throat.

There is clearly a need to develop more acceptable, patient-friendly interfaces for improving aerosol delivery to infants. Head canopies, or hoods, have long been used for delivery of oxygen and saline aerosols (eg, mist tents) in neonates and infants. In an attempt to minimize environmental contamination, Wahlin et al[19] used a hood to deliver aerosolized ribavirin to infants with RSV bronchiolitis. The Baby Air hood was developed to address the tolerability problem and has been shown to be a promising modality in infants.[7] The results of the present study confirm its clinical advantages for the first time. The greater preference demonstrated in this study may result in better compliance and therefore a better outcome for these infants. The Baby Air device is equipped with a replaceable transparent enclosure. It was easily cleaned and sterilized between patients. In contrast to the face mask, the transparent hood provides similarly efficient aerosol delivery without facial contact. Little cooperation from the infant is required, aerosol delivery is entirely passive, parents are relaxed, and the baby comfortably inhales the medication while tidal breathing, awake or asleep.

We chose to use normal saline as the placebo arm rather than 3% hypertonic, as we believe that 3% hypertonic saline is indeed an active drug in acute viral bronchiolitis. This is based on recent observations that inhaled epinephrine/hypertonic saline combination is significantly effective in bronchiolitis, whereas inhaled epinephrine/normal saline combination did not reach a statistically significant effect.[8] Moreover, hypertonic saline has recently proven to be an active drug even in normal volunteers increasing the volume of airway surface liquid and increasing rates of mucociliary clearance.[20]

The results of the current study further strengthen our previous finding that delivering of bronchodilators with hypertonic saline to infants with RSV bronchiolitis is an effective therapy modality.[8,9] Compared with our previous study in hospitalized infants,[8] the magnitude of effect was even greater (15% to 17% vs 7% to 10%, P < .05). Considering that the patient population and the medications used were similar, it appears that this greater degree of improvement in the current study probably resulted from the difference in delivery devices. The delivery devices consisted of the nebulizer and the patient interface (face mask or Baby Air). Because no difference was observed in the present study between the Baby Air and the face mask groups and both were better than the previous studies with face mask, it is reasonable to assume that it is the nebulizer that might have been more efficient. Indeed, the nebulizer we used in the previous study, Aeromist Nebulizer (Set 61400; B&F Medical by Allied; Toledo, OH), may have 1 to 2 mL residual drug volume at the completion of dose, whereas the nebulizer used in the current study, the Aeroneb, has approximately 0.1 mL residual (product label). This offers 20% to 40% more drug as aerosol to be inhaled. In addition, the Aeroneb is a new-generation electronic micro pump device that operates very quietly. This "silent" operation may be less disconcerting to the child, resulting in less agitation compared with jet nebulizers. A head-to-head study of Aeroneb versus Aeromist nebulizers would provide the best data regarding a comparison of their utility.

In conclusion, in infants hospitalized with viral bronchiolitis in whom aerosol treatment is considered, the use of the Baby Air hood is as effective as the use of a face mask. On

the basis of infant behavioral response and parent preferences, the tolerability of the Baby Air hood is significantly better than that of a mask in this infant population, which may improve compliance and therapeutic outcomes.

Mona Boaz, PhD, Bio-statisticians of the Edith Wolfson Medical Center, Holon, advised on statistics. Sylvia Walters of Sieff Hospital, Safed, assisted in reviewing the manuscript.

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