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ORIGINAL ARTICLE

Comparison of the Bronchodilative Effects of Salbutamol Delivered via Three Mesh Nebulizers in Children with Bronchial Asthma

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ABSTRACT

Background: We compared the bronchodilative effects of salbutamol delivered via 3 different mesh nebulizers, Aeroneb-go®(AE), Omron-NE-U22®(OM) and Pari-eMotion®(PA).

Methods: We enrolled 36 children with asthma who visited the Kurosaka Pediatrics and Allergy Clinic, randomly assigned to 3 groups for treatment with AE, OM or PA. The dose of salbutamol in the solution was 0.15 mg × body weight (kg) (minimum 2.5 mg, maximum 5 mg). FEV_1, PEFR and V_{50} were measured in these patients before treatment, and at 15 and 30 minutes after salbutamol inhalation using one of the 3 mesh nebulizers.

Results: All groups showed a significant improvement of FEV_1, PEFR and V_{50} at 30 minutes after salbutamol inhalation. The AE group did not show a significant improvement in PEFR at 15 minutes after inhalation, whereas a significant improvement in FEV_1 and V_{50} was evident at the same time point. The OM group showed no significant improvement in V_{50} at 15 minutes after inhalation, whereas this group clearly showed a significant improvement in PEFR and FEV_1 at the same time point.

Conclusions: Overall, all 3 mesh nebulizers were useful devices in treating bronchial asthma, although some differences in lung function improvement were evident. The limitation of this study is that subjects did not include patients with severe asthma attacks.

KEY WORDS

asthma therapy, lung function, mesh nebulizer, residual volume, salbutamol

INTRODUCTION

Inhalation therapy with nebulizers which can deliver drugs to the lungs directly and increase their therapeutic effects began in the 1950s.[1] Inhalation therapy with nebulizers is advantageous because the risk of adverse effects is lower than systemic drug administration, such as oral administration.[2] Inhalation therapy with steroids and bronchodilators has been increasing in importance, and now represents the mainstream of treatment for bronchial asthma in all age groups,[3] both for long-term control and relief of acute exacerbation.[4]

Jet nebulizers now occupy an important position in inhalation therapy, although the Global Initiative for Asthma (GINA) recommend a metered-dose inhaler (MDI) with a spacer as the first choice for children with bronchial asthma, and nebulizer therapy as the second choice.[4] However, it is well known that jet nebulizers are noisy and have a large residual nebulizer-solution volume (or dead volume) within the reservoir that cannot be nebulized.[5,6]

Recent developments in mesh nebulizers have improved their practical use. Compared with jet nebulizers, mesh nebulizers have several distinct merits: (1) consistent and high aerosol generation efficiency, (2) predominant delivery of a fine-particle aerosol capable of reaching the peripheral airways, (3) a low re-

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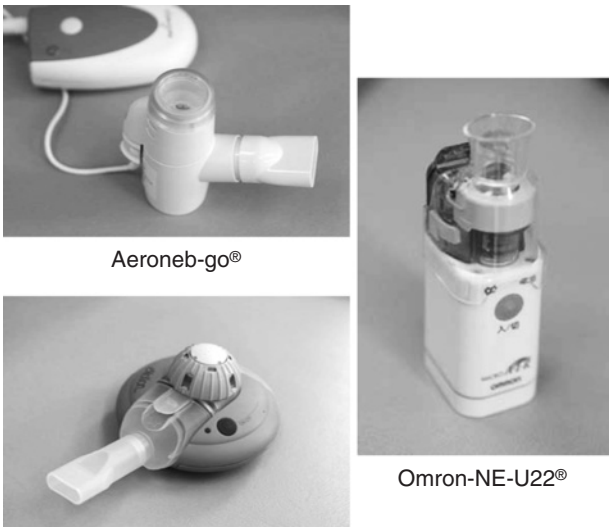

Fig. 1 The 3 mesh nebulizers.

sidual nebulizer-solution volume, and (4) the ability to nebulize even microliter volumes.[1]

However, the kinds of mesh nebulizers that are best suited for inhalation treatment of bronchial asthma are yet to be clarified. In this study, we compared the bronchodilator effects of salbutamol delivered via 3 different mesh nebulizers used in Japan.

METHODS

PATIENTS AND NEBULIZERS

A total of 36 children with asthma aged between 8 and 13 years with less than 70% of predicted forced expiratory volume in 1 second (FEV_1), who had not used any bronchodilators during the previous 12 hours, were studied. They visited the Kurosaka Pediatrics and Allergy Clinic because of their asthmatic attack. Patients with lung functions which could not be measured due to acute severe asthma were excluded. Predicted FEV_1 was expressed according to the formula reported by Nishima.[7] Written informed consent was obtained from all patients and/or their parents.

Three mesh nebulizers used in this study were as follows: Aeroneb-go®(AE) (Aerogen Ltd., Galway, Ireland), Omron-NE-U22®(OM) (Omron, Kyoto, Japan) and Pari-eMotion®(PA) (PARI Gmbh, Starnberg, Germany) (Fig. 1).

Patients were randomly assigned to 3 groups, according to treatment with either of AE, OM or PA. As shown in Table 1, there were no significant differences in age and FEV_1, peak expiratory flow rate (PEFR) and maximum expiratory flow rate at 50% of forced vital capacity (V_{50}) before treatment among the groups.

SALBUTAMOL DOSES

Salbutamol dose was determined as 0.03 ml (0.15 mg) × body weight (kg) (min. 0.5 ml [2.5 mg], max.1.0 ml [5 mg]) in accordance with the Expert Panel Report 3.[8] The mean salbutamol dose was 0.8 ml for the AE and OM groups, and 0.9 ml for the PA group. Nebulized salbutamol was administered via a mouthpiece.

Physiological saline was added so that the inhalation time was 5 minutes and total inhalation volumes for the AE, OM and PA were 2.3, 2.3 and 4.3 ml, respectively, following the recommendations of the British Thoracic Society Nebuliser Project Group.[9]

LUNG FUNCTION

Lung function parameters were measured with a spirometer, Auto Spiro AS-303 (Minato Medical Science, Osaka, Japan) which was calibrated each day using a 2-liter syringe (Minato Medical Science, Osaka, Japan). Subjects performed forced expiratory maneuvers and were verbally encouraged to continue to exhale at the end of expiration to obtain optimal effort. At least 3 maneuvers were required to obtain the most acceptable flow volume curve.[10] FEV_1, PEFR and V50 were measured based on the best curve before salbutamol inhalation and at 15 and 30 minutes after inhalation.

RESIDUAL NEBULIZER-SOLUTION VOLUME

Residual nebulizer-solution volume in the aerosolization head of the nebulizers was measured using an electronic balance (Shimadzu, Kyoto, Japan). The weight of the nebulizer head were compared before and after inhalation.

STATISTICAL ANALYSIS

Data were expressed as means and standard deviations. One-way ANOVA and Kruskal-Wallis test were used for comparisons between groups. Dunnett's test was applied for comparisons before and after inhalation. For repeated measures ANOVA was used to analyze groups and changes in lung function at 0, 15 and 30 minutes. Probability (p) values of less than 0.05 were considered to indicate statistically significant differences. Statistical analysis was performed with SPSS version 13 (SPSS, Tokyo, Japan).

RESULTS

LUNG FUNCTION CHANGES

All three groups, AE, OM and PA, showed significant improvement in FEV_1 at 15 and 30 minutes after salbutamol inhalation (Fig. 2, Table 2) in comparison with the baseline values. Although the order of the average rank of the degree of lung function change for the 3 mesh nebulizers were estimated (PA>OM> AE for FEV1 at 15 minutes, and PA>AE>OM for FEV 1 at 30 minutes), they did not show any significant changes on the Kruskal-Wallis test (Table 3).

Table 1 Demography of patient population

Patient	Aeroneb-go®	Omron-U-22	Pari-eMotion	*P*-value
n	12	12	12	
Boy/girl	7/5	8/3	8/4	ns†
Age (y)	9.0 (1.3)	9.9 (1.9)	9.9 (1.4)	ns†
Height (cm)	131.7 (10.1)	137.0 (16.8)	134.5 (9.2)	ns†
Body weight (kg)	28.4 (6.9)	34.5 (18.3)	30.8 (6.7)	ns†
%FEV_1	56.9 (9.2)	56.8 (8.8)	51.0 (11.6)	ns†
FEV_1 (L)	1.00 (0.28)	1.12 (0.49)	0.97 (0.32)	ns†
PEFR (L/s)	2.21 (0.64)	2.38 (0.99)	2.15 (0.68)	ns†
V_{50} (L/s)	1.00 (0.28)	1.12 (0.28)	0.97 (0.32)	ns†
Heart rate (bpm)	101 (15)	97 (16)	106 (20)	ns†
Dose (mL)‡, §	0.81 (0.16)	0.83 (0.13)	0.88 (0.14)	ns†

† Kruskal-Wallis test.

‡ One-way ANOVA.

§ Salbutamol dose.

Data are expressed as mean (standard deviation). ns, not significant.

Regarding PEFR, the OM and PA groups, showed significant improvement at 15 minutes after salbutamol inhalation compared with the baseline. However, the AE group did not show any significant improvement at the same time point. All 3 mesh nebulizers achieved a significant improvement in PEFR at 30 minutes after salbutamol inhalation compared with the baseline (Fig. 2, Table 2). Although the order of the average rank of the degree of lung function change for the 3 mesh nebulizers were estimated (OM>PA>AE for PEFR at 15 and 30 minutes), they did not indicate any significant differences on the Kruskal-Wallis test (Table 3).

With regard to V_{50}, the 2 groups, AE and PA, showed significant improvement at 15 minutes after salbutamol inhalation compared with the baseline. The OM group, however, did not show any significant improvement at the same time point but all 3 mesh nebulizers achieved a significant improvement in V_{50} at 30 minutes after salbutamol inhalation compared with the baseline (Fig. 2, Table 2). Although the order of the average rank of the degree of lung function change for the 3 mesh nebulizers were estimated (PA>AE>OM for V_{50} at 15 minutes, and PA> OM>AE for V_{50} at 30 minutes), they showed no significant differences on the Kruskal-Wallis test (Table 3).

HEART RATES

None of the patients complained of adverse reactions. However, the patients' heart rates significantly increased at 30 minutes after salbutamol inhalation (Fig. 3). The increase in heart rate may have been due to the beta 2-agonist effect of salbutamol, although this has not been used as an indicator of bronchodilative effects.[11] There was no significant difference in the patients' heart rates among cases using the 3 mesh nebulizers at 15 and 30 minutes after salbutamol inhalation.

RESIDUAL NEBULIZER-SOLUTION VOLUME

Mean residual nebulizer-solution volumes in the AE, OM and PA groups were 1.11 ± 0.17 (mean ± SD, n = 5), 0.17 ± 0.07 and 0.73 ± 0.08 grams, respectively. Residual nebulizer-solution volume in the OM was significantly less than in the other 2 nebulizers on the Kruskal-Wallis test, and that of the AE was the largest among the three (Fig. 4).

DISCUSSION

AEROSOL MASS MEDIAN AERODYNAMIC DIAMETER (MMAD)

This is the first reported study to have compared the bronchodilative effects of salbutamol delivered via 3 mesh nebulizers; the AE, OM and PA, in children with bronchial asthma. We demonstrated that all 3 nebulizers improved lung function in children with moderate exacerbations at 30 minutes after salbutamol inhalation.

Whether inhalation using a nebulizer brings about successful improvement in lung function depends mainly on the respirable particles.[8] Aerosol particles larger than 5 to 7 μm tend to halt in the upper airway, either at the internal ostium (located at the entrance to the nasal cavity) when inhaled through the nose, or in the oral cavity, oropharynx and larynx when inhaled through the mouth.[12-15] In general, the MMAD should be less than 5 μm to deliver aerosol particles generated by a nebulizer into the lung. Here, we discuss the bronchodilative effects of salbutamol delivered via 3 mesh nebulizers, from the viewpoint of MMAD.

Aeroneb-go®(AE)

The AE utilizes "Aeroneb Pro" technology. Ease of assembly, silent operation and simplified cleaning im-

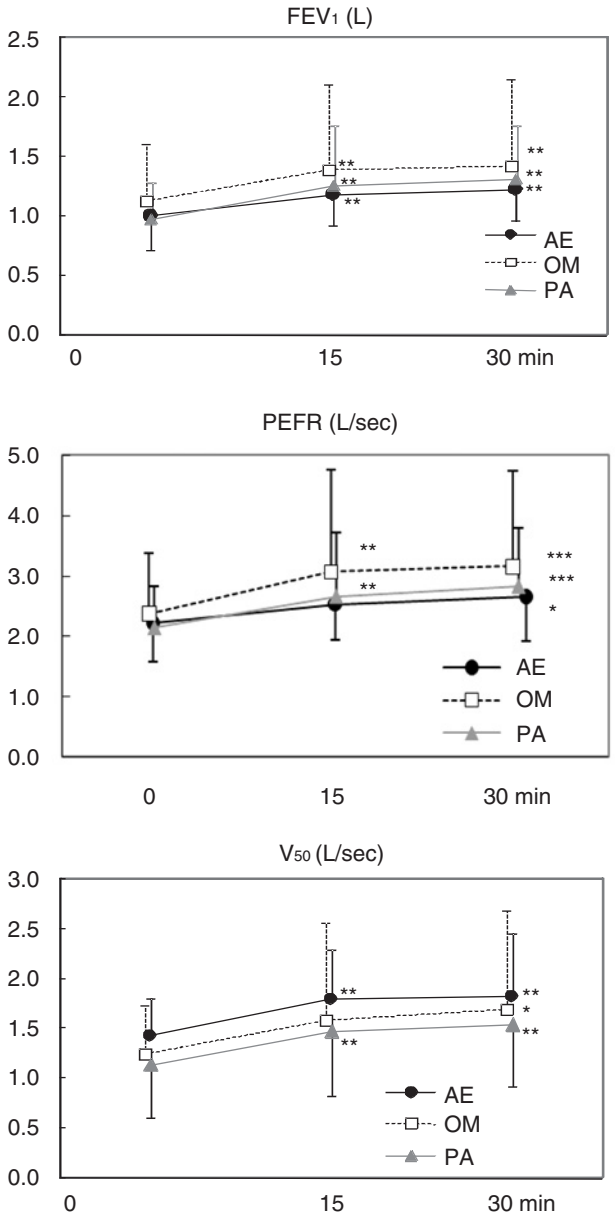

Fig. 2 Changes in lung function following salbutamol inhalation in patients with asthma exacerbattion. AE, Aeronebgo®; OM, Omron-NE-U22®; PA, Pari-eMotion®. *P < 0.05, **P < 0.005. Each point represents the mean and S.D.

proves the treatment regimen for patients and caregivers and can facilitate discrete therapy within a shorter duration for each treatment compared with conventional jet nebulizers.[1] The MMAD of aerosol particles with a budesonide suspension delivered by the AE is 3.1 ± 1.6 μm.[16]

In our study, the AE group did not show a significant improvement in PEFR at 15 minutes after salbutamol inhalation, while there was a significant improvement in FEV_1 and V at the same time point $_{50}$. Since PEFR represents large airway function,[17] the failure to improve PEFR implies that the aerosol particles generated by the AE were so small that they passed through the large airway. Another possible explanation is that the amount of salbutamol delivered via the AE was insufficient to improve PEFR at 15 minutes, because the AE had the largest residual nebulizer-solution volume among the 3 nebulizers, suggesting that a proportion of the solution cannot be nebulized effectively.

Omron-NE-U22®(OM)

The vibrating mesh of the OM consists of a metal alloy with approximately 6,000 holes.[1] Pulmonary bioavailability assessments of salbutamol nebulized by the OM using 99mTc gamma-scintigraphy have demonstrated a lung drug deposition approximately 2.8 times higher than that achieved with a jet nebulizer.[1] The MMAD of aerosol particles generated by the OM at room temperature or 4℃ for NaF and salbutamol is 4.3-4.5 μm.[18]

In the present study, the OM group did not show a significant improvement in V_{50} at 15 minutes after salbutamol inhalation, whereas significant improvements in PEFR and FEV_1 were evident at the same time point. The average residual volume of the OM was only 0.17 g, suggesting that sufficient volume can be inhaled with this nebulizer. Since V_{50} represents small airway function,[18] in children[19] as well as adults, the failure to improve V_{50} implies that the aerosol particles generated by the OM are large enough to be trapped in the large airway and cannot facilitate significant improvement in small airway function.

Pari-eMotion®(PA)

The PA is a small, silent and portable device. If the drug solution disappears, a sensor terminates delivery automatically. According to the manufacturer's specifications, MMADs of aerosolized particles of budesonide, salbutamol and disodium cromoglycate are 4.5, 4.3 and 4.3 μm, respectively. The PA, which is available only in Japan, is similar to the mesh nebulizer eFlow®, used widely in European countries.

In our study, PA showed the greatest improvement in the degree of change in FEV_1 (15 and 30 minutes) and V_{50} (15 and 30 minutes) among the 3 mesh nebulizers. Significant differences in FEV_1, PEFR and V_{50} for the PA after 15 minutes may indicate that both particle size and the amount of actually inhaled salbutamol are sufficiently effective.

SALBUTAMOL DOSES AND ABSORPTION IN THE BODY

Salbutamol dose (0.15 mg/kg) is widely accepted for nebulization in the USA[8] and the UK.[9] The dose was decided based on those described in Expert Panel Report 3 2007,[8] which were higher than those recommended in the Japan guidelines for child asthma.[19] In

Table 2 Comparison of lung function parameters before and after inhalation for each of the nebulizers by Dunnett's test

	Time	Aeroneb-go®			Omron-NE-U22®			Pari-eMotion®		
		P value	95% CI		*P* value	95% CI		*P* value	95% CI	
FEV_1	15min	0.005	0.054	0.301	0.003	0.093	0.429	0.000	0.153	0.428
	30min	0.001	0.096	0.343	0.001	0.134	0.469	0.000	0.199	0.474
PEFR	15min	0.076	-0.030	0.656	0.004	0.229	1.151	0.002	0.195	0.837
	30min	0.012	0.096	0.782	0.001	0.321	1.242	0.001	0.247	0.889
V_{50}	15min	0.005	0.117	0.641	0.112	-0.072	0.767	0.005	0.099	0.573
	30min	0.003	0.138	0.662	0.034	0.033	0.872	0.001	0.169	0.643

Table 3 Comparison of lung function among three kinds of mesh nebulizers using Kruskal-Wallis one-way analysis of variance of rank

Variance	*P*	Average rank			Rank order
		Aeroneb-go®	Omron-NE-U22®	Pari-eMotion®	
Change rate of FEV_1 (15-0 min)	0.368	16.5	17.00	22.00	PA>OM>AE†
(30-0 min)	0.406	16.92	16.75	21.83	PA>AE>OM
PEFR (15-0 min)	0.782	17.08	20.08	18.33	OM>PA>AE
(30-0 min)	0.448	16.42	21.58	17.50	OM>PA>AE
V_{50} (15-0 min)	0.837	18.83	17.08	19.58	PA>AE>OM
V_{50} (30-0 min)	0.577	15.92	19.50	20.08	PA>OM>AE

† AE, Aeroneb-go®; OM, Omron-NE-U22®; PA, Pari-eMotion®.

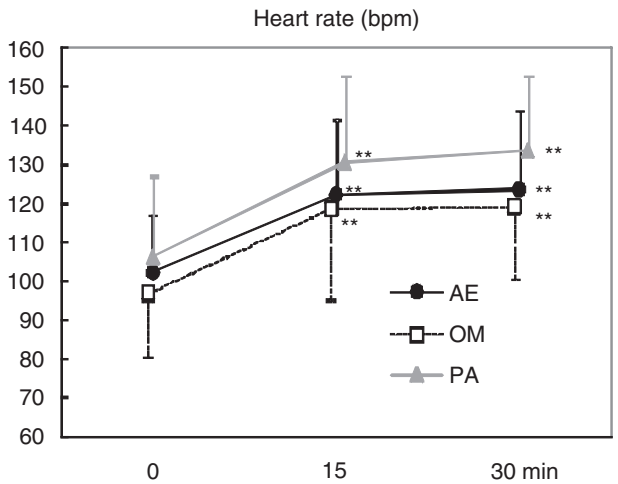

Fig. 3 Changes in heart rate by salbutamol inhalation in patients with asthma exacerbation. AE, Aeroneb-go®; OM, Omron-NE-U22®; PA, Pari-eMotion®. **P* < 0.05, ***P* < 0.005. Each point represents the mean and S.D.

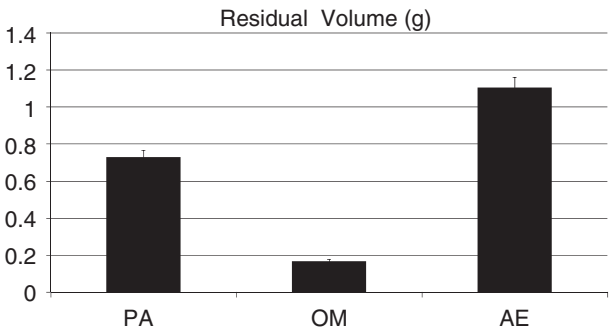

Fig. 4 Differences in residual nebulizer-solution volume after inhalation of OM among the 3 nebulizers by Kruskal-Wallis test (*P* = 0.002). AE, Aeroneb-go®; OM, Omron-NE-U22®, PA, Pari-eMotion®. Each bar represents the mean and S.D.

Japan, however, there have been no reported studies on the amounts of salbutamol administered via nebulizer inhalation. As patients with exacerbated asthma require immediate and full-dose treatments, there has been a need for discussion in Japan about the dose of salbutamol for this group of patients. The Expert Panel Report 3 (2007) described that salbutamol is an effective agonist and has few negative cardiovascular effects.[8] In the present study, no patients complained of palpitation or tremor.

The results at 15 minutes after inhalation might reflect the performance of nebulizers, although the results at 30 minutes are more useful for the management of asthma attacks. In the present study, all 3 of the AE, OM and PA groups showed a significant improvement of FEV_1, PEFR and V_{50} at 30 minutes after salbutamol inhalation. This can be explained partly by absorption of salbutamol through the gastro-intestinal system within 30 minutes after sabutamol inhalation.[12-14]

RESIDUAL NEBULIZER-SOLUTION VOLUME

The average residual volume for the AE was 1.11 g,

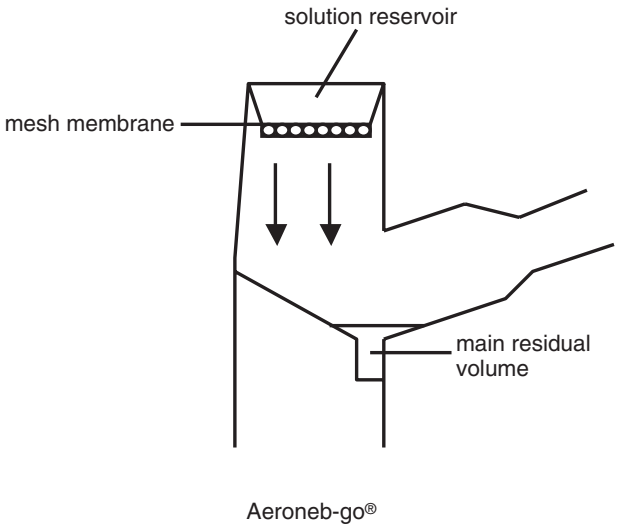

Fig. 5 Main residual volume site of AE. AE, Aeroneb-go®.

i.e., 48.3% of total volume. British nebulizer guidelines have suggested that nebulizers with residual volumes of more than 1.0 ml generally require full volumes of approximately 4 ml.[9] More viscous fluids require a longer nebulization time and are associated with increased residual amounts. Ultrasonic nebulizers are less effective for these more viscous fluids, and occasionally are unable to nebulize them.[20] The main residual volume of mesh nebulizers lies outside the mesh membrane and solution reservoir (Fig. 5), and thus does not affect viscosity. However, the possibility remains that an excessively large proportion of residual volume to total volume for the AE will influence the effectiveness of inhalation. Although the residual nebulizer-solution volume was significantly smaller in the OM than in the other 2 nebulizers, the OM did not yield the greatest improvement in FEV_1 and V_{50}. This may suggest that the aerosol from the OM cannot reach small airways effectively. A limitation of our study may be that our subjects did not include the patients with severe asthma. There is a possibility that different results might be gained in the cases of severe asthma patients whose lung functions cannot be measured.

CONCLUSIONS

In conclusion, the 3 mesh nebulizers we tested were shown to be clinically useful for the treatment of patients with bronchial asthma whose lung function could be measured, although there were some differences in the improvement of lung function among them. In our study, PA showed the greatest improvement in the degree of change of FEV_1 (15 and 30 minutes) and V_{50} (15 and 30 minutes) among the 3 mesh nebulizers. The failure of the AE to improve PEFR at 15 minutes after inhalation may be related to the small size of the aerosol particles or the large amount of residual nebulizer solution in the device. The failure of the OM to improve V_{50} at 15 minutes after inhalation may be related to the large size of the aerosol particles.

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