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Efficiency of a New Mesh-Type Nebulizer (NE-SM1 NEPLUS) for Intrapulmonary Delivery of Ipratropium Bromide in Surgical Patients

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Abstract: This study was aimed to evaluate the efficiency of a new mesh-type nebulizer for the intrapulmonary delivery of ipratropium bromide in surgical patients under mechanical ventilation. A total of 20 patients were randomly allocated to receive 0.5 mg ipratropium bromide using either a control (Pariboy SX, Pari, Co., Starnberg, Germany, n = 10) or test (NE-SM1 NEPLUS, KTMED INC., Seoul, Korea, n = 10) nebulizer during general anaesthesia. Ipratropium bromide was nebulized continuously for 20 min. in each group. Plasma concentrations of ipratropium bromide were obtained from blood samples at preset intervals. Non-compartmental analysis of ipratropium bromide was performed to compare the efficiency of pulmonary drug delivery in both nebulizers. Population pharmacokinetic analysis of ipratropium bromide was performed. Additionally, the noise level during the nebulizer operation and the aerosol particle size for each device were measured. The dose-normalized AUC_{last} was 0.10 min/L for both nebulizers. The pharmacokinetics of nebulized ipratropium bromide can be described best by a one-compartment model with first-order absorption. The apparent volume of distribution and metabolic clearance were 1340 L and 6.78 L/min, respectively. Type of nebulizer was a significant covariate for absorption rate constant. The equivalent sound level and median aerosol particle diameter were 35.0 dB and 4.52 μm for the test nebulizer, and 60.2 dB and 3.85 μm for the control nebulizer, respectively. From the standpoint of the dose-normalized AUC_{last}, a new vibrating mesh-type nebulizer shows similar performance in the intrapulmonary delivery of ipratropium bromide to that of a jet-type nebulizer in surgical patients.

Pulmonary drug delivery is an effective route for bronchodilator administration to manage obstructive lung diseases, including asthma and chronic obstructive pulmonary disease. Nebulizers have been used to deliver bronchodilators to the lung in various clinical situations [1]. Nebulizers can be classified into two major types according to their operating principle, jet- and ultrasonic-type nebulizers [2]. For aerosol generation, jet nebulizers function via the Bernoulli principle and use high-speed velocity compressed gas, whereas ultrasonic nebulizers use a piezoelectric crystal that vibrates at a high frequency [2]. A class of advanced ultrasonic nebulizers that used ultrasonic vibrating mesh technology were launched around 2005. In these nebulizers, a mesh with 1000–7000 laser-drilled holes vibrates at the top of the liquid reservoir, and this technology is more effective than those with a vibrating piezoelectric element at the bottom of the liquid reservoir [3]. It is known that the type of nebulizer is an important factor for determining the efficiency of pulmonary drug delivery during mechanical ventilation [4]. Recently, a vibrating mesh-type nebulizer (NE-SM1 NEPLUS, KTMED INC., Seoul, Korea) was commercialized and approved for the Korean market by the Korean Ministry of Food & Drug Safety. To the best of our knowledge, few clinical studies have assessed the efficiency of mesh-type nebulizers for pulmonary drug delivery using pharmacokinetic analysis.

Ipratropium bromide, an anticholinergic bronchodilator, inhibits vagally mediated reflexes by antagonizing the action of acetylcholine and shows similar efficacy to an inhaled β_2-agonist [5]. Thus, combinations of nebulized ipratropium bromide and a nebulized β_2-agonist produce a greater bronchodilation effect than β_2-agonist alone [6]. Furthermore, inhaled ipratropium bromide has been the treatment of choice in intra-operative bronchospasm for those showing poor response to β2-agonist, with intravenous aminophylline being not indicated in acute bronchospasm for lacking additional bronchodilation [6]. However, the pharmacokinetic characteristics of ipratropium bromide delivered to the lungs by nebulization have never been determined in surgical patients under mechanical ventilation.

This study was aimed to compare the efficiency of the intrapulmonary delivery of ipratropium bromide between vibrating

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mesh- and jet-type nebulizers using non-compartment analysis. In addition, pharmacokinetics of ipratropium bromide was characterized using nonlinear mixed effects modelling in surgical patients.

Materials and Methods

Pilot studies for the determination of ipratropium bromide dosage and duration of nebulization. The clinical dose of inhaled ipratropium bromide was 0.5 mg every 20 min. for 1 hr in patients who exhibited life-threatening bronchospasm or those with a poor initial response to a β_2-agonist [6]. In a preliminary study, 6 surgical patients were allocated an ipratropium bromide dose of 0.25 mg (n = 2), 0.5 mg (n = 2) or 1.0 mg (n = 2). Arterial samples of 5 mL each were collected before (0 min.) and at 5, 10, 20, 30, 40, 50, 60 and 90 min. after administration of ipratropium bromide using a test nebulizer. Concentrations of plasma ipratropium bromide over time and concentrations below the lower limit of quantification (LLOQ) were observed at selected sampling time-points. We confirmed that the administration of 0.5 mg (2 ml) ipratropium bromide produced an appropriate concentration above LLOQ without adverse reactions. Also, nebulizers no longer produced aerosol after 20 min. of nebulization.

Investigational devices. The control device used was a Pariboy SX (Pari Co., Starnberg, Germany), a jet-type nebulizer that is one of the most commonly used nebulizers in clinical settings in Korea. The test device was a NE-SM1 NEPLUS (KTMED Co., Seoul, Korea), which is an ultrasonic vibrating mesh-type nebulizer.

Study end-points. The primary end-point of this study was to compare the efficiency of the intrapulmonary delivery of ipratropium bromide between vibrating mesh- and jet-type nebulizers using non-compartmental analysis. The secondary end-point was to characterize pharmacokinetics of ipratropium bromide in surgical patients under mechanical ventilation. Additionally, the noise level during the nebulizer application and the aerosol particle size for each device were measured during.

Patient population. This study was approved by the Institutional Review Board of the Asan Medical Centre (Seoul, Korea), and written informed consent was obtained from all patients. A total of 20 ASA PS 1, 2 or 3 patients who were scheduled for elective stomach and colorectal surgery were enrolled and randomly allocated to receive ipratropium bromide using either a control or a test nebulizer during general anaesthesia.

Study procedure. All patients fasted from midnight. Once in the operating room, electrocardiography, pulse oximetry, the end-tidal carbon dioxide partial pressure, the non-invasive and/or invasive blood pressure (Datex-Ohmeda S/5, Planar Systems Inc., Beaverton, OR, USA), and the bispectral index (BIS, Aspect 2000, Aspect Medical Systems Inc., Newton, MA, USA) were measured in each patient. Data were continuously downloaded to personal computers using RS232C cables until the patient recovered from anaesthesia. Each patient was pre-oxygenated with 100% oxygen using a facemask. Anaesthesia was induced and maintained with target effect-site concentration-controlled infusion of propofol and remifentanil (Asan Pump version 2.1.3, Bionet Co., Seoul, Korea) [7,8]. Tracheal intubation was facilitated by administering 0.2 mg/kg cisatracurium. Patient lungs were then ventilated in a volume-controlled mode with oxygen in air (1:2), and the ventilation rate was adjusted to maintain the end-tidal carbon dioxide partial pressure between 35 and 45 mmHg. A 20-gauge catheter was placed in a radial artery for frequent blood sampling and continuous blood pressure monitoring. The target concentrations of propofol and remifentanil were adjusted to maintain BIS values that were < 60 and stable haemodynamics (SBP > 80 mmHg and HR > 45 beats/min), respectively. If necessary, ephedrine or atropine was administered to maintain a systolic blood pressure > 80 mmHg and heart rate > 45 beats/min during anaesthesia. After achieving stable haemodynamics and pseudo-steady-state anaesthetic drug concentrations, 0.5 mg ipratropium bromide was placed in the reservoir of each nebulizer and it was administered using a nebulizer. The T-connector of each nebulizer was designed specifically for surgical patients undergoing general anaesthesia and was used to make a connection with the anaesthetic breathing circuit (Fig. S1). After nebulization during 20 min., residual volumes in T-connector and reservoir in each nebulizer were measured using a micropipette. The ventilator settings after the administration of ipratropium bromide were changed to the following: V_T, 8 ml/kg; respiratory rate, 10 breaths/min; and inspiratory pause, 50%. These settings were maintained until 30 min. after discontinuation of ipratropium bromide. Neuromuscular blockade was reversed by administering neostigmine and glycopyrrolate at the end of surgery.

Blood sample acquisition and assays. For ipratropium bromide analysis, 5-ml arterial blood samples were obtained before (0 min.) and at 5, 10, 20, 25, 30, 40, 50, 60, 90, 150 and 240 min. after the administration of ipratropium bromide. Samples were collected in ethylene-diamine-tetra-acetic acid (EDTA) tubes and centrifuged for 10 min. at 252 × *g*. Plasma was stored at −70°C until use in assays. A LC-MS/MS assay was used for ipratropium bromide in plasma, and its detailed explanation for the assay is described in the supplementary material. The mean (S.D.) of the peak area ratios of LLOQ was 0.04 (0.003), and the coefficient of variation was 6.77. The linearity of the calibration curve, ranging from 3 to 200 pg/ml, was validated using three different calibration curves. Intraday measurements of precision were between 2.478% and 14.116%, while interday accuracies ranged from 96.298% to 99.553%.

Non-compartmental analysis of ipratropium bromide to compare the efficiency of pulmonary drug delivery in both nebulizers. Pharmacokinetic parameters were calculated using non-compartmental methods with WinNonlin 6.3 (Pharsight, St. Louis, MO, USA). The area under the curve from administration to the last measured concentration (AUC_{last}) was calculated by linear trapezoidal integration. The area under the curve from administration to infinity (AUC_{inf}) was calculated as $AUC_{last} + C_{last}/\lambda z$, in which C_{last} is the last measured concentration and λz is the apparent terminal rate constant estimated by unweighted linear regression for the linear portion of the terminal log concentration–time curve. The maximal concentration (C_{max}) and the time to reach C_{max} (t_{max}) after administration of ipratropium bromide with control or test nebulizers were determined based on the observed data. Summary statistics were determined for each parameter.

Population pharmacokinetic analysis. The procedures of NONMEM VII level 3 (ICON Development Solutions, Ellicott City, MD, USA) employed in pharmacokinetic modelling were the ADVAN 6 subroutine and first-order conditional estimation with interaction. The inter-individual random variability of each pharmacokinetic parameter was modelled using a log-normal or additive model, as appropriate. Diagonal matrices were estimated for the various distributions of η, where η represented inter-individual random variability with a mean of zero and a variance of ω^2. Additive, constant coefficient of variation, and combined additive and constant coefficient of variation residual error models were evaluated during the model building process. NONMEM was used to compute the minimum value of the objective function, a statistic equivalent to the −2 log likelihood of the model. An α level of 0.05, which corresponds to a reduction in the objective function value of 3.84 (chi-squared distribution, degree

of freedom = 1, $p < 0.05$), was used to discriminate between hierarchical models [9]. In addition to obtaining minimal objective function values, improvements in diagnostic goodness-of-fit plots were used to evaluate different models. R software (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria) was used to construct graphical model diagnostics. Covariate model building was performed using manual covariate selection.

One-, two- and three-compartment disposition models with first-order absorption and first-order elimination were tested. The covariates analysed were age, sex (0: male, 1: female), weight, height, body surface area [10], body mass index, lean body mass [11], type of nebulizer (0: test, 1: control), creatinine clearance [12], estimated glomerular filtration [13], forced vital capacity as a percentage of the predicted value (FVC%) and forced expiratory volume in 1 sec. as a percentage of the predicted value (FEV_1%). Nonparametric bootstrap analysis was used to internally validate models (fit4NM 3.7.9, Eun-Kyung Lee and Gyu-Jeong Noh, http://www.fit4nm.org/download, last accessed: Oct 17, 2011) [14]. Briefly, 2000 bootstrap replicates were generated by random sampling from the original data set, with replacement. Parameter estimates were compared with the median parameter values and the 2.5–97.5 percentiles of the nonparametric bootstrap replicates. Predictive checks were performed by simulating 2000 iterations and comparing the 90% prediction intervals to the original data (fit4NM 3.7.9) [15].

In vitro *studies for noise levels during nebulizer operation, particle size of aerosols and residual volume remaining in the reservoir of a nebulizer.* Noise levels during the operation of each nebulizer were measured in an audiometric examination room in Asan Medical Centre, in which the background noise was negligible (0 dB). After the operation using each nebulizer, the noise level was measured with an acoustimeter (Center 322 sound level meter, Center Technology, Taipei City, Taiwan) every 5 sec. for 5 min. Equivalent sound levels (L_{eq}) of the two nebulizers were calculated as follows:

$$L_{\mathrm{eq}} = 10 \log\left\{\frac{1}{60}\left(10^{0.1\times L_1} + 10^{0.1\times L_2} + \ldots + 10^{0.1\times L_{60}}\right)\right\} \quad (1)$$

The particle size of nebulized aerosols was measured directly using a laser diffraction method [16]. A sophisticated laser diffraction particle size analyzer (Spraytec; Malvern Instruments, Worcestershire, UK) was used to serially measure the size distribution of nebulized particles that passed through the laser detection fields at 1-sec. intervals for the duration of the nebulization [17]. With the receiver lens attached, droplets with diameters between 0.1 and 100 μm could be measured.

A total of 0.5 mg ipratropium bromide (2 ml) was placed in the reservoir of each nebulizer. Aerosol was generated for 20 min., and the residual volume was measured using a micropipette. This process was repeated five times for each nebulizer.

Statistics. Statistical analysis was conducted using R (version 3.1.1, R Foundation for Statistical Computing) or SigmaStat 3.5 for Windows (Systat Software Inc., Chicago, IL, USA). Data are expressed as means (S.D.) for normally distributed continuous variables, medians (25–75%) for non-normally distributed continuous variables, and counts and percentages for categorical variables. A p-value < 0.05 was considered to indicate a statistically significant difference.

Results

In total, 25 patients were screened, among which 5 patients were excluded because of the following reasons: 1, violation of inclusion criteria; 1, withdrawal of consent; 2, failure of acquiring blood sample; and 1, failure of measuring the concentration. Hence, 20 patients were included in the safety and pharmacokinetic analysis. Patient characteristics are summarized in table 1.

A total of 239 plasma concentration measurements were used to determine the pharmacokinetics. A plasma ipratropium bromide concentration at 25 min. after discontinuation of nebulization for one patient allocated to a control nebulizer was 600.2 pg/ml. The maximal plasma concentration in this patient was 401.6 pg/ml at 15 min. of nebulization, and the concentrations at 10 and 40 min. after discontinuation of nebulization were 244.8 and 206.4 pg/ml, respectively. This was therefore considered to be a measurement error and was excluded from the non-compartmental and population pharmacokinetic analysis. Plasma concentrations of ipratropium bromide over time are shown in fig. 1. Overall, the plasma concentrations in patients allocated to control nebulizers were higher than those who received a test nebulizer during the study period.

Table 2 lists the pharmacokinetic parameters for ipratropium bromide. Dose-normalized AUC_{last} (AUC_{last} / nebulized dose) and AUC_{inf} (AUC_{inf} / nebulized dose) did not show significant differences between both nebulizers.

The pharmacokinetics of ipratropium bromide in surgical patients could be described best using a one-compartment model with first-order absorption and first-order elimination. The type of nebulizer was a significant covariate for the absorption rate constant (equation 1), resulting in an improvement in OFV (12.52, $p < 0.001$, degree of freedom = 1), compared with the basic model (number of model parameters = 7).

$$k_{\mathrm{a}} = 0.237 \times (1 - \mathrm{NEB}) + 1.09 \times \mathrm{NEB} \quad (2)$$

in which NEB indicates the type of nebulizer (1, control; 0, test). table 3 shows the population pharmacokinetic parameter

Table 1.
Characteristics of the patients.

	Test nebulizer (n = 10)	Control nebulizer (n = 10)
ASA PS 1/2/3	0/9/1	0/10/0
Age, yr	58.5 ± 8.7	66.7 ± 8.6
Weight, kg	67.7 ± 8.5	59.9 ± 10.3
Height, cm	171.1 ± 5.3*	158.4 ± 10.6
FVC, %	82.3 ± 11.9	74.4 ± 15.7
FEV_1, %	65.7 ± 10.0	67.6 ± 10.6
Sex (M/F)	10/0*	5/5
NPO time, hr	12.5 (8.1–13.5)	9.1 (8.1–11.5)
Duration of anaesthesia, min.	145.0 (110.0–243.0)	126.5 (91.0–180.0)

Data are expressed as the mean (S.D.), median (25–75%) or count, as appropriate. Patient characteristics were compared using the two-tailed *t*-test, Mann–Whitney rank sum test or chi-square test, as appropriate. ASA PS, American Society of Anesthesiologists Physical Status; FVC, forced vital capacity as per cent of the predicted value; FEV_1, forced expiratory volume in 1 sec. as a percent of the predicted value. NPO, noting per oral.
*$p < 0.05$ *versus* the control nebulizer.

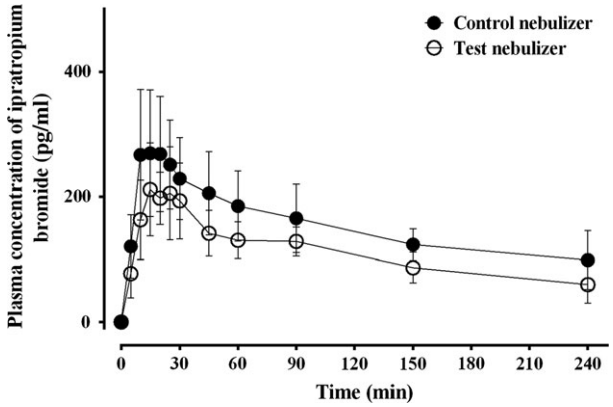

Fig. 1. Changes in the plasma concentration of ipratropium bromide over time. Data are expressed as means with error bars. Ipratropium bromide was nebulized with a control or test device for 20 min.

Table 2.
Non-compartmental pharmacokinetic parameters of the ipratropium bromide concentration in plasma.

	Test nebulizer (n = 10)	Control nebulizer (n = 10)
C_{max}, pg/ml	263.9 ± 63.5*	313.4 ± 103.0
t_{max}, min.	21.3 ± 6.9	15.0 ± 4.5
AUC_{last}, min. ng/ml	263.4 ± 5.3*	378.3 ± 9.8
AUC_{inf}, min. ng/ml	354.0 (295.9–439.7)*	616.2 (527.4–903.3)
λ_z, 1/min.	0.006 ± 0.002	0.004 ± 0.002
Residual volume in T-connector, ml	0.93 ± 0.2*	–[1]
Residual volume in reservoir, ml	–[1]	0.51 ± 0.09
Dose-normalized AUC_{last}, min/L	0.10 ± 0.04	0.10 ± 0.03
Dose-normalized AUC_{inf}, min/L	0.14 (0.10–0.18)	0.17 (0.15–0.22)

Data are expressed as means (S.D.) or medians (25–75%), as appropriate. Variables were compared using the two-tailed *t*-test or Mann–Whitney rank sum test, as appropriate. C_{max}, maximal concentration; t_{max}, time at maximal concentration; AUC_{last}, area under the curve from administration to the last measured concentration; AUC_{inf}, area under the curve from administration to infinity; λ_z, terminal elimination rate constant.
[1]Negligible residual volume in the reservoir or T-connector of each nebulizer.
*$p < 0.05$ *versus* control nebulizer.

estimates and the results of the nonparametric bootstrap replicates of the final pharmacokinetic model for ipratropium bromide. Overall, the bootstrap medians were close to the population parameter estimates and the 95% confidence intervals of these parameters were relatively small, indicating that the parameter estimates of the final pharmacokinetic model were both accurate and precise. Predictive checks of the final pharmacokinetic model are shown in fig. 2. The percentage of data distributed outside of the 90% prediction intervals of the predictive check was 12.3%.

L_{eq} of test and control nebulizers were 35.0 and 60.2 dB, respectively, indicating that the noise of a control nebulizer was ~1000 times higher than that of a test nebulizer. Distribution of aerosol ipratropium bromide particle sizes is shown in fig. 3. The median diameter of nebulized particles was 4.52 μm for test nebulizers and 3.85 μm for control nebulizers, respectively. A summary of the residual volume of ipratropium bromide remaining in the reservoir of each nebulizer after 10 min. of nebulization is shown in table 4. Approximately 33% of the total volume remained within the reservoir of control nebulizers, whereas the residual volumes in the test nebulizers were negligible.

When nebulization of ipratropium bromide was performed with a control nebulizer, the monitoring of respiratory parameters was mitigated, including tidal volume at expiration period and end-tidal carbon dioxide (CO_2) partial pressure. End-tidal CO_2 levels immediately decreased, and the downslope of the

Table 3.
Population pharmacokinetic parameter estimates, inter-individual variability and median parameter values (2.5–97.5%) of the non-parametric bootstrap replicates of the final pharmacokinetic model for ipratropium bromide.

Model	Parameters	Estimates (RSE, %)	CV (%)	Median (2.5–97.5%)
Basic	*CL/F*, L/min	6.82 (9.6)	40.5	–
	V/F, L	1360 (7.9)	34.2	–
	k_a, 1/min	0.526 (20.2)	108.2	–
	σ^2	0.19 (6.4)	–	–
Final	*CL/F*, L/min	6.78 (10.7)	40.6	6.73 (5.62–8.13)
	V/F, L	1340 (7.8)	34.8	1350 (1190–1580)
	k_a, 1/min			
	θ_1	0.25 (28.1)	71.6	0.245 (0.171–0.387)
	θ_2	1.17 (44.2)		1.28 (0.574–56.1)
	σ^2	0.19 (6.5)	–	0.19 (0.17–0.22)

A log-normal distribution of inter-individual random variability was assumed. Residual random variability was modelled using a constant coefficient of variation (CV) model. Nonparametric bootstrap analysis was repeated 2000 times. *Cl/F*, apparent metabolic clearance; *V/F*, apparent volume of distribution; k_a, absorption rate constant $\theta_1 \times (1 - \text{NEB}) + \theta_2 \times \text{NEB}$; NEB, type of nebulizer (1, control; 0, test); σ^2, variance of residual random variability; RSE, relative standard error = SE/mean × 100 (%).

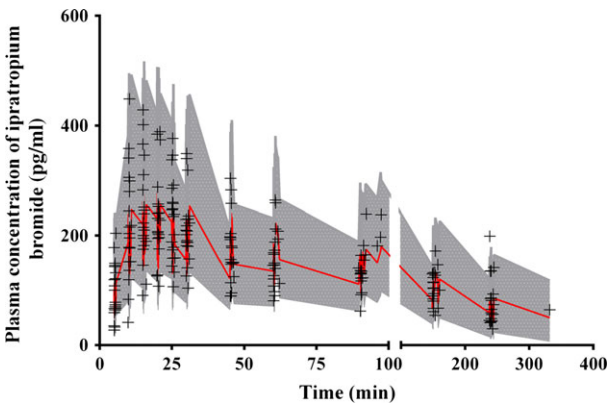

Fig. 2. Predictive checks of the final pharmacokinetic model for ipratropium bromide. +, observed plasma concentrations of ipratropium bromide. Red solid line and shaded areas indicate the 50% prediction line and 90% prediction intervals, respectively.

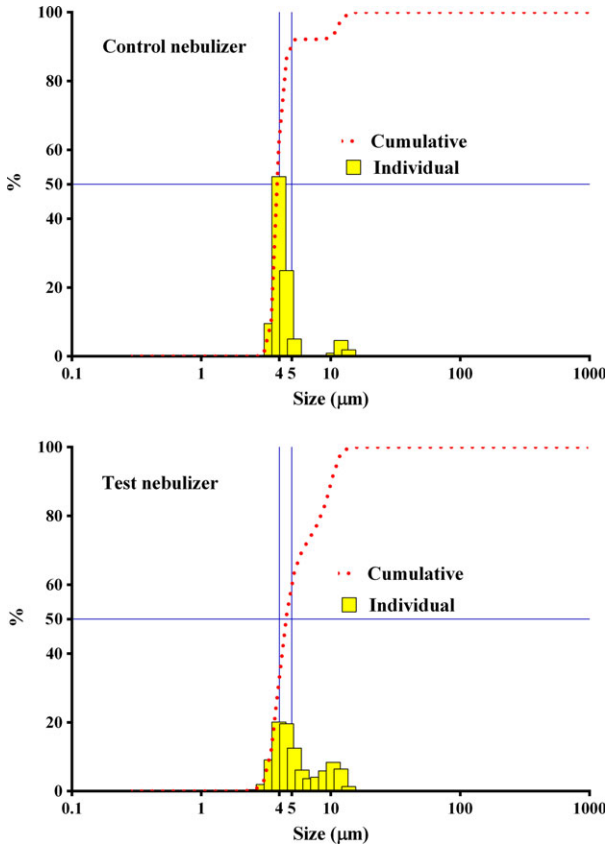

Fig. 3. Distribution of aerosol ipratropium bromide particle sizes for control (upper) and test (lower) nebulizers.

capnogram was observed at the alveolar plateau phase. Additionally, minute ventilation and tidal volume at the expiratory period were increased. However, these phenomena were not observed at nebulization with a test nebulizer. Representative screen images of a patient monitor displaying haemodynamic and respiratory parameters before and after operation using a control nebulizer in a patient are shown in supplementary material, Fig. S2. Leakage or obstruction of the anaesthetic breathing circuit during nebulization with control or test nebulizers was not observed in any patient.

Discussion

Generally, it is known that the efficiency of pulmonary drug delivery using a vibrating mesh nebulizer is better than the jet nebulizer; differences between these two versions include how the aerosol is generated and how much residual drug volume remains in the nebulizer [4,18,19]. Vibrating mesh technology has solved the drawback of jet nebulizers, which had generated excess liquid waste. In our present study, about 25% of the total volume of ipratropium bromide remained in the reservoir of the jet nebulizer, whereas no residual volume remained in the reservoir of the mesh nebulizer. However, about 46% of the total volume remained within the T-connector of the mesh nebulizer, and residual volumes within the T-connector of the jet nebulizer were negligible. These phenomena might be explained by differences in the operating principles that lead to aerosol generation between the nebulizer types. The jet nebulizer is connected by a tubing line to a compressor that causes compressed air to be delivered at high velocity through a liquid to turn it into an aerosol. This compression effect could contribute to efficient delivery of aerosol to an anaesthetic breathing circuit through the T-connector. However, aerosol generated by the vibration of mesh might be more likely to remain within the T-connector of a mesh nebulizer. For this reason, the residual volume of the mesh nebulizer was larger than that of the jet nebulizer, which indicates that the dose delivered to the lung using a mesh nebulizer was significantly smaller than that delivered by a jet nebulizer.

Table 4.
Residual volume of ipratropium bromide remaining in each nebulizer reservoir after 20 min. of nebulization

	Test nebulizer (n = 10)	Control nebulizer (n = 10)
Residual volume, ml	<0.01*	0.67 ± 0.03
Waste time[1], min.	7.17 ± 0.04*	10 ± 0
Infusion rate of nebulization[2], ml/min.	0.275 ± 0.002*	0.133 ± 0.003

Data are expressed as means (S.D.). Variables were compared using the two-tailed *t*-test.
[1]Waste time was determined from the start of nebulization to the end of aerosol generation.
[2]Infusion rate was calculated as follows: Infusion rate = $\frac{(2-\text{residual volume})}{\text{Waste time}}$
*$p < 0.05$ *versus* the control nebulizer.

Population pharmacokinetics of inhaled agents has been modelled using one- or two-compartment absorption models [20,21]. In our current study, the one-compartment absorption model showed a lower Akaike information criterion than the two-compartment model and robustly described the time course of ipratropium bromide concentrations graphically. Specifically, the k_a of jet nebulizers was approximately 5 times greater than that of the mesh nebulizer, which might be caused by differences in the operating principles depending on the nebulizer types. Inclusion of the lag time did not improve the objective function values of the final pharmacokinetic model.

It is difficult to make any conclusive statements about performance comparisons between nebulizers [3], because there are many confounding factors that can affect nebulizer performance, such as environmental context (the hospital and the availability of trained respiratory therapists to deliver a drug) and patient-related factors (breathing mode, pattern, severity of illness and age) [22–25]. Comparisons of dose-normalized AUC can be used as an objective method to compare performance between nebulizers.

It is important to monitor changes in the shape and level of the expiratory CO_2 waveform in intubated surgical patients under mechanical ventilation. The slope of the CO_2 waveform during the expiratory phase increased in the mechanically ventilated patients with chronic obstructive pulmonary disease. Additionally, a sudden reduction in end-tidal CO_2 level can be a sign of pulmonary embolism, although it is not specific

[26]. Aerosols delivered at a high velocity influenced the aspiration of CO_2 samples, which produced changes in CO_2 shape and levels caused by operation of the jet nebulizer. However, arterial oxygen and carbon dioxide saturation measured from arterial blood gas analysis showed constant values before and during nebulization with a jet nebulizer. This inconvenience of CO_2 monitoring might be a major factor leading a clinician to avoid the use of a jet nebulizer in surgical patients undergoing general anaesthesia. In a previous case report, intra-operative albuterol nebulization caused breathing circuit obstruction induced by the blockage of an expiratory filter [27]. In this present study, obstruction of an expiratory filter was not observed in any patient. Additionally, commercially available jet nebulizers produce more noise during nebulization, which might be a factor leading a clinician to hesitate about using a jet nebulizer in an operating room.

There were some issues to be considered as limitations of this study. Firstly, sample size of the study was relatively small, which could lead to drawing improper conclusion. However, non-compartmental analysis was used to compare the efficiency of two nebulizers in the study. This method is commonly used to compare pharmacokinetic characteristics of two drugs in bioequivalence studies. The number of patients enrolled in the study was comparable to other previous bioequivalence studies [28–30]. Secondly, the difference in anaesthetic techniques could have had an influence on the amount of ipratropium bromide delivered to patients. If inhalational anaesthetics were used for the maintenance of anaesthesia, the agents may have been diluted and lesser amount would have been delivered to the patients. However, anaesthetic methods could not have affected the results because the primary end-point of this study was to compare the efficiency of these two nebulizers.

In conclusion, from the standpoint of the dose-normalized AUC_{last}, a new vibrating mesh-type nebulizer, NE-SM1 NEPLUS, shows a comparable performance for pulmonary drug delivery as the jet-type nebulizer in surgical patients under mechanical ventilation. The pharmacokinetics of nebulized ipratropium bromide is best described by a one-compartment model with first-order absorption.

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Disclosure of Competing Interests

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Test (left panel) and control nebulizers (right panel) connected with anaesthetic breathing circuit using T-connector designed specifically.

Figure S2. Screen images of a patient monitor displaying hemodynamic and respiratory parameters before (left) and after (right) operation using a control nebulizer in a patient.