The Efficiency and Safety of a New Mesh Type Nebulizer (NE-SM1 NEPLUS) for Intrapulmonary Delivery of Ipratropium Bromide in Surgical Patients under Mechanical Ventilation

1. Introduction

Pulmonary drug delivery is an effective route of bronchodilator administration to manage obstructive lung diseases including asthma and chronic obstructive pulmonary disease. Recently, a vibrating mesh type nebulizer (NE-SM1 NEPLUS, KTMED INC., Seoul, Korea) was commercialized and got approval of CE Mark(SGS, England) for worldwide market. To our knowledge, few clinical studies have assessed the efficiency of mesh type nebulizers for pulmonary drug delivery using pharmacokinetic analysis. This study aimed to compare the efficiency and safety for intrapulmonary delivery of ipratropium bromide using vibrating mesh and jet type nebulizers in surgical patients under mechanical ventilation.

2. Methods

2.1. Investigational devices

2.1.1. Control device : P* SX (P* Co. Ltd), which is a jet type nebulizer.

2.1.2. Test device : NE-SM1 NEPLUS (KTMED Inc., Seoul, Korea), which is a vibrating mesh type nebulizer.

2.2. Study design

This study was designed as a randomized, active-controlled, parallel, clinical trial.

2.3. Patient population

The study was approved by the Institutional Review Board of the Asan Medical Centre(Seoul, Korea) and written informed consent was obtained from all patients.

2.4. Study endpoints

2.4.1. Primary endpoints _ Dose normalized AUC

2.4.2. Additional endpoints _ Noise during the operation of each nebulizer

_ Particle size of aerosol inhaled by each nebulizer

2.5. Study procedures

All patients fasted from midnight. A 20-gauge catheter was placed in a radial artery for frequent blood sampling and continuous blood pressure monitoring. Ipratropium bromide of 0.5 mg was placed in the reservoir of each nebulizer. T-connector of each nebulizer designed specifically for surgical patients undergoing general anesthesia were used to connect with anesthetic breathing circuit.

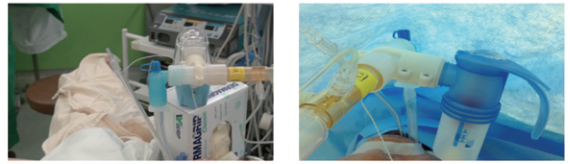

Fig. 1. Test (left panel) and control nebulizers (right panel) connected with anesthetic breathing cir cuit using T-connector designed specifically.

2.6. Determination of ipratropium bromide dosage

Clinical dose of inhaled ipratropium bromide is 0.5 mg every 20 min for 1 hour in patients showing life-threatening bronchospasm or those with a poor initial response to β2-agonist.

2.7. Blood sample acquisition and Assay

For ipratropium bromide analysis, arterial blood samples of 8 mL each were obtained at before (0 min) and at 5, 10, 20, 30, 40, 50, 60, 90, 150 and 240 min after administration of ipratropium bromide min.

2.8. Non-compartmental analysis of ipratropium bromide

Pharmacokinetic parameters were calculated by non-compartmental methods using WinNonlin 6.3 (Pharsight, a Certara Company, St. Louis, MO). The area under the curve from administration to the last measured concentration (AUC_{last}) was calculated by linear trapezoidal integration. Summary statistics were determined for each parameter.

2.9. Noise level during the operation of nebulizers

Noise level during operation of each nebulizer was measured at an audiometric examination room in Asan Medical Center, where background noise was negligible (0 dB).

2.10. Particle size of aerosol

Particle size of nebulized aerosols was measured directly using laser diffraction method.

2.11. Residual volume remained in the reservoir of a nebulizer

Ipratropium bromide of 0.5 mg (2 ml) was placed in the reservoir of each nebulizer. Aerosol was generated for 10 min, and residual volume measured using a micropipette.

2.12. Statistics

Statistical analysis was conducted using R (version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat 3.5 for Windows (Systat Software, Inc., Chicago, IL).

3. Results

In total, 25 patients were screened, and of these, 5 patients were excluded (violation of inclusion criteria: 1, withdrawal of consent: 1, failure of acquiring blood sampling: 2, failure of measuring concentration: 1). Hence, 20 patients were included in the safety and pharmacokinetic analysis.

Table 1. Patient characteristics for safety and pharmacokinetic analysis

	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
FVC, %	82.3 ± 11.9	74.4 ± 15.7
FEV1, %	65.7 ± 10.0	67.6 ± 10.6

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3.1. Non-compartmental analysis of ipratropium bromide

A total of 239 plasma concentration measurements were used to determine the pharmacokinetics. Table 2 shows the pharmacokinetic parameters of 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. Plasma concentrations of ipratropium bromide over time are shown in Fig. 2.

Table 2. Noncompartmental pharmacokinetic parameters of the plasma concentration of ipratropium bromide

	Test nebulizer (n=10)	Control nebulizer (n=10)
Dose-normalized AUC_{last}, min/L	0.11 ± 0.04	0.11 ± 0.03
Dose-normalized AUC_{inf}, min/L	0.14 (0.10–0.15)	0.17 (0.16–0.25)

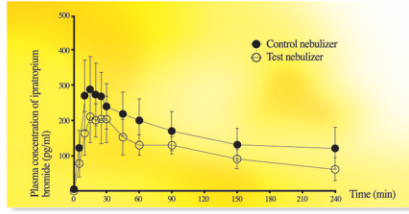

Fig. 2. Plasma concentration of ipratropium bromide over time. Data are expressed as mean and error bar. Ipratropium bromide was nebulized with a control or test device for 20 min.

3.2. Noise level during the operation of nebulizers

Leq of test and control nebulizers were 35.0 and 60.2 dB, respectively, indicating noise of a control nebulizer was approximately 1,000 times higher than that of a test nebulizer.

3.3. Particle size of ipratropium bromide

The median diameter of particle nebulized was 4.52 μm for test nebulizer and 3.85 μm for control nebulizer, respectively.

3.4. Residual volume remained in the reservoir of a nebulizer

The summary of residual volume of ipratropium bromide remaining in the each nebulizer reservoir after 10 min of nebulization was presented in Table 3.

Table 3. Residual volume of ipratropium bromide remaining in the each nebulizer reservoir after 10 min of nebulization

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

4. Discussion

Vibrating mesh technology has solved the drawback of jet nebulizer which had too much liquid waste. In this study, about 25% of total volume of ipratropium bromide was remained in the reservoir of jet nebulizer, whereas no residual volume in the reservoir of mesh nebulizer.

5. Conclusion

A new vibrating mesh type nebulizer, NE-SM1 NEPLUS, showed similar performance of pulmonary drug delivery as the jet type nebulizer in surgical patients under mechanical ventilation. There was no leakage or obstruction of anesthetic breathing circuit during nebulization. The mesh nebulizer did not impede accurate expiratory CO2 monitoring and operated quietly.