Research on Safe Nebulizer Inhalation Therapy Using Clean Booth during COVID-19 Pandemic

Yuka Uchida[1], Haruhiko Ogawa[1], Isao Ninomiya [2], Masato Mizuno[2], Bao Li[3], Yoshio Otani[4]
[1]Kanazawa Kasuga Clinic Kanazawa, Japan, y-uchida@jintikai.com, h-ogawa@jintikai.com
[2]Particles Plus, Ltd., Japan, Tokyo, Japan, isao.ninomiya@particlesplus.com, masato.mizuno@particlesplus.com
[3]Nippon Muki Co., Ltd., Yuki, Japan, l.bao@nipponmuki.co.jp
[4]JSPS Bangkok office, Bangkok, Thailand, yotani@jsps-th.org

Abstract

Nebulizer inhalation therapy for acute allergic bronchial diseases is not recommended during COVID-19 pandemic. However, it is an important treatment not only for asthma exacerbations, but also in otolaryngology and pediatrics in a variety of settings. In order to administrate safe nebulizer inhalation therapy, a clean booth equipped with Push & Pull fan filter units with HEPA filter was constructed, and the change in particle concentration in clean booth with different operating conditions of fan filter unit was measured with optical particle counters (OPC). It was found that all particles in the size ranges measured by OPC were purged from the clean booth within 180 s by continuous operation of FFU without the nebulization of droplets. A clean booth would be useful in providing a safe and convenient inhalation therapy environment but cautions are required to take into account the differences in dynamic and evaporation behavior of nebulized droplets.

1. Introduction

Nebulizer inhalation therapy is useful for symptomatic relief in the acute phase of allergic airway diseases such as bronchial asthma and atopic cough, as well as for improving airway clearance in patients with difficulty in sputum evacuation such as sino-bronchial syndrome. It is also one of the main therapeutic strategies for the direct treatment of cough-related laryngeal sensations, and the combination (cocktail) of precise inhalation agents is important as a tailor-made treatment method.

2. Background

Since COVID-19 is infectious even two days before the onset of symptoms and the droplets from coughing also pose a risk of infection, nebulizer therapy has become known as a treatment that is not recommended during the corona disaster. However, because nebulizer therapy is important not only for bronchial asthma attacks but also for various acute treatments in otolaryngology and pediatrics, environmental facilities that enable safe implementation of nebulizer therapy are demanded.[1)]

3. Research overview

We hypothesized that “Viruses cannot be airborne in a space without aerosols” in order to establish a safe method of nebulizer inhalation therapy by constructing a clean booth isolated from the surrounding air with minimum particle leakage. We measured the particle concentration evolutions in the clean booth after the nebulization with various operation conditions of FFUs. Moreover, we also studied the influences of nebulized drugs (Venetlin® and Mucofilin®) on the evolution of particle concentration in the clean booth.

4. Installation of clean booth

Nippon Muki Co., Ltd. constructed 1 m×1 m×1.8 m clean booth equipped with Push & Pull fan filter units with HEPA filter (FFU) for research and treatment of patients.

Fig.1 Nebulizer and OPC setting in clean booth.

Fig.2 Optical particle counter
(Model 8306, Particles Plus, Ltd.)

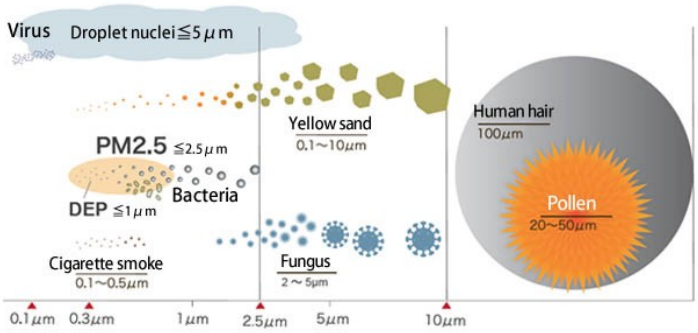

Fig.3 Typical particle size ranges of common aerosols.

The clean booth can keep the background particle concentration in clean booth to be zero when there are no subjects inside without nebulization of drug. Figure 1 shows a clean booth. Air enters on the booth ceiling through Push FFU and leaves through Pull FFU on the side of clean booth.
A negative pressure inside the booth is created by keeping Pull FFU airflow rate higher than Push FFU. We placed OPC inlet and nebulization air outlet at the same level of patient mouth. In the clean booth, we placed a nebulizer, a luggage storage, a chair, a camera tripod and an OPC. We did not place anything else that may affect the airflow inside.

5. Measuring instrument

Optical Particle Counter (OPC) is an instrument that can measure particle size distribution and particle number concentration in real time. Conventional OPC is used mostly for cleanliness measurement of clean rooms, namely for low concentration particles. OPC (Particles Plus Model 8306) which we used in this study is capable of measuring relatively high concentration of aerosols even atmospheric particles (Figure 2).

6. Particle size of interest

Figure 3 shows typical particle size ranges of common aerosols, the causes of allergy, the causative agent of infection and microorganisms. Corona viruses may exist in air as virus cluster droplets and nuclei under 5 μm, and therefore we set the OPC thresholds: 0.3 μm, 0.5 μm, 0.9 μm, 2 μm, 2.5 μm, 3 μm of 6 particle size ranges.[2)3)]

7. Method and Result

7.1 Purging of clean booth without nebulization

After measuring the particle concentration for 60 s in unattended clean booth, we measured the decrease in particle concentration during 300 s operation of FFU and then the increase after stopping the FFU with the clean booth door open. Figure 4 shows that FFU can purge all the particles in the clean booth in about 180 s. It seems there is no difference in purging rate by the particles size.

7.2 Purging of clean booth with nebulization

Based on the purging experiment of clean booth without nebulization, we focused

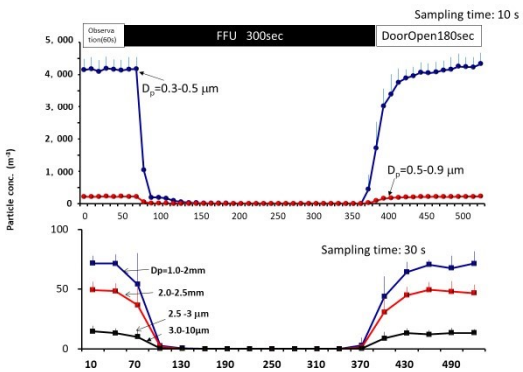

Fig.4 Purging performance of clean booth

on 0.3-0.5 μm particles and evaluated the change in particle concentration in clean booth with nebulization under various operating conditions of FFU (divided into the following three groups):

Group A : FFU continuous operation

Group B : FFU is stopped at the end of nebulization

Group C : No operation of FFU from the beginning of nebulization

After 120 s FFU operation, we started Venetlin® nebulization (about 0.4 ml/min) using Omron compressor nebulization inhalation equipment (NE-C28 Household use standard Model).

Figure 5 shows the concentration change of 0.3-0.5 μm particles when Venetlin® was nebulized under different operation conditions of FFU. We see in Fig.5 that the particle concentration decreases in both group A (FFU continuous operation) and group B (FFU is operated during nebulization and stopped at the end of nebulization), whereas in group C (no operation of FFU from the beginning of nebulization), the particle concentration increases after nebulization to a constant concentration and then decreases gradually after stopping the nebulizer. We may confirm the data reproducibility because there is no difference in particle concentration between A and B groups during the nebulization. However, comparing the data after the nebulization with and without the operation of FFU, there is no clear difference in particle concentration between A and B groups. This implies that the FFU is not effectively working for purging 0.3-0.5 μm particles. This kind of data were obtained only when the nebulizer was operated, although the purging performance of clean booth was confirmed in Fig.4. Figure 6 shows the concentration change of 0.5-0.9 μm particles, the data of which were obtained with those of Fig.5 simultaneously. We can see a clear difference in 0.5-0.9 μm particle concentration between A and B group, indicating that FFU is working to purge 0.5-0.9 μm particles. It can be considered

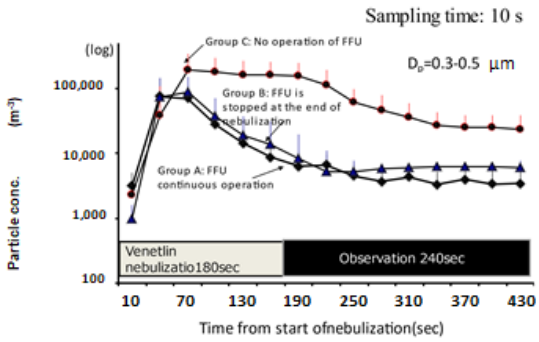

Fig.5 0.3-0.5μm particle concentration change in clean booth during nebulization with various operation conditions of FFU

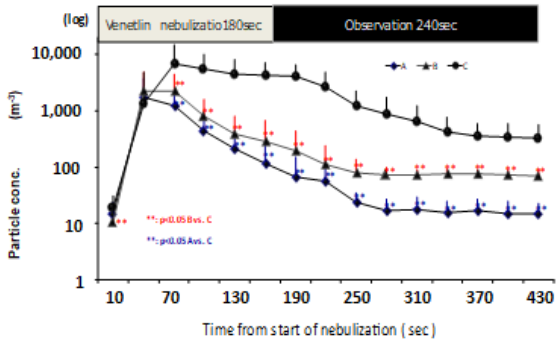

Fig.6 0.5-0.9 μm particle concentration change in clean booth during nebulization with various operation conditions of FFU

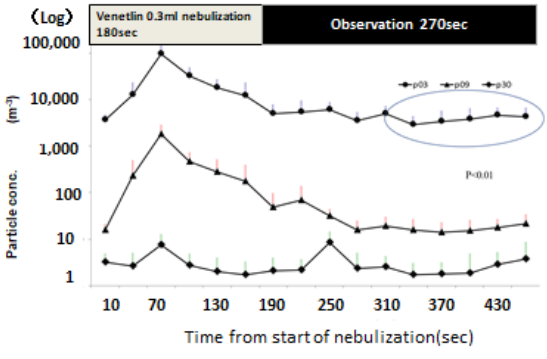

Fig.7 0.3-0.5 μm,0.5 -0.9μm, 3.0-10 μm particle concentration change in clean booth during 0.3ml Ventlin® nebulization with continuous operation of FFU.

that the particles in 0.3-0.5 µm size range may be supplied from the other size range of particles existing in the dead spaces of clean booth as a result of evaporation of larger droplets. Because the outlet FFU is placed on the side wall of clean booth, airflow should change to exit the booth, and there would be a big dead space at the bottom corner of clean booth. The droplets remaining in the death space evaporate to become smaller particles and gradually infiltrate into the main airflow. Next, we measured the time changes in particle concentration when two inhalation drugs, Venetlin® and Mucofilin®, were nebulized. Figure 7 shows 0.3-0.5 µm, 0.5-0.9 µm and 3.0-10µm particle concentration changes in clean booth with FFU continuous operation when 0.3 ml Venetlin® was nebulized. In each size range, the particle concentration increases promptly after the nebulization and especially 0.3-0.5 µm particle concentration remains high even under continuous operation of FFU. Figure 8 shows 0.3-0.5 µm, 0.5-0.9 µm and 3.0-10 µm particle concentration changes in clean booth with FFU continuous operation when 0.3 ml of Mucofilin® was nebulized. Comparing Fig.8 with Fig.7 of Venetlin® nebulization, the concentration of particles of each size decreases quickly, and even that of 0.3-0.5 µm particles becomes lower than 10 particles/m^3 in about 2 min. Next, in order to investigate the dose-dependent change in particle concentration, Mucofilin® was nebulized in different volume: 0.3 ml, 1.0 ml, and 2.0 ml. As shown in Figure 9, the concentration of 0.3-0.5 µm particles increased rapidly in 30 s and there is no difference in maximum concentrations of 1.0 and 2.0 ml Mucofilin® nebulization. The decreasing rate of 0.3-0.5 µm particles is faster for less amount of nebulization.Being different from Fig.8 of Venetlin® nebulization, the particle concentrations of all sizes decrease to 10 m^{-3} in 370 s. Consequently, we may conclude that the purging rates of nebulizedroplet are greatly dependent on the type of drugs. Figure 10 compares the changes of 0.3-

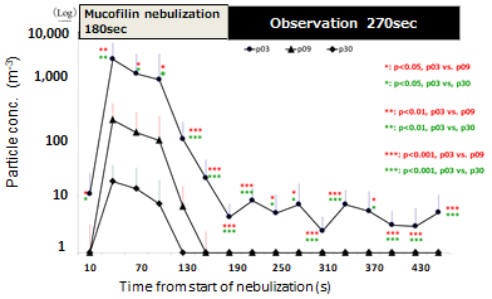

Fig.8 0.5-0.9 µm, 0.5-0.9 µm, 3.0-10 µm particle concentration change in clean booth during 0.3ml Mucofilin® nebulization with continuous operation of FFU

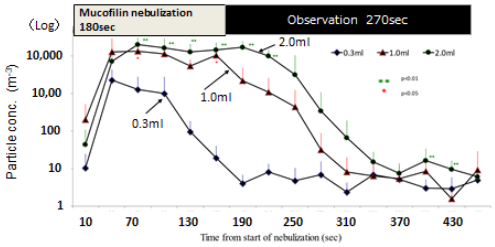

Fig.9 0.3-0.5 µm particle concentration change with different nebulized volume of Mucofilin®, 0.3 ml, 1.0 ml and 2.0 ml with Continuous operation of FFU

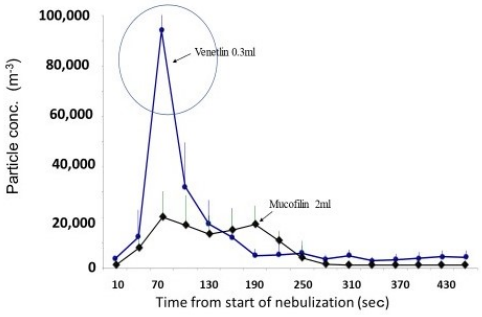

Fig.10 Comparison of 0.3-0.5 µm particle concentrationchange of 0.3 ml Venetlin® and 2 ml volume of Mucofilin® neblization

0.5 μm particle concentration when 0.3 ml Venetlin® and 2.0 ml Mucofilin® were nebulized. The maximum 0.3-0.5 μm particle concentration of Venetlin® nebulization is much higher than that of Mucofilin®(Fig.10), and Venetlin® particles remain longer at a higher concentration in the clean booth (Figure 11) , although the amount of nebulized drug is much smaller than that of Mucofilin®.

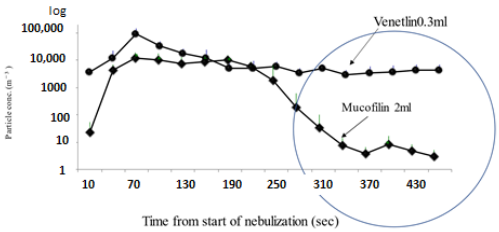

Fig.11 A logarthmic comparison of 0.3-0.5μm particle concentration change between in 0.3ml Venetlin® and in 2.0ml Mucofilin® neblization

8. Future work

In the present work, the particle concentrations of Venetlin®, a typical bronchodilator inhalation treatment, and Mucofilin® inhalation solution which reduces the viscosity of sputum and promotes expectoration, were measured by OPC in a newly designed clean booth. We found that the purging characteristic of particles in clean booth is markedly dependent upon the types of drug nebulized Future studies are required to find out what properties of nebulized drug brought the differences in particle behavior in the clean booth. In addition, we plan to clarify particle behavior when two or three different inhalation solutions are combined for actual clinical use. In the near future, we hope to conduct studies on actual patients in a clean booth to design a safer and more convenient inhalation therapy environment and to improve inhalation therapy methods.[4)]

9. References

1)Mario Cazzola, Josuel Ora, Andrea Bianco, Parola Rogliani, Maria Gabriella Matera: Guidance on nebulization during the current COVID-19 pandemic 2021.Jan;176:106236 Published online 2020 November 19.doi:10.10161/j.rmed.2020.106236

2) Álvaro del Real Andrea, Expósito Laura, Ruiz Azcona, Miguel Santibáñez, Ignacio Fernández Olmo: SARS CoV 2 surveillance in indoor and outdoor size segregated aerosol samples, Environmental Science and Pollution Research 2022 29:62973-62983. https://doi.org/10.1007/s11356-022-20237-7

3) Junjie Wang, Haida Tang, Jingwei Wang, Zhitao Zhong: An agent-based study on the airborne transmission risk of infectious disease in a fever clinic during COVID-19 pandemic:,Building and Environment 2022 Jun 15:218:109118,1-14. doi:10/1016/j.buildenv.2022.109118.1-14

4) Chiu-sen Wang: Face Masks and Prevention of Respiratory Viral Infections: An Overview: Aerosol and Air Quality Research 2022 January 2023 Volume23,Issue1,1-13. https://doi.prg/10.4209/aaqr.220343