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Aerosol delivery aspects within a high flow therapy system in chronic obstructive pulmonary disease patients

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Short title: Delivery in high flow therapy with a different interface
Keywords: titrated oxygen; nasal cannula; bronchodilator; high flow; COPD

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**Abstract**

There is a lack of information about the influence of patient interfaces like facemask or mouthpiece on the effective dose of aerosolized drugs while using high flow therapy in a clinical setting. These interfaces can improve pulmonary drug delivery over nasal cannula but patient preference and comfort should also be considered.

The present work was to determine the effect of three different interfaces (nasal cannula, valved face mask, and mouthpiece) when combined with titrated oxygen flow on aerosol delivery in chronic obstructive pulmonary disease (COPD) patients hospitalized due to acute exacerbation.

The variations between these interfaces were addressed in terms of change in lung function measurements pre-and post-inhalation, the delivered salbutamol dose, and patient tolerance to each interface.

High flow nasal cannula was the most comfortable interface used. However, its pulmonary drug delivery was significantly lower than both the valved face mask and mouthpiece (p<0.05). Although drug delivery was different with the three tested interfaces, the lung function improvements were similar.

**Introduction:**

High flow therapy (HFT) had acquired a great concern in the past two decades as an alternative modality for providing respiratory support in critically ill patients.

Emerging respiratory support by HFT as it is a well-tolerated and less invasive procedure.[1] However, the troublesome issue about HFT is the delivery of inhaled drugs efficiently to the lungs without temporarily stopping the gas flow to the patient. The obstacles which hinder efficient nebulization and favour aerosol deposition within the HFT circuit are the existing humidified conditions and the use of higher flows in adults up to 60 L/min. Inhaling an aerosol through nasal cannula creates
turbulence and increases aerosol loss within the nasopharynx.[2] The use of patient interfaces like facemask or mouthpiece over nasal cannula within a high flow system can improve pulmonary drug delivery but patient preference would be affected. [3, 4] The present work was to determine the effect of three different interfaces on aerosol delivery when combined with titrated oxygen flow within a high flow system in chronic obstructive pulmonary disease (COPD) patients. The variations were addressed between these interfaces in terms of change in lung function measurements pre and post-inhalation, the delivered salbutamol dose, and patient tolerance to each interface.

Methods
The effects of high flow nasal cannula (HFNC; Jiaxing Sim Medical Device Co. Ltd., Zhejiang, and China), high flow valved facemask (HFM; Aerogen Limited, Galway, Ireland), and high flow mouthpiece (HMP; NingboFiner Medical Instruments Co., Limited, Zhejiang China) were reported on the relative lung deposition and systemic bioavailability of salbutamol, routinely used in the management of acute exacerbations of chronic obstructive pulmonary disease (COPD). COPD patients admitted to Beni-Suef University Hospital due to the incidence of acute exacerbations fallen into GOLD stages (II and III), were randomized to receive the study dose of salbutamol by one of three interfaces (HFNC, HMP, and HFM) in a parallel design. The study was approved by the Ethical Committee of Faculty of Pharmacy, Beni-Suef University (REC-H-PhBSU-18002), and written informed consent was signed by all participants.

2.5 mg (2500 µg) of salbutamol (Farcolin respiratory solution, 5 mg/mL; Pharco Pharmaceuticals, Alexandria, Egypt) was delivered using a vibrating mesh nebulizer, Aerogon Solo nebulizer (Aerogen Limited, Galway, Ireland) placed proximal to
Fisher & Paykel heated humidifier (MR810, Fisher & Paykel Healthcare, Auckland, New Zealand) as shown in Figure 1. A mixture of oxygen and room air was driven from the gas wall supply to obtain the target oxygen saturation (88-92%). The use of salbutamol by the patients was not allowed at least 12 h (washout period) before the experiments to ensure accurate measurement of salbutamol level in urine. Ipratropium bromide (Atrovent Inhalation Solution, 2500 µg/mL, Boehringer Ingelheim, Egypt) was used as an alternative to relieve existing bronchoconstriction as the patients were hospitalized due to acute exacerbation.

The study exclusion criteria were hypotension (systolic blood pressure < 100 mmHg) as salbutamol use was contraindicated because of its vasodilator effect or arrhythmia or hypokalemia or previously known hypersensitivity to salbutamol. Also, patients were not eligible to participate in the study if they had severe kidney dysfunction (GFR < 20 L/min) since the kidney function was a fundamental parameter in our study based on the measurement of urinary pharmacokinetic parameters of the drug. The parent salbutamol drug and its metabolite are actively eliminated via renal excretion.[5] Consequently, if kidney function severely decreases, the drug will exhibit a longer half-life, and then its urinary pharmacokinetic parameters will be noticeably changed.

Pulmonary function tests were measured by a handheld spirometer (One Flow, Clement Clarke International, UK) before salbutamol inhalation (pre-BD) and 30 min after inhalation (post-BD). The maneuver was repeated three times to take the highest readings of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and FEV₁/FVC ratio according to the American Thoracic Society Guidelines. [6] Each patient included in the study collected a urine sample 30 min following dose inhalation and all urine up to 24 h following inhalation (cumulative 24-h urine
sample). 30-min urine sample and cumulative 24 h samples were used as indexes of pulmonary salbutamol bioavailability and systemic bioavailability, respectively.[7] Any complaint from the patient regarding the interface was recorded.

On the next day, the ex-vivo procedure was performed where patients received their salbutamol dose by the same interface previously used. This time, a breathing filter was placed after the interface to collect the entire dose delivered. This procedure ensured that no salbutamol would reach the patient. [8] Measurement of salbutamol mass in urine samples and breathing filters was performed by high-performance liquid chromatography (HPLC). [9] Statistical analysis was performed by one-way ANOVA with the application of least significant difference (LSD) correction to determine any difference between interfaces. A Chi-square test was conducted to compare the number of patients complaining from each interface.

**Results**

Thirty-six COPD patients with a mean (SD) age of 62.6 (9.1), respiratory rate of 19.4(3), and heart rate of 88.7(8.6) recorded by the multi-parameter patient monitor (Multi-parameter ECG monitor Macs 10, SternMed, Germany) were included where 12 patients were allocated in each group. The body mass index (BMI) was 25.9(4.2), 27.2(3.5), and 26.3(3.8) for HFNC, HMP, and HFM groups, respectively.

Comorbidities identified were hypertension, diabetes mellitus (DM), and gastro-esophageal reflux disease (GERD). The percentage of participants who suffered from hypertension in each group was 25, 33, and 25% for HFNC, HMP, and HFM groups, respectively while the percentage of participants with DM was 25, 17, and 17% for HFNC, HMP and HFM groups, respectively. The percentage of participants had GERD was similar in each group (8%). No significant difference was found between the three groups in their demographic data and GOLD grading. The lowest salbutamol
delivery to the ex-vivo inhalation filter was found with HFNC compared to HFM and HMP at p=0.032 and p=0.002, respectively while the salbutamol delivery with both HFM and HMP was statistically similar as shown in Figure 2 a. Also, HFM and HMP showed statistically similar salbutamol amounts excreted in both 30-min and cumulative 24-h urine samples post-BD inhalation (Figure 2 b). HFNC resulted in the lowest salbutamol amount recovered from both 30-min urine samples (p<0.001) and cumulative 24-h urine samples (p=0.048 vs HMP and p= 0.007 vs HFM). The oxygen flow reached by HFNC, HMP, and HFM to maintain target SpO₂ measured by pulse-oximeter was 12(1.4), 16(1.5), and 17.1(1.1) L/min, respectively and FiO₂ was 30.2(1.6), 37.8(2.8) and 39.1(2.2) for HFNC, HMP, and HFM, respectively.

Mean (SD) spirometric parameters were as follow for HFNC, HMP and HFM groups: pre-BD FEV₁=1.03 (0.21), 1.05(0.19) and 1.07(0.17) L, respectively and pre-BD FVC= 1.71(0.48), 1.75(0.41) and 1.88(0.37) L, respectively where post-BD FEV₁ = 1.09(0.35), 1.12(0.31) and 1.135(0.26) L, respectively and post-BD FVC= 1.79(0.53), 1.84(0.6) and 1.97 (0.46), respectively. These parameters were also expressed in % of predicted values for HFNC, HMP and HFM groups: pre-BD FEV₁=37 (5.3) %, 37 (5) % and 36 (4.7) %, respectively and pre-BD FVC= 46 (4.9) %, 47 (4.5) % and 49 (4) %, respectively where post-BD FEV₁ = 40 (4.6) %, 40 (4.3) % and 38 (3.6) %, respectively and post-BD FVC= 48 (5) %, 49 (5.3) % and 52 (3.9) %, respectively. Change in pre-and post-BD values of FEV₁ and FVC for each group is illustrated in figure 2 c, where no significant difference was found between different groups in the measured lung function parameters.

The numbers of patients complained from HFNC, HPM, HFM use were 8.3%, 33.3%, and 50%, respectively. Examples of patient complaints recorded by the researcher were asking the nurse to remove the interface or intentionally removing it once or
several times or noncompliance during the aerosol delivery procedure. The highest percentage of complaints were seen with HFM (p=0.001 and p=0.041 vs HFNC and HMP, respectively).

Discussion

The lowest values of ex-vivo total delivered salbutamol dose and fractions recovered from 30-min and 24-urine samples were noticed with HFNC. These findings were consistent with many previous studies indicated the lower delivery efficiency of such interface.[2, 10] However, the highest patient tolerability and preference were reported with HFNC as only 8% of participants complained of this interface.[2, 8, 10] HMP and HFM showed approximately similar results of the ex-vivo total delivered dose and the recovered fractions of salbutamol from urine samples and were significantly higher than that of HFNC (p<0.05). Consequently, a better pulmonary deposition could be obtained with HMP and HFM interfaces. The difference between these interfaces could be due to the breathing route targeted by each interface which plays an important role in determining the dose reaching the lungs. HFNC targets nasal aerosol inhalation while the nose acts as an efficient filter decreasing the penetration of the inhaled particles into the lower respiratory tract compared to the oral inhalation through the mouth targeted by either HMP or HFM.[11] However, the percentage of patients complained about the use of HMP or HFM was significantly higher compared to the HFNC group (p<0.05). Also, the fraction of salbutamol recovered from 24-h urine samples significantly increased with using HMP or HFM compared to HFNC (p<0.05), and therefore patients would be subjected to more systemic side effects of the drug.[12] Facial and ocular depositions were the main complaints previously reported with the use of facemask in addition to hindering eating and speech leading to interface displacement and less compliance. [13, 14] The
main problem noticed with HMP use was related to the inability of the patient to cooperate to maintain the interface in the mouth during the whole procedure. Therefore, its use in unconsciousness patients, during sleep, and for drug delivery with prolonged nebulization time may be discouraged. The change in lung function parameters (FEV₁, and FVC) post-dose inhalation was approximately similar to three tested interfaces ensuring their ability to saturate the target β2 receptors even with the lowest dose delivered by the HFNC. The increase in FEV₁ was noted to be below that indicated for significant bronchodilator response (≥ 200 ml from pre-BD values). As three tested interfaces showed different drug delivery but with similar lung function improvements, the preference of one interface use within the HFT system could depend on the patient comfort and tolerability.

Limitations of the study included the absence of urinary salbutamol level pre-intervention (baseline level), small sample size, and the non-blinded and parallel design of the trial.

**Conclusions**

HFNC was the most comfortable interface used but lower aerosol delivery was achieved with its use. Although drug delivery was different with the three tested interfaces, the lung function improvements were similar. HFNC could be replaced by either HMP or HFM to guarantee better delivery without temporary stopping of gas flow during dose administration.

**Figure legends**

Figure 1: schematic diagram of in-vivo setting showing the position of the aerosol generator and three different interfaces within the HFT circuit
Figure 2: Inhaled salbutamol delivery within the HFT system. a) Mean (SD) total emitted dose of salbutamol collected on ex-vivo filters using different interfaces (nasal cannula, mouthpiece, and valved facemask), b) Mean (SD) salbutamol mass excreted in urine samples through the use of different interfaces c) Mean (SD) change in FEV₁ and FVC pre and post-BD inhalation by different interfaces.

References:


C) Change in FEV₁ and FVC in L

Type of aerosol delivery

- Nasal delivery
- Oral delivery
- Oronasal delivery

ΔFEV₁
ΔFVC