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Inhaled salbutamol dose delivered by jet nebulizer, vibrating mesh nebulizer and metered dose inhaler with spacer during invasive mechanical ventilation

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ABSTRACT

Background: Patient receiving invasive mechanical ventilation (IMV) may benefit from medical aerosol, but guidance on dosing with different aerosol devices is limited to in-vitro studies. The study was designed to compare aerosol delivery with five different types of aerosol generators during IMV.
Method: In randomized design, 60 (30 female) mechanically ventilated chronic obstructive pulmonary disease (COPD) patients were assigned to one of 5 groups. Groups 1–4 received 5000 μg salbutamol using Aerogen Pro (PRO), Aerogen Solo (SOLO), NIVO vibrating mesh and jet nebulizers (JN), respectively, while group 5 received 800 μg (8 puffs) of salbutamol via metered dose inhaler with AeroChamber-MV (MDI-AC). All devices were place in the inspiratory limb of ventilator downstream from humidifier which was switched off while delivery. Patients received the inhaled dose on day 1 and provided urine 30 post dosing. They also recived the same inhaled dose with a filter before the endotracheal tube on day 2. Amount of salbutamol excreted in urine 30 min post inhalation and the amount deposited on the filter from all the COPD patients were determined as indeces of pulmonary deposition and systemic absorption, respectively.
Results: No significant difference was found between the 3 vibrating mesh nebulizers (VMNs). The in-vivo and ex-vivo testing showed that all the VMNs resulted in better aerosol delivery compared to JN ($p < 0.01$). However, MDI-AC resulted in better aerosol delivery to VMNs but must be accompanied with careful attention and proper delivery of MDI-AC doses by healthcare provider.
Conclusions: VMNs can be exchanged with each other, with no dose adjustment. However, dose adjustment is a must when replacing VMNs by JN or MDI-AC. This similarity and difference between the 5 aerosol delivery methods suggest that for IMV patients, aerosol delivery methods should be chosen or substituted with care.

1. Introduction

Aerosol delivery using nebulizers or metered dose inhaler (MDI) with spacers to mechanically ventilated patient was shown to be feasible and beneficial [1–3].

Many variables affect inhaled dose and aerodynamic properties of aerosol delivery within ventilation circuit [2,4–9]. Nebulizer type effect on the aerodynamic characteristics of the emitted dose in ventilation circuit has been well studied [2,7,9–13]. The effect of position of the aerosol delivery method in different type of ventilation circuit has been also studied [13–17]. Even the ventilator

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setting and heat and humidification effects has been studied [17–21]. Many studies recommended reduction of dose when using vibrating mesh nebulizers compared to jet nebulizers [2,7,9–12,17,18,20]. However, no suggestion is available about dose adjustment when substituting nebulizers by MDI with spacers in ventilation circuit. Substitution without dose adjustment might result in different delivery dose to patient which might cause unexpected side effect in such a critically ill patient. Since, there are many different types of inhaled medication that can be delivered using these aerosol generators which have different side effects that could worsen the status of them. Especially when it has been shown that even substitution of one jet nebulizer by another jet nebulizer have some effect on aerosol delivery [22].

Hindle et al., 1992 developed a urinary pharmacokinetic method to determine relative lung bioavailability of salbutamol following inhalation [23]. This methods used the amount of drug excreted in first 30 min post dosing as an index of the lung deposition [23]. This non-invasive pharmacokinetic method has been used to detect lung deposition of aerosolized drug to healthy volunteers [24], patients admitted with an acute exacerbation of either asthma or COPD [25] and non-invasively ventilated patients [26–28]. This method have been extended to many other medications [29–31].

The aim of the present work was to compare aerosol delivery from MDI with spacer, vibrating mesh nebulizer and jet nebulizer in dual limb invasive mechanical ventilation, using Hindle et al. non-invasive urinary salbutamol method in addition to ex-vivo method, to help in dose adjustment when substituting any of them by the other in ventilated patient.

2. Materials and methods

2.1. Patients

This study was conducted in accordance with amended Declaration of Helsinki. Local institutional review boards and independent ethics committees approved protocol. Written informed consent was obtained from all patients. Patients with previous diagnosis of chronic obstructive pulmonary disease (COPD) that had been admitted to respiratory unit with an acute exacerbation and required invasive mechanical ventilation for respiratory acidosis [32] and were prescribed salbutamol were eligible for study. All patients were recruited using hospital approved delayed consent procedure.

Patients were ineligible to be included in this study if they had taken part in research study during previous 6 months, had known hypersensitivity to salbutamol, systolic blood pressure of <100 mmHg or severe renal impairment defined as Creatinine Clearance or eGFR of <20 mL min^{-1}.

2.2. Study design and procedures

Hindle et al. non-invasive urinary salbutamol methodology [23] were used to compare lung deposition of 5 aerosol delivery methods. Ventilated patients were set on pressure support ventilation (PSV) with a positive end-expiratory pressure (P_{EEP}) = 5 cmH_2O and the clinician checked the patient's spontaneous tidal volumes (TV). If the patients could not achieve a TV of 500 ml, then the clinician titrated the inspiratory pressure support to reach the targeted TV = 500 ml. The inspiratory pressures in PSV were between 15 and 20 cmH_2O. We tried to minimize pressures to avoid pulmonary barotraumas unless the patient had higher ventilatory requirements. Schematic design of the experimental setting and the aerosol generator position in the invasive ventilation circuit is shown in Fig. 1. All devices were place in the inspiratory limb of ventilator downstream from humidifier which was switched off while delivery. Day 1 study doses occurred between 12 and 24 h after start of IMV.

Salbutamol administration was avoided for at least 12 h prior start of the study. Patients received ipratropium bromide (Atrovent inhalation solution containing nominal dose of 25 μg mL^{-1}, Boehringer Ingelheim, Egypt) in place of their normal salbutamol dose in this period. High Performance Liquid Chromatography (HPLC) analysis method used differentiates between these two drugs.

In day 1, patients voided their urine 15 min before each study dose. Each group of the five groups used one type of the aerosol generator for aerosol delivery. 5000 μg (in 1 ml) of salbutamol respiratory solution (Farcolin, 5000 μg mL^{-1}; Pharco Pharmaceuticals, Egypt) was nebulized using Aerogen® Pro vibrating mesh nebulizer [PRO], Aerogen Solo vibrating mesh nebulizer [SOLO] (Aerogen Limited, Ireland), NIVO™ vibrating mesh nebulizer (Aerogen/Philips, Andover, MA, USA) and jet nebulizer [JN] attached to PortaNeb compressor (Philips Respironics, UK). PortaNeb compressor provided an air flow of 6 L min^{-1} into nebulizer to aerosolize liquid. 8 MDI doses containing 100 μg salbutamol (Ventoline, GlaxoSmithKline, Egypt) each were delivered using AeroChamber® MV [MDI-AC] (Trudell Medical International, Canada). In all experiments, MDI was shaken well and primed twice prior to use. The choices of salbutamol dosage for different devices were in accordance with the previous literatures [33–39].

After dose administration, patients provided urine sample 30 min (USAL0.5) from commencement of dosing as recommended by Hindle et al. [23] Volume of 30 min collection urine samples were measured and assayed using HPLC. Salbutamol was extracted from urine samples using solid phase extraction with Oasis Isolute MCX cartridge (Waters corporation, USA), with bambuterol hydrochloride added as internal standard, and then injected into HPLC system. The solid-phase extraction method using Isolute MCX Cartridges was developed to extract salbutamol and bambuterol from urine. The amino group of salbutamol is linked to the sulphonic acid group on the sorbent bed. A pre-treated sample was prepared by adding 10 ml of urine, 2 ml of aqueous solution of 1000 μg/ml (w/v) bambuterol HCL as internal standard as appropriate and 2 ml of 0.5 N hydrochloric acid (HCL). Then, these ingredients were mixed well by vortex for 1 min. Each Isolute cartridge was conditioned with 6 ml methanol followed by 6 ml of double distilled water. The pre-treated sample was then loaded to the cartridges. The cartridge was firstly washed with 10 ml of 5% methanol in 0.1N HCL. The cartridge was then washed with 10 ml methanol. The third washing of the cartilage was done by adding 6 ml of 2.5% triethanolamine in methanol. The interaction between the analytes and the sorbent bed was then broken by increasing the pH of the column. Hence, the analyte was eluted from the cartridge into a sample tube using 10 ml of 5% (v/v) ammonia in methanol with the application of a low vacuum (less than 3 bars). After evaporation to dryness using a water bath, the residue was reconstituted in 1 ml mobile phase and 100 μl was injected into the HPLC system. An ODS 5 μm, (4.6 × 250 mm, ZORBAX Eclipse) C-18 HPLC column with (4 mmx3mm, Agilent, USA) C-18 (ODS) guard column was used. Mobile phase, acetonitrile: water containing 0.1% orthophosphoric acid (90:10, v/v), was pumped through columns at flow of 1 mL min^{-1} maintained at 25 °C and photodiode array detection was set at 220 nm. Limit of detection and lower limit of quantification for salbutamol was 0.36 and 1.00 μg mL^{-1}, respectively.

2.3. Ex-vivo method

On day 2 subjects also received the study doses using his selected aerosol generator with a filter (Filta Guard breathing filter, Intersurgical limited, UK) placed before their endotracheal tube