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Study:

Individualized Dosing Schedule of Inhaled Bronchodilator for Endotracheally Intubated COPD Patients: A Randomized Control Trial

NCT01933984

1. Methods

1.1. Study design

This was an open-label, randomized controlled study comparing a personalized versus fixed MDI dosing schedule for intubated COPD patients with acute respiratory failure.

1.2. Patient enrollment

We enrolled intubated COPD patients who were newly admitted to the intensive care unit of Changhua Christian Hospital (Changhua, Taiwan). A diagnosis of COPD was defined as audible expiratory wheezing or rhonchus or obstructive ventilatory impairment when assessed by spirometry, in addition to a history of smoking or exposure to other forms of toxic stimuli. All of the enrolled patients were endotracheally intubated and had been mechanically ventilated for less than 72 h. The exclusion criteria were: (1) age less than 18 years, (2) confirmed history of asthma, (3) an Acute Physiology and Chronic Health Evaluation II score of more than 35, and (4) comorbid septic shock. The study was approved by the Institutional Review Board of Changhua Christian Hospital (approval No. 120703). Informed consent was obtained from the surrogates of all participants. All of the participants were randomly assigned to the personalized-dosing or fixed-dosing group according to a computer-generated allocation sequence in a block size of four patients.

1.3. R_{aw} determination

The enrolled patients were ventilated with either an AVEA® (CareFusion, Yorba Linda, CA, USA), e500 (Newport Medical Instrument Inc. CA, USA), or Evita® 4 (Drager, Lubeck, Germany) ventilator. When evaluating R_{aw}, the ventilator settings were transiently switched to volume control

mode with a fixed tidal volume (500 ml) and constant flow (with a rate of 60 L/min). Plateau pressure was measured using a manually controlled end-inspiratory pause lasting for 0.5–1.0 s by qualified respiratory therapists [11]. Consistent with several previous clinical studies [12, 13], our patients were not routinely sedated before R_{aw} measurements. We made every effort to ensure that the patients were calm during the measurements, including additional sedation if necessary. Each measurement was repeated three times with an interval of at least 1 min, and the average value was calculated. R_{aw} was calculated using the equation (peak inspiratory pressure − plateau pressure)/flow [14]. After each measurement, the ventilator was set to its usual settings. Thereafter, R_{aw} was routinely determined every 8 h until the discontinuation of ventilation or the 28th day of the study.

1.4. Technique of MDI administration through the ventilator circuit

The technique of MDI administration was based on that reported by Dhand and Guntur [15]. Airway secretions were sucked out before drug administration. The heat moisture exchanger was removed, but the humidifier was not. After shaking and warming the MDI to hand temperature, the canister was connected to an AeroChamber® HC MV spacer (Trudell Medical International, London, Canada) and placed in the inspiratory limb of the ventilator circuit 15 cm away from the endotracheal tube. Actuation was synchronized with the initiation of inspiration. Each actuation was performed with an interval of at least 15 s.

1.5. Personal target R_{aw} determination

The target R_{aw} of each patient was determined within 72 h after their admission to the intensive care unit. After confirming that no inhaled bronchodilator has been administered in the preceding 2 h (for fenoterol) or 12 h (for salmeterol/fluticasone), four puffs of fenoterol MDI (100 μg/puff, Berotec®; Boehringer Ingelheim, Ingelheim, Germany) were administered, followed by 8 puffs after 15 minutes, and then 16 puffs after another 15-minute interval. These intensive doses were intended to produce near maximum bronchodilation. Fifteen minutes after these 28 puffs of bronchodilators, we measured R_{aw}. This R_{aw} value was possibly the lowest achievable, and was assigned as the patient's personal target R_{aw} [16]. This personal target R_{aw} served as the standard (or baseline) to judge responsiveness to subsequent bronchodilator doses.

1.6. Bronchodilator delivery schedule

All patients in both the personalized-dosing and fixed-dosing groups routinely received four puffs of 25 μg salmeterol/250 μg fluticasone (Seretide® Evohaler® 250; GlaxoSmithKline Inc. Evreux, France) every 12 h until the discontinuation of ventilation. Each patient also routinely received one vial of ipratropium bromide 0.5 mg and salbutamol sulfate 2.5 mg (Combivent®; Boehringer Ingelheim, Ingelheim, Germany) every 6 h, and an injection of intravenous methylprednisolone 40 mg every 8 h for the first 3 days. The use of short-acting bronchodilators on an as-needed basis was not restricted. Based on the R_{aw} data determined every 8 h, the personalized-dosing group received an additional four puffs of 25 μg salmeterol/250 μg fluticasone plus four puffs of fenoterol (0.1 mg/puff) if the R_{aw} value was higher than the personal target R_{aw} (once it coincided with the regular dosing period of salmeterol/fluticasone, only fenoterol was added). No extra doses were

given to the fixed-dosing (control) group of patients regardless of their R_{aw} value. The bronchodilator delivery schedules are summarized in Fig. 1.

1.7. Outcome measurements

The primary outcome was the deviation of R_{aw} from the personal target, which was calculated as (measured R_{aw} − target R_{aw})/target R_{aw}. The evolution of this deviation over the treatment course was also calculated. The secondary outcomes included the number of ventilator-free days from day 1 to day 28, the percentage of breathing without assistance by day 28, the number of episodes of nosocomial pneumonia, the total number of puffs of rescue short-acting bronchodilators, the number of drug-related adverse effects (arrhythmia or hypokalemia with a Naranjo score [17] of more than 4), and the mortality rate at day 180.

1.8. Statistical analysis

Data were expressed as number (percentage), mean ± standard deviation or median, inter-quartile range (IQR). Each variable was tested for normal distribution using the Kolmogorov-Smirnov test. To compare two continuous variables, we used the Student's *t*-test or the Wilcoxon rank sum test depending on their distribution. For categorical variables, we used the chi-square test or Fisher's exact test as appropriate. A general linear mixed regression model was used to analyze the relative deviation of R_{aw} over time. This model included fixed effects for the personalized-dosing group, time, and an interaction term of group-by-time, as well as a random intercept and slope. Different durations of stay were considered as the random slope. A P value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS

Statistics, version 20, IBM Corporation, Chicago, IL, USA). The power of calculating the difference in mean R_{aw} deviation was 100% with a sample size of 51 and an alpha value of 0.05.