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Budesonide facilitates weaning from mechanical ventilation in difficult-to-wean very severe COPD patients: Association with inflammatory mediators and cells

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ABSTRACT

Introduction: Mechanical ventilatory support is life-saving therapy for patients with respiratory failure in intensive care units (ICU) but is linked to ventilator-associated pneumonia and other nosocomial infections. Interventions that improve the efficiency of weaning from mechanical ventilation may improve patient outcomes.
Objective: To determine whether inhaled budesonide decreases time-to-weaning in COPD stage 4 difficult-to-wean patients and reduces the release of pro-inflammatory cytokines in ICU patients.
Materials and methods: We recruited 55 difficult-to-wean COPD patients (Stage 4) within the ICU of the Masih Daneshvari Hospital. Subjects were randomly assigned to receive inhaled budesonide (0.5 mg/day) or placebo (normal saline). Dynamic compliance and BAL cytokines were measured.
Results: Budesonide significantly reduced the number of days on MV (days-to-weaning = 4.6 ± 1.6 days) compared to that seen in the control group (7.2 ± 2.7 days, $p = 0.014$). Dynamic compliance was significantly improved in the budesonide group on days 3 ($p = 0.018$) and 5 ($p = 0.011$) The levels of CXCL-8 and IL-6 diminished on days 3–5 after start of budesonide ($p < 0.05$).
Conclusion: In COPD patients on MV, nebulized budesonide was associated with reduced BAL CXCL8 and IL-6 levels and neutrophil numbers as well as an improvement in ventilatory mechanics and facilitated weaning.

1. Introduction

Mechanical ventilatory support is a critical component of intensive care unit (ICU) management of many patients with respiratory failure. However, prolonged mechanical ventilation is associated with increased complications and cost [1,2] and therefore, efficient weaning is of paramount importance [3]. Weaning from mechanical ventilation (MV) can be defined as the process of withdrawing ventilatory support. About 70% of intubated mechanically ventilated patients are extubated after the first spontaneous breathing trial (SBT) [4]. The remaining 30% are classified as "difficult-to-wean" when they require three or more SBTs to achieve successful weaning.

The mortality rate for difficult-to-wean patients is higher than for those who wean readily [5]. This is due not only to the greater number of co-morbidities, but also because prolongation of MV increases the risk of complications including ventilator-associated pneumonia (VAP), barotrauma, ventilator induced lung injury (VILI), tracheal injuries and respiratory muscle weakness [6]. Mechanisms that prolong the weaning process might include inflammation that could be related to infection, sepsis or lung over-distention and recruitment of deflated alveoli during mechanical ventilation. These promote release of cytokines and activation of neutrophils [7] that could contribute to mechanical and gas exchange defects via exudation of fluid and cells into interstitial spaces and airways and also retard resolution of lung injury. Thus, anti-inflammatory agents such as inhaled corticosteroids (ICS) [8]

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could have clinical utility by decreasing lung inflammation in patients recovering from bouts of acute respiratory failure.

Inhaled budesonide is a potent anti-inflammatory agent which decreases asthmatic inflammation, including inflammatory cytokines and remodeling agents, that impairs lung function [9]. In addition, inhaled budesonide has a similar inhibitory effect as systemic methylprednisolone on lung inflammation in acute exacerbations of COPD but with fewer systemic side effects [10].

Various clinical strategies including earlier recognition of readiness to wean and minimization of sedative and analgesic drugs [11] have been used to decrease the time-to-weaning [12], but to date, few studies have examined the role of anti-inflammatory therapies in facilitating weaning from MV in COPD patients. Thus, the objective was to perform a pilot study to assess the effect of inhaled budesonide on time to weaning in difficult-to-wean severe COPD patients.

2. Materials and methods

2.1. Patient selection

The study was reviewed and approved by the university Ethics Committee. All procedures performed were in accordance with the ethical standards of the institutional and national research. Information about the study was given both orally and in written form to all patients or their accompanying adult. Informed written consent was obtained prior to their inclusion in the study. The study was registered at the Shahid Beheshti University clinical trial registry as IRCT20160392059N5.

The study was performed in the Masih Daneshvari Hospital ICU from June 2014 to June 2015. Patients receiving invasive mechanical ventilation in the ICU were randomly assigned to receive inhaled budesonide or inhaled normal saline (control group) if they were difficult-to-wean and had stage 4 COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (FEV_1 < 30% predicted). Difficult-to-wean patients were defined as those who require more than three SBTs or >7 days from the first SBT to achieve successful weaning [13].

Exclusion criteria were intubation for 21 or more days, bronchiectasis, sepsis or SIRS, heart failure (EF < 25%), multi-organ system dysfunction (≥2 organ failures), pleural effusion, ventilator associated pneumonia (VAP) or terminal status.

2.2. Budesonide dose

Randomization was performed using a computer-based random number generating scheme. Clinicians and patients were blinded to study assignment via concealment using identical unidentified syringes and solution appearance for all study drug administrations. Patients inhaled budesonide (0.5 mg/Bid) diluted in 50 ml of normal saline or saline alone for 1 h from a jet nebulizer connected to the ventilator circuit [14,15]. The precise model of nebulizer used was based on the type of ventilator used for each patient. The budesonide dose (0.5 mg twice daily) was given by nebulizer every day for 7 days.

If the patient was extubated prior to 7 days, then the study drug was discontinued but the patient remained in the study for evaluation purposes. Patients in both budesonide and controls were treated with parenteral steroid from the time of admission (oral prednisolone 30 mg once daily).

2.3. Mechanical ventilation

Mechanical ventilation was initiated using Drager Eita XL or Infinity ventilators (Lubeck, Germany) for standard indications. COPD exacerbation was the main reason for MV. Indications for intubation and MV included severe dyspnea, respiratory frequency > 35 breaths/min, hypoxemia (PaO_2 < 40 mm Hg on room air or PaO_2/FIO_2 < 200 mm Hg), severe acidosis (pH < 7.25) and hypercapnia ($PaCO_2$ > 60 mm Hg) or respiratory arrest. Patients were sedated based on a standard protocol using midazolam and fentanyl.

Ventilator settings initially used a lung protective strategy with tidal volumes of 6 to 8 ml/kg predicted body weight via volume-limited synchronized mandatory intermittent ventilation (V-SIMV). PEEP was adjusted to maintain SPO_2 in the 88 to 95% range as per ARDS net recommendations. For weaning patients, pressure support using pressure-limited SIMV was reduced to <10 cm H_2O if RR remained <25/min, which was used as a criterion for initiating a spontaneous breathing trial (SBT).

2.4. Weaning and extubation

Daily screening of patients for weaning was performed by looking at 5 criteria: PaO_2/FiO_2 > 200, PEEP ≤ 5, adequate cough during suctioning, f/VT ≤ 105, arterial oxygen saturation ≥ 90% and no continuous infusion of sedatives or vasopressors [10]. To determine weaning ability, an SBT was performed using a CPAP level of 5 cm H_2O for 2 h if tolerated. The SBT was discontinued if RR > 35/min for 5 min or longer, SaO_2 < 90%, HR > 140/min, sustained increases in HR > 20%, Systolic BP > 180 mm Hg or increased anxiety and diaphoresis. Criteria for extubation were passing a SBT, no signs of respiratory failure, air leak after cuff deflation, adequate cough and no excessive tracheal secretions or signs of VAP.

All patients were investigated for SBT failure including, cardiac monitoring, hemodynamics, CVP measurements, and diuretics trials.

The criteria for re-intubation were unremitting respiratory distress, respiratory rate > 35, decreased SPO_2 < 80% with oxygen face mask, worsening respiratory acidosis or failure of NIV after extubation. The criteria for initiation of NIV were respiratory distress, RR > 24 but <35, SPO_2 < 95% but >80%, no severe hypercarbia (PCO_2 < 90) or acidosis (pH between 7.1 and 7.35), improvements in gas exchange and heart and respiratory rates within first 2 h and a co-operative patient.

2.5. Data collection

All variables were measured at baseline (day 0) and on days 1, 3 and 5. The main outcome variable was time to wean as primary outcome, days to extubation, starting with randomization to budesonide or placebo and finishing with extubation (and remaining extubated for at least 48 h to count). Secondary outcome variables were level of pressure support and dynamic compliance which was calculated in calm, sedated patients using volume-controlled ventilation and positive end expiratory pressure (PEEP) and the equation: dynamic compliance = tidal volume / (peak pressure − PEEP).

Dynamic compliance was measured in all patients using the following method: Sedated patients not making active breathing efforts during the inspiratory hold at zero PEEP, after several breaths, the airway opening was occluded at the end of a tidal expiration, using the end-expiratory hold button.

Twenty non-lung disease controls were selected from non-intubated patients undergoing diagnostic fiberoptic bronchoscopy. Diagnostic BAL samples were obtained during this procedure and only samples obtained from subjects who had no detectable presence of disease were used. Ethical approval was obtained and written consent was obtained from all of these subjects. The mean age of these healthy volunteers was 44.2 ± 8.7 (12 male, 8 female).

At each time point, a sample of bronchoalveolar lavage (BAL) fluid was collected using a flexible fiberoptic bronchoscope. Cell pellets were stained for CD4+ and CD8+ lymphocytes, macrophages and neutrophils and a total cell count was performed. BAL supernatants were kept at −80 °C until cytokine levels were determined using ELISA.

2.6. BAL fluid collection and analysis

BAL fluid was collected by fiberoptic bronchoscopy. Six aliquots (20 ml each) of sterile normal saline were instilled and the fluid was