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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

aspirated immediately after each instillation. BAL fluid was filtered through sterile gauze to exclude mucus plugs and was then centrifuged to obtain a cell pellet. The first retrieved BAL sample, which contains excessive bronchial material, was discarded and the remaining BAL fluid was pooled in ice-cold tubes and stored at −20 °C until used. BAL was centrifuged at 200 × *g* for 10 min at 4 °C to obtain the supernatant which was aliquoted and stored at −80 °C until analysis. Samples were frozen within 30 min of the bronchoscopy procedure and all assays were performed at the same time on defrosted samples. The cell pellet was washed once in 50 ml of Ca^{2+}/Mg^{2+} free Hanks' balanced salt solution (HBSS). The cells were counted on a hemocytometer slide using a Kimura counterstain and viability assessed by trypan blue exclusion. Cytospins were obtained and stained with May-Grunwald-Giemsa in order to obtain differential cell counts as previously described [16].

2.7. Flow cytometry of BAL cells

Flow cytometric analysis of BAL cells was performed using a BD FACS Calibour (BD, USA). To enhance the number of lymphocytes for analysis, an acquisition gate was set using the lower third of the side scatter field. The results were expressed as a percentage of the cells detected by fluorescence and not as a percentage of the gate because of contaminating debris in the sputum. Pairs of monoclonal antibodies to CD4 + and CD8 + lymphocytes (Sigma Diagnostics, Poole, UK) were then added to the suspension and incubated for 30 min before flow cytometry was performed. All data analyses were performed using Statistics for Windows (StatSoft, Tulsa, OK, USA). The results were expressed as means ± SD or median (range), unless otherwise indicated. The Shapiro-Wilkoxon W test was applied to assess normality.

2.8. Cytokine ELISA assays

BAL levels of IL-6 (R&D system, UK), CXCL8 (BD, USA), IL-1β (Invitrogen, USA) and TNFα (Bioscience, USA) were measured by ELISA kits according to the manufacturers' instructions.

2.9. Statistical analysis

Sample size was estimated to be 27 in each group using sample size calculator software with 95% confidence interval, p = 0.05 and power of 80% based on a pilot study of 14 subjects. The primary outcome (time-to-extubation) estimated mean was 4.21 days and a variance of 1.6 days in the budesonide group versus a mean of 5.38 days and a variance of 1.5 days in control group. All multiple comparison tests were two-tailed. Direct comparisons between two treatment groups were performed with the unpaired Student *t*-test or the non-parametric Mann–Whitney test when the data sets were not normally distributed. Pearson's correlation of coefficient was used to analyze correlations between the inflammatory mediators and the various parameters measured. A p value < 0.05 was considered significant. All statistical analyses were performed with GraphPad Prim version5.

3. Results

A total of 78 patients was screened and 23 were excluded (Fig. 1). Of the 55 GOLD stage 4 COPD patients enrolled, 28 were randomly assigned to receive nebulized budesonide and 27 received normal saline as a placebo control. There were no significant differences in age, sex or BMI between the budesonide and control groups (Table 1). In addition, there was no difference between the groups in the number of days in the ICU or of MV prior to enrolment in the study (Tables 1 and 2). Of

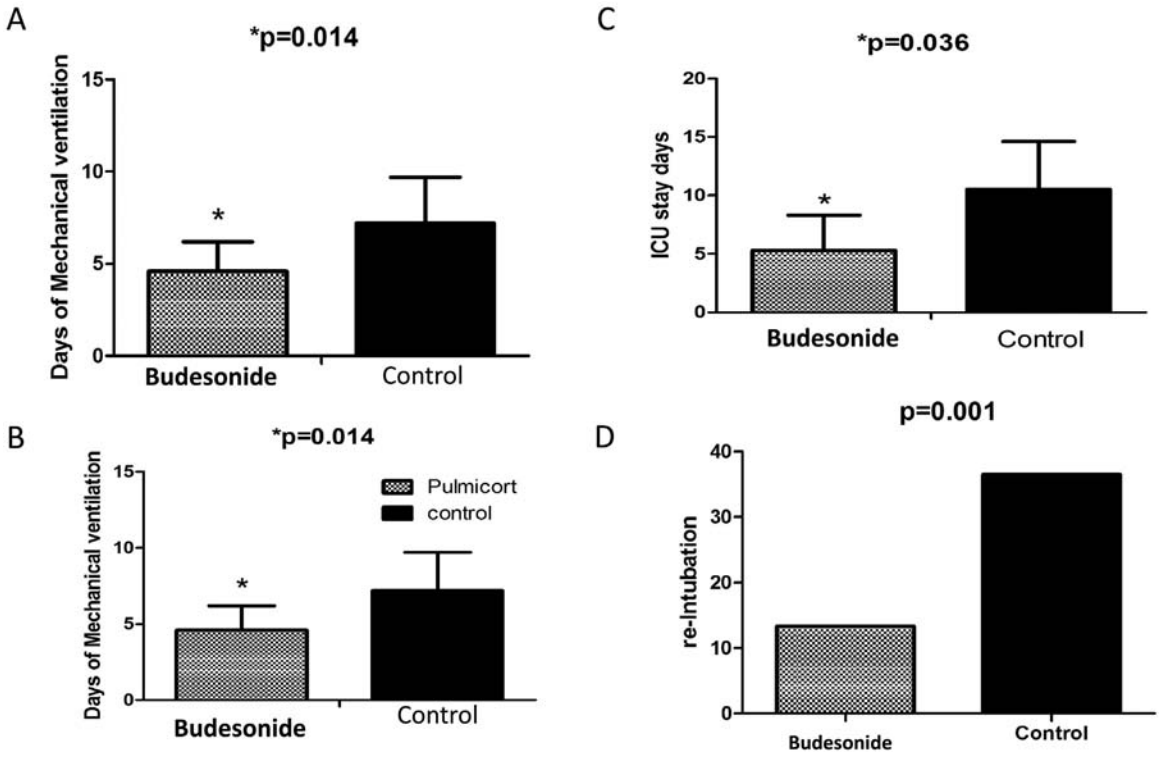


Fig. 1. The effect of budesonide on ICU parameters. Budesonide caused a significant reduction in the mean number of days that difficult-to-wean patients were on mechanical ventilation (MV) (days to weaning from MV) (A). This was accompanied by a reduction in the number of days that patients remained in the ICU (ICU stay days) (B), and a reduction in proportion of re-intubation after extubation in difficult to wean patients after administration of Budesonide in compare to control group (C). Data are presented as mean ± SD except for (D) where the percentage value alone is given. p values are given for each comparison against placebo control.

Table 1
Characteristics of patients prior to inclusion in the study.

	Budesonide (n = 27)	Control (n = 28)	p-Value
Topographic character of patients			
Age	55.7 ± 14.7	57.3 ± 18.4	NS
Sex (female/male)	36%/64%	42%/58%	NS
BMI	25.2 ± 4.6	24.9 ± 4.7	NS
Days in ICU prior to drugs	9.7 ± 5.6	10.1 ± 5.2	NS
Days of MV prior to dugs	6.8 ± 2.4	6.5 ± 2.5	NS
APACHE (2) score			
Admission to ICU	25.4 ± 4.5	25.7 ± 3.8	NS
Discharge from ICU	16.6 ± 3.1	19.8 ± 3.5	0.01
Co-morbidities			
CHF	5	6	
HTN	8	10	NS
ESRD	1	2	
DM	14	13	
Indication for mechanical ventilation			
RR > 35	12	12	NS
SPO_2 < 90%	10	8	NS
Acidosis or hypercapnia	5	8	NS

BMI: body mass index, ICU: intensive care unit, MV: mechanical ventilation, APACHE: acute physiology and chronic health evaluation II, CHF: congestive heart failure, HTN: hypertension, ESRD: end-stage renal disease, DM: diabetes mellitus, RR: respiratory rate, SPO_2: saturation of peripheral oxygen.

the patients who failed an SBT, 5 patients in the budesonide group and 6 in the control had cardiac failure (25% < EF < 40%), 7 patients in the budesonide group and 6 in the control group had hemodynamic instability.

3.1. Weaning from mechanical ventilation

Days-to-weaning was 4.6 ± 1.6 days in budesonide group which was significantly lower compared to control group 7.2 ± 2.7 days (p = 0.014) (Fig. 1). Also, length of stay in the ICU was significantly shorter in the budesonide group (5.3 ± 1.6 days) than controls (6.2 ± 1.7 days) (p = 0.033). Four budesonide patients required re-intubation (13.3%) compared to 11 controls (36.5%, p = 0.023, log-rank (Mantel-Cox) test) (Fig. 1). NIV was used post-extubation in 8 (28%) patients in the budesonide group and in 12 (44%) controls (p = 0.22).

Three patients in the budesonide group and 4 controls received NIV prior to intubation. Five patients (17%) in the budesonide group and 6 controls (22%) died after study.

3.2. Ventilator variables

Pressure support was significantly lower in the budesonide group than in controls at days 3 (8.6 ± 2.6 versus 14.5 ± 2.9 cm H_2O, p = 0.020) and 5 (8.4 ± 2.9 versus 14.6 ± 3.2 cm H_2O, p = 0.025) (Fig. 2A) but not at earlier time points. Similarly, dynamic compliance manifested no differences until days 3 and 5 when the values for the budesonide and control groups were 51.3 ± 3.4 versus 42.5 ± 2.3 ml/-cm H_2O (p = 0.010) and 57.3 ± 4.7 versus 47.3 ± 3.6 ml/cm H_2O (p = 0.001) for the 2 days, respectively (Fig. 2B).

RR at the optimum pressure support was 15.7 ± 6.5 breaths per minute in the budesonide group and 20.7 ± 5.7 breaths per minute in the control group (p = 0.012). During the SBT when the patient was set to spontaneous breathing in the CPAP, mode, VT was 11.8 ± 3.4 ml/kg in the budesonide group and 8.8 ± 3.7 ml/kg in the control group (p = 0.022).

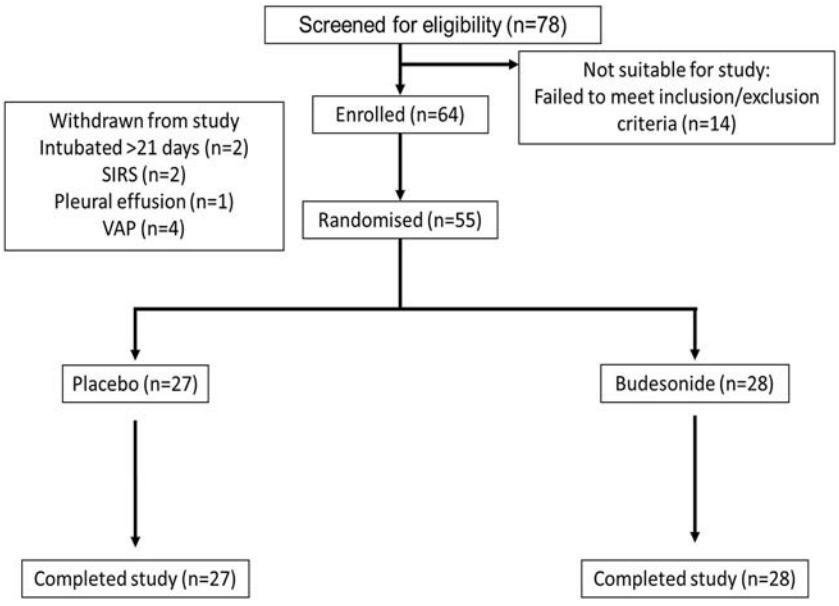
3.3. Effects of budesonide on BAL inflammatory cells

Total and T-cell differential cell counts in BAL fluid are shown in Tables 3 and 4. The total BAL cell count was significantly lower in patients on nebulized budesonide than those in the control group after 5 days (Table 3, p < 0.05). This was related to a significant reduction in the percentage of lymphocytes and neutrophils in the budesonide-treated subjects with a concomitant increase in the percentage of macrophages (Table 3, p < 0.05). There was a greater percentage of CD8 + T-cells compared to CD4 + T-cells in patients at baseline (Table 4) but budesonide reduced each cell type by a similar percentage (Table 4). The total cell count and the percentage of individual CD3 +, CD4 + and CD8 + cell types remained unchanged in the control group (Tables 3 and 4).

3.4. Inflammatory cytokines in BAL

The expression of CXCL8 (Fig. 3A) and IL-6 (Fig. 3B) was significantly increased in BAL fluid of difficult-to-wean COPD patients compared to non-lung disease controls. Levels of these cytokines fell significantly in

Table 2
Consort diagram of invited and recruited subjects.



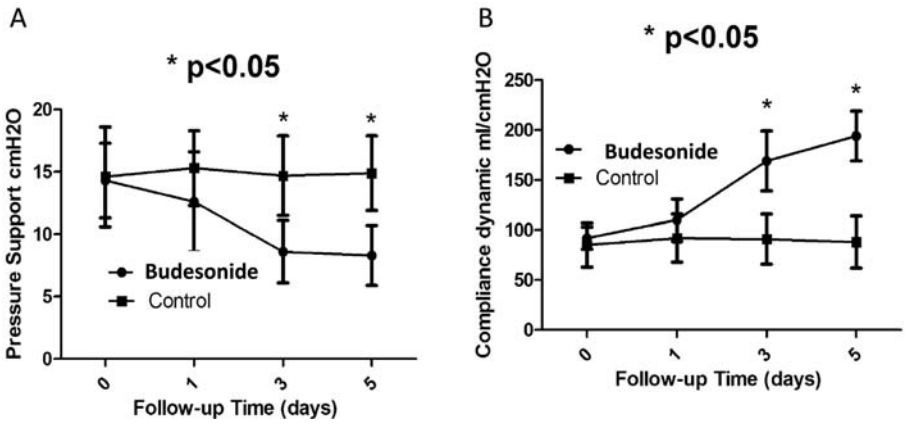


Fig. 2. Effect of budesonide on lung physiology over time. Budesonide caused a time-dependent reduction in pressure support (A) and an increase in dynamic compliance (B) compared to the control group over the 5 day follow-up period. Data are reported as mean ± SEM. *p < 0.05.

Table 3
Total cell counts.

Cell type	Budesonide					Placebo					p-Value day 5
	Pre-treatment	Day 0	Day 1	Day 3	Day 5	Pre-treatment	Day 0	Day 1	Day 3	Day 5	
Total cell count (×1000/μl)	38.7 (35.4)	37.2 (28.4)	36.8 (26.4)	33.7 (23.4)	30.2 (19.4)	39.1 ± 2 (40.1)	37.9 ± 0.2 (38.8)	38.3 ± 0.3 (39.3)	39.2 ± 0.2 (37.9)	38.3 ± 2 (38.4)	0.05
Macrophages (%)	52.6 ± 4.0	58.4 ± 0.28	66.3 ± 0.68	69.4 ± 0.28	72.4 ± 0.44	51.3 ± 2	50.1 ± 3	51 ± 1	49.8 ± 1	49.9 ± 1	0.045
Neutrophils (%)	50.1 ± 2.3	37.3 ± 3.2	32.3 ± 1.2	32.3 ± 1.2	28.3 ± 1.1	48.9 ± 3	48.1 ± 4	49.2 ± 1	50.1 ± 0.1	48.5 ± 2	0.031
Lymphocytes (%)	9.32 ± 0.49	6.32 ± 0.22	4.17 ± 0.88	4.12 ± 0.32	4.32 ± 0.22	12.3 ± 3	11.8 ± 0.3	10.9 ± 0.3	11.3 ± 0.2	12.1 ± 0.2	0.025

Total cell counts are presented as median (95% CI) and specific cell percentages as mean ± SEM.

the budesonide group, reaching significance at days 3 and 5 ($p < 0.05$). In contrast, the expression of TNF-α (Fig. 3C) and of IL-1β (Fig. 3D) was not significantly different in the ventilated patients compared to non-lung disease controls. Furthermore, there was no change in TNF-α and IL-1β BAL fluid cytokine levels over time in the ventilated budesonide-treated patients (Fig. 3). Furthermore, the levels of these BAL mediators did not change over time in the patient control group (CXCL8: 1981 ± 3 at day 0 versus 2001 ± 41 at day 5, IL-6: 68 ± 3 at day 0 versus 58 ± 03 at day 5, TNF-α: 13 ± 3 at day 0 versus 16 ± 1 at day 5, IL-1β: 75 ± 7 at day 0 versus 81 ± 2.1 at day 5).

4. Discussion

In this study, we show that budesonide facilitates weaning from MV in GOLD stage 4 COPD patients in the ICU who are having difficulty weaning. This was accompanied by improved lung dynamic compliance and a reduction in BAL concentrations of CXCL8, IL-6 and of BAL neutrophils. The study was performed in carefully selected patients who were considered to be difficult-to-wean because they had previously failed at least 3 SBTs [1,13].

Budesonide is a non-halogenated synthetic ICS that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. Corticosteroid actions are mediated by the glucocorticoid receptor that is present in the cytoplasm of all cell types [17,18]. The relatively high affinity of budesonide for the glucocorticoid receptor along with its moderate lipophilia and rapid uptake into airway mucosa make budesonide a good anti-inflammatory drug within the airway with negligible systemic absorption [19]. Nebulized budesonide induces topical anti-inflammatory activity while minimizing systemic effects [19]. One study [20] showed that biochemical markers associated with corticosteroid side effects were lower in patients treated with nebulized budesonide than in those given oral prednisolone in the treatment of exacerbations of obstructive pulmonary disease [20].

In this study, nebulized budesonide reduced the expression of CXCL8 and IL-6 but not of TNF-α and IL-1β. All are classic inflammatory cytokines with slightly distinct functions [21]. CXCL8 (IL-8) is released from macrophages and structural cells and is part of the innate immune response to damage- and pathogen-associated molecular patterns (DAMPs and PAMPs). It recruits neutrophils and enhances macrophage phagocytosis. Reductions in BAL CXCL8 levels by budesonide may potentially account for the reductions in BAL neutrophilia observed. IL-6 is an acute phase cytokine known to activate B- and T-cells and has a specific role in the generation of Th17 cells. IL-1β, which is also implicated in neutrophil recruitment and activation and Th17 differentiation, and TNF-α, an acute phase mediator linked to Treg function and responses to infection, are not affected by budesonide. This may reflect

Table 4
Percent of T cells (CD4 and CD8) in BAL before and after budesonide treatment in treated and Placebo control patient.

Cell type	Budesonide					Placebo					p-Value day 5
	Pre-treatment	Day 0	Day 1	Day 3	Day 5	Pre-treatment	Day 0	Day 1	Day 3	Day 5	
CD4 + (%)	53 (50–65)	49 (41–51)	45 (43–51)	39 (34–49)	34 (22–48)	53 (50–65)	55 (51–65)	53 (50–59)	51 (48–65)	52 (47–58)	0.045
CD8 + (%)	44 (44–45)	41 (39–45)	35 (31–44)	33 (30–43)	26 (22–35)	44 (42–49)	43 (41–49)	45 (41–55)	41 (37–45)	47 (40–55)	0.05

Results are presented as median (95% CI).

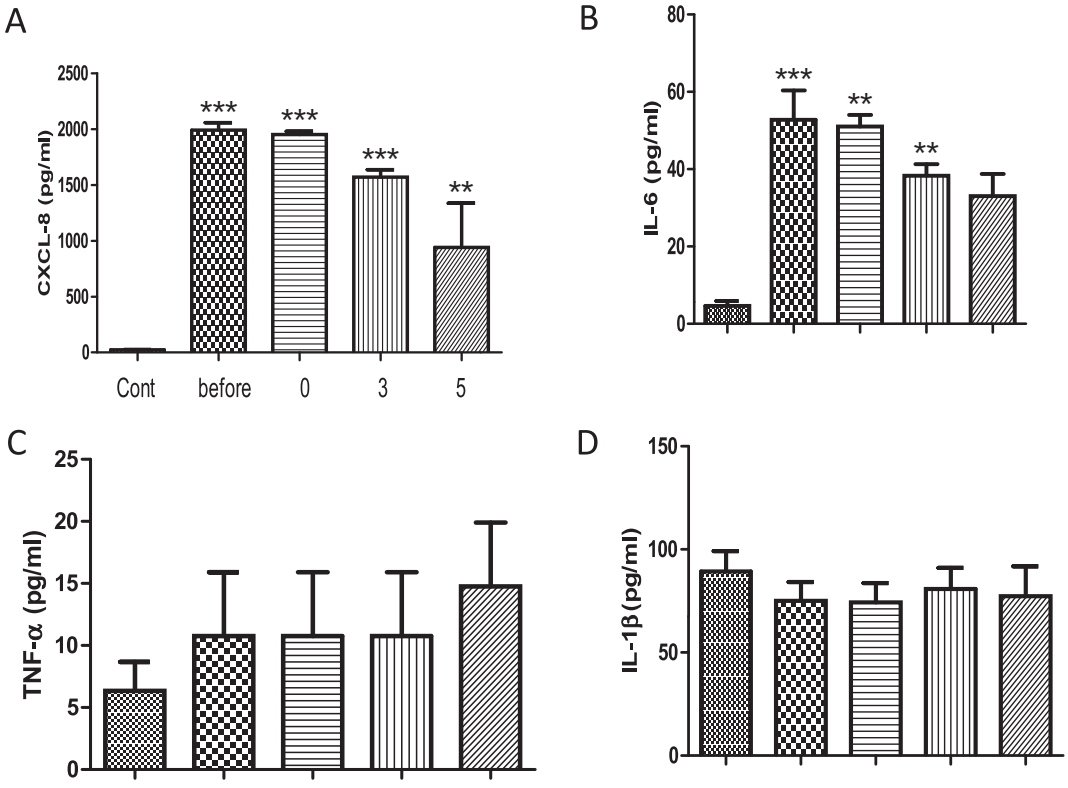


Fig. 3. Effect of budesonide intervention on bronchoalveolar lavage (BAL) inflammatory mediator expression. The expression of CXCL8 (A) and IL-6 (B) was elevated in patients compared to healthy controls and decreased over time. In contrast, the BAL levels of TNF-α (C) and IL-1β (D) were similar to those seen in healthy control subjects and did not vary over time with budesonide. Data are reported as mean ± SEM. *$p < 0.05$; **$p < 0.01$ and ***$p < 0.001$ versus control.

differences in the regulatory mechanisms involved in the expression of these mediators and the ability of the activated glucocorticoid receptor to target specific cell types [17,18].

In our study, budesonide was discontinued once the patient was extubated. This was to isolate the effect of nebulised budesonide on the facilitation of the weaning process during MV and to reduce the potential risk of side effects and adrenal insufficiency. On the other hand, a potential advantage of nebulized budesonide is that it offers topical anti-inflammatory activity while minimizing undesirable systemic effects [17,18]. It is remarkable that the beneficial effects of budesonide in our study were achieved despite background therapy with systemic corticosteroids. This finding suggests that the topical delivery of anti-inflammatory agents to the lung can enhance the effects of systemic delivery, perhaps by reaching receptors inaccessible to systemic drugs or by achieving greater local concentrations. Thus, nebulized budesonide might accelerate the resolution of the inflammatory process that occurs during exacerbations and MV and facilitate weaning by reducing airway resistance and improving lung compliance [22].

Even in normal lungs, it is well known that high tidal volume ventilation contributes to ventilator-induced lung injury (VILI), leading to increased permeability pulmonary edema and elevation of circulating plasma cytokines [24,25]. These circulating cytokines themselves can have adverse effects on endothelial permeability [21,24,25] and attract other immune cells to the site of injury, intensifying the severity of the injury. By suppressing the release of cytokines from airway inflammatory cells, budesonide could limit the severity of injury and speed its resolution. In particular, budesonide use was associated with significantly decreased BAL cytokine levels. This is particularly impressive considering that patients in the budesonide group had VTs of 11.8 ml/kg, a level generally considered to raise the risk of VILI, compared to 8.8 ml/kg in controls. This effect was significant even in the face of background parenteral corticosteroids. Thus, nebulized budesonide appears to break the vicious cycle of inflammation seen in these intubated subjects and facilitate weaning. This would confirm earlier data showing that budesonide given after extubation is effective in reducing the incidence of re-intubation and respiratory distress in adults [22].

Limitations of this study include its performance at a single center and use of ventilator modes that are less often used today. However, we did use lung protective strategy prior to initiation of the weaning phase. Furthermore, we were unable to assess the dose-response relationship of budesonide due to recruitment constraints. Our study was not designed to determine the causal relationship between the alterations in cytokine levels and clinical outcomes, nor was it powered to assess mortality. On the other hand, the study was sufficiently powered to demonstrate shorter duration of MV, an outcome that has been associated with less morbidity and mortality in earlier studies (Nava S, NIV to facilitate weaning in MV COPD pts. Ann Intern Med 1998 [26]). Jet nebulizers, as used in this study, are relatively inexpensive compared with vibrating mesh and ultrasonic nebulizers and in combination with budesonide and the type of ventilators used makes the approach applicable in the developing world where resources to support more sophisticated approaches may be quite limited.

In conclusion, in this pilot study budesonide decreased the time to wean in difficult-to-wean GOLD stage 4 COPD patients receiving invasive mechanical ventilation in the ICU. This was correlated temporally with a reduction in BAL CXCL8 and IL-6 expression and in BAL neutrophils and an improvement in lung dynamic and ventilator variables. We hope that these findings can serve as the basis for further larger studies that will be needed to confirm the present findings, to determine the mechanisms of these anti-inflammatory effects of budesonide on weaning and whether outcomes such as mortality can be altered.

Declaration

The authors have nothing to declare.

Ethics approval and consent to participate

The study was registered at the Shahid Beheshti University clinical trial registry as IRCT20160392059N5.

Availability of data and materials

In case of individual research groups would like to access our raw data, we would be happy to collaborate with individual requests for this. Please contact the corresponding author for further information.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SMH, EM, SAM collected follow-up data, performed data analysis and wrote the manuscript. Data collection was also performed by LB, HRJ, MM, JG, IMA and NSH. Expert statistical guidance was given by IMA. NH, PJB and HRJ provided overall supervision of the study and assisted with revising the manuscript. NSH contributed to the manuscript and provided expert guidance in the field of intensive care. All authors read and approved the final manuscript.

Abbreviations

BAL	bronchoalveolar lavage
COPD	Chronic Obstructive Lung Disease
ICU	intensive care units
SBT	spontaneous breathing trial
VAP	ventilator-associated pneumonia
PEEP	positive end expiratory pressure
PAMP	pathogen-associated molecular patterns

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