Journal of Critical Care 29 (2014) 420–425

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

The potential efficacy of noninvasive ventilation with administration of a neutrophil elastase inhibitor for acute respiratory distress syndrome☆

Kenji Tsushima, MD, PhD [a,b,*], Toshiki Yokoyama, MD, PhD [a], Takuya Matsumura, MD [b], Tomonobu Koizumi, MD, PhD [a], Keishi Kubo, MD, PhD [a], Koichiro Tatsumi, MD, PhD [b] Acute Lung Injury Group in Nagano

[a] First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi Matsumoto Nagano 390–8621 Japan
[b] Department of Respirology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana Chuo-ku Chiba 260–8670 Japan

ARTICLE INFO

Keywords:
Noninvasive ventilation
Berlin definition
Acute respiratory distress syndrome
Neutrophil elastase inhibitor
Pao_2/Fio_2

ABSTRACT

Purpose: Noninvasive ventilation (NIV) can reduce the need for invasive mechanical ventilation. The aim of this investigation was to determine whether the combination of NIV with administration of a neutrophil elastase inhibitor could improve outcome and respiratory conditions in acute respiratory distress syndrome (ARDS)-patients, according to the Berlin definition.
Methods: ARDS-patients were treated with NIV and a neutrophil elastase inhibitor. Patients were classified as having mild, moderate, and severe ARDS. ARDS-patients were divided into survivors and nonsurvivors on day 28 after the induction of NIV.
Results: A total of 47 ARDS-patients received NIV, and 37 of these patients did not require endotracheal intubation. Eight mild, 17 moderate, and 10 severe ARDS-patients were alive on day 28 after the induction of NIV. When ARDS-patients were divided into groups based upon an initial Pao_2/Fio_2 greater or less than 150 torr, the serial changes of both the Pao_2/Fio_2 and the lung injury score improved dramatically in those patients with a Pao_2/Fio_2 >150. The survival ratio showed statistically significant differences in mild and moderate ARDS-patients treated with the neutrophil elastase inhibitor.
Conclusions: Administration of neutrophil elastase inhibitor with NIV may be associated with successful outcome in mild-to-moderate ARDS-patients with initial Pao_2/Fio_2 >150.

1. Introduction

In patients with acute respiratory failure (ARF), early introduction of noninvasive mechanical ventilation may reverse the acute episode, obviating the need for endotracheal intubation [1,2]. Invasive mechanical ventilation is generally required by more than 40% of patients with ARF who initially undergo noninvasive ventilation (NIV) [3]. Most of the complications of invasive mechanical ventilation, that is, ventilator-acquired pneumonia (VAP), are related to endotracheal intubation [4]. NIV preserves the airway defense mechanisms and thus reduces the need for invasive monitoring, and consequently reduces VAP and other nosocomial infections [5]. A multivariate analysis of five randomized studies of patients with ARF of various etiologies showed that NIV was independently associated with a lower risk of intubation and a lower 90-day mortality rate [5].

Acute respiratory distress syndrome (ARDS) represents a severe form of hypoxemic acute respiratory failure. Although data regarding the use of NIV for patients with ARDS are currently limited, the use of NIV may avoid the need for endotracheal intubation in 50% to 86% of such patients [6–8]. Mechanical ventilation is potentially lifesaving in ARDS-patients, as it provides adequate tissue oxygenation and allows the respiratory muscles to rest. While endotracheal intubation has potentially harmful consequences, ARDS-patients need to maintain adequate tissue oxygen levels. In a small feasibility study, NIV has been shown to be effective for the treatment of early ARDS [9].

To date, mechanical ventilation remains the only treatment available for ARDS. In the pathogenesis of ARDS, suppression of the production of neutrophil elastase is one potential treatment target for such patients. Neutrophil elastase inhibitors are believed to exhibit maximal efficacy when they are administered before the development of severe inflammation in the injured lungs. While the therapeutic effect of a neutrophil elastase inhibitor (Elaspol) for ARDS has been demonstrated in some animal models [10,11], 2 human clinical trials have shown contradictory results [12,13]. Accordingly, we prospectively studied patients with newly diagnosed ARDS, according to the Berlin definition [14], who underwent NIV as their first-line intervention. We investigated whether NIV reduced the need for

☆ We had no funds for this study.
* Corresponding author at: Department of Respirology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana Chuo-ku Chiba 260–8670 Japan. Tel.: +81 43 226 2800.
E-mail address: tsushimakenji@yahoo.co.jp (K. Tsushima).

0883-9441/$ – see front matter
http://dx.doi.org/10.1016/j.jcrc.2014.01.018

endotracheal intubation and the ARDS grade for which administration of neutrophil elastase inhibitors was effective with NIV.

2. Methods

2.1. Study design and patient selection

This study was approved by the ethics committee of Shinshu University, and all patients and/or their family gave written informed consent. We performed a prospective study of adult patients admitted with ARDS. This study was conducted at Shinshu University School of Medicine and by the Acute Lung Injury Group of Nagano (ALI Group of Nagano).

The ALI Group of Nagano includes Shinshu University Hospital, Nagano Red Cross Hospital, Shinonoi General Hospital, Iida Municipal Hospital, Suwa Red Cross Hospital, Matsumoto Kyoritsu Hospital, Aizawa Hospital, Shinshu Ueda Medical Center, Nagano Matsushiro General Hospital, Nagano Municipal Hospital, and Nagano Chuo Hospital.

2.2. Subjects

Enrolled patients were diagnosed as having ARDS on admission. All centers applied the same criteria in selecting ARDS-patients as candidates for NIV: (*a*) severe dyspnea at rest; (*b*) respiration rate >30 breaths/minute; (*c*) infiltration in the lung and/or (*d*) fulfilling the diagnostic criteria for ARDS, as outlined in the ARDS Berlin definition [14]. Patients who showed acute hypoxemic respiratory failure received appropriate medication for their underlying diseases, i.e., antibiotics, bronchodilators, vasopressors, or diuretics. Patients with ARDS initially received oxygen via a nasal cannula to maintain an oxygen concentration of more than 60 torr. If they could not maintain oxygen saturation of more than 90% or an arterial oxygen partial pressure of more than 60 torr with 5 L/minute of oxygen via the nasal cannula, we recommended the initiation of NIV with an oronasal mask and bi-level positive airway pressure ventilation (BiPAP) with a BiPAP Vision (Respironics; Murrysville, PA).

Patients were excluded if they had obvious signs of hypoxemia with acute hypercapnic respiratory failure, apparent pulmonary fibrosis, preexisting pulmonary embolism, left heart failure, pulmonary hypertension due to pulmonary thromboemboli or phlebitis based on the findings of color Doppler ultrasonography or enhanced high-resolution computed tomography. Patients were also excluded if they had used NIV at home or had been intubated upon admission. Patient or their family refusal of NIV was an exclusion criterion for this study.

2.3. NIV

The spontaneous timing mode was used in all patients, with a back-up rate of 14 breaths/minute. The expiratory positive airway pressure (EPAP) was started at 4 cmH_2O. The inspiratory positive airway pressure (IPAP) was adjusted to achieve the target level of oxygenation with minimal carbon dioxide partial pressure. The IPAP, EPAP and fraction of inspired oxygen (FIO_2) were adjusted to maintain the SpO_2 > 90% or PaO_2 >60 torr, respiratory rate <35 breaths/minute and pH > 7.3. All patients were maintained continuously on NIV for at least 24 hours after initiation. If the patients were unable to maintain an oxygen saturation of more than 90% or an arterial oxygen partial pressure of more than 60 torr with the BiPAP Vision® Ventilatory Support System after initiation of NIV, we recommended endotracheal intubation to the patients and/or their families. If the patients refused endotracheal intubation, we continued to use NIV, increasing the EPAP setting to 10 cmH_2O and increasing the FIO_2 to 1.0, until the patients recovered from ARDS or died.

Endotracheal intubation was performed in patients with decreased alertness or exhibiting major agitation requiring sedation, clinical signs of exhaustion (active contraction of the accessory muscles with paradoxical abdominal or thoracic motion), hemodynamic instability, cardiac arrest, refractory hypoxemia, or a ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FIO_2) (PF) of less than 100 after treatment with NIV.

2.4. Treatment

In patients who underwent NIV, a selective neutrophil elastase inhibitor (Ono Pharmaceutical Co Ltd, Chuo-ku, Osaka, Japan) was also administered continuously at the physician's discretion. The physician decided whether or not to administer the neutrophil elastase inhibitor, depending on severity of lung injury in each ARDS-patient. The administration of neutrophil elastase inhibitor was initiated as soon as possible after beginning the mechanical ventilation. If the ARDS-patient was severe or near to the severe grades according to the Berlin definition, the physicians declined administration of the neutrophil elastase inhibitor based on the results of the STRIVE study [12]. The infusion rate of the neutrophil elastase inhibitor was 0.20 mg/kg per hour, based upon the results of a late phase II study [15], and administration was continued for up to 14 days. If ARDS-patients did not need NIV or the chest X-ray findings of ARDS-patients showed the improvement of infiltration shadow, these patients stopped to administer the neutrophil elastase inhibitor.

2.5. Radiologic study

Chest X-rays were performed prior to the initiation of NIV and on days 1, 3, 5, 7, and 14 after commencing NIV. The lung injury score, as defined by Murray [16], was independently measured by two pulmonologists.

2.6. Data collection

A standard form was used to collect computerized data from each patient's chart, including admission details, age, sex, blood pressure, heart rate, blood gases on admission, supplemental oxygen use, initial setting of NIV, need for intubation, actual intubation, underlying disease,

Table 1
Comparison of enrolled ARDS patients

	Mild ARDS (n = 10)	Moderate ARDS (n = 22)	Severe ARDS (n = 15)
Age, years	66.4 ± 19.5	73.0 ± 13.1	75.6 ± 6.6
Sex, M/F, n	7/3	18/4	11/4
Direct/Indirect ARDS, n	8/2	15/7	12/3
Initial EPAP, cmH_2O	5.7 ± 1.9	5.9 ± 1.6	6.1 ± 1.2
Initial IPAP, cmH_2O	9.2 ± 3.9	9.6 ± 1.7	9.9 ± 1.6
PF ratio before NIV	242.7 ± 23.1	145.9 ± 26.2	67.5 ± 16.2
Lung injury score	1.30 ± 0.38	2.26 ± 0.22	2.43 ± 0.38
Infection, n	10 (100%)	15 (68%)	14 (93%)
Number of MOF	1.6 ± 1.2	1.7 ± 0.9	1.6 ± 1.2
Time until starting NIV after onset, days	1.8 ±1.5	1.7 ± 2.6	1.9 ± 2.3
Duration of NIV, days	6.4 ± 5.5	10.3 ± 11.2	15.4 ± 2.9
Usage of neutrophil elastase inhibitor, n	9 (90%)	19 (86%)	11 (73%)
Survivors with neutrophil elastase inhibitor, n	7 (78%)	17 (89%)	7 (64%)
Intubation/Refusal intubation, n	2/0 (20%)	4/4 (18%/18%)	4/3 (27%/20%)
Survivors with intubation/Refusal intubation, n	0/0 (0%/0%)	3/0 (75%/0%)	2/0 (50%/0%)
28-day mortality, n	2 (20%)	5 (23%)	5 (30%)
Successful NIV, n	8 (80%)	14 (64%)	8 (53%)

MOF, multiple organ failure.