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ORIGINAL ARTICLE

Impact of steroid medication before hospital admission on barotrauma in mechanically ventilated patients with acute respiratory distress syndrome in intensive care units

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Abstract
Purpose To investigate the association between steroid medication before hospital admission and barotrauma in mechanically ventilated patients with acute respiratory distress syndrome (ARDS).
Methods An observational single-center retrospective study was conducted using patients admitted to the general intensive care unit (ICU) of a university hospital in Japan. We analyzed 149 mechanically ventilated patients with ARDS hospitalized between March 2008 and March 2011. ARDS was identified according to criteria from the Berlin Definition. Barotrauma was defined as pneumothorax, subcutaneous emphysema, or mediastinal emphysema occurring during mechanical ventilation in the ICU. The influence of steroid medication before hospital admission on barotrauma was studied using multiple logistic regression analysis.
Results There were no differences in baseline patient characteristics except for congestive heart failure, peak pressure during mechanical ventilation, and steroid pulse therapy between the barotrauma and non-barotrauma groups. Logistic regression analysis showed that peak pressure $\geq$35 cmH_2O was associated with barotrauma in patients with ARDS [odds ratio (OR), 17.34; $P < 0.01$], whereas steroid medication before hospital admission was not a significant factor for barotrauma (OR, 1.63; $P = 0.51$).
Conclusions Barotrauma in ARDS patients was associated with higher pressure during mechanical ventilation but not with steroid medication before hospital admission.

Keywords Steroid · Barotrauma · Acute respiratory distress syndrome · Intensive care unit

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Introduction

Acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lungs that can result in refractory and life-threatening hypoxemic respiratory failure [1]. Although ARDS was initially described by Ashbaugh et al. in 1967 [2] and its associated mortality has shown a trend of gradual decrease, mortality rates remains higher than 25 % [3, 4]. Supportive therapy such as the management of mechanical ventilation can contribute to improved prognoses of ARDS [5], but there are few evidence-based approaches to treating this disease entity, except in the treatment of underlying diseases. Frequent causes of ARDS include sepsis and pneumonia [6, 7].

The comorbidities in patients with ARDS have been investigated in a previous single-center study using the Charlson comorbidity index [6]; the study showed that patients with ARDS often also presented with diabetes mellitus, cardiovascular disease, chronic kidney disease, solid tumor, chronic pulmonary disease, or connective tissue disease. Many patients are therefore prescribed steroid medication before hospital admission, such as corticosteroids, to control their comorbidities.

Steroid medication before hospital admission can include adverse effects such as infection, diabetes mellitus, peptic ulcer, adrenal cortical insufficiency, and osteonecrosis of the femoral head. In addition, Swift et al. [8] reported that approximately 20 % of patients with chronic obstructive pulmonary disease who were prescribed chronic systemic corticosteroids also had emphysema, compared with approximately 10 % for patients not on corticosteroid medication. Kishi et al. [9] have also reported that a patient administered daily systemic corticosteroids developed pneumomediastinum. We therefore hypothesize that ARDS patients on steroid medication before hospital admission undergoing mechanical ventilation may be at a greater risk of barotrauma when compared with patients not on corticosteroids.

The objective of this study was to investigate the association between steroid medication before hospital admission and barotrauma in mechanically ventilated patients with ARDS.

Materials and methods

Study design

We conducted a retrospective single-center cohort study using data of patients hospitalized between March 2008 and March 2011. This study was approved by the internal ethics review board of our institution. We analyzed all ARDS patients who had undergone mechanical ventilation while admitted to the general intensive care unit (ICU) at Hirakata Hospital, Kansai Medical University. The data used in analysis were obtained from clinical records and administrative claims data.

Patient characteristics

The diagnosis of ARDS was based on criteria stipulated by the Berlin Definition [10]. We excluded from analysis patients younger than 20 years of age and cases with pneumothorax complicating central venous catheter insertion. Patient characteristics such as age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and sequential organ failure assessment (SOFA) score (without neurological score) were collected from clinical records. The neurological score component in the SOFA score was constructed from the Glasgow Coma Scale (GCS). However, the moderate accuracy of central nervous system (CNS) component scores in the SOFA score resulting from sedative drugs in an ICU has been previously reported, with other component scores showing higher accuracy [11]. In our study population, many mechanically ventilated patients had been administered sedative drugs such as propofol, midazolam, and/or dexmedetomidine. Accordingly, we conducted SOFA scoring without including the CNS component for this study.

The Charlson comorbidity index was calculated from codes from the International Classification of Diseases, 10th version [12].

Peak pressure during mechanical ventilation was recorded in all patients, and in the barotrauma group, peak pressure was defined as the highest value before onset of barotrauma. Duration of mechanical ventilation, length of ICU stay, and hospital mortality were calculated as outcome measures.

Definition of barotrauma and steroid medication before hospital admission

Barotrauma was defined as pneumothorax, subcutaneous emphysema, or mediastinal emphysema during mechanical ventilation in the ICU. All administered medications were identified from the clinical records. We limited our analysis to corticosteroids that had been prescribed for internal use and excluded those for external use. Because it was difficult to ascertain the direct period of medication administration, long-term therapy was identified as medications administered up to the point just before hospitalization.

Statistical analysis

Continuous variables are analyzed as means and standard deviations and categorical variables as percentages (%). Univariate analyses were performed using the Student's t test for analysis of continuous variables and the c^2 test for categorical variables, with P values less than 0.1 regarded as significant.

To evaluate the association between barotrauma and patient characteristics, multiple logistic regression analysis was performed using barotrauma incidence as the dependent variable in ARDS patients identified according to the Berlin Definition criteria. The explanatory variables were steroid medication before hospital admission and those showing statistical significance in the univariate analyses. Statistical significance in the regression analyses were identified using P values less than 0.05. Discrimination of the model was specified by the C statistic. All analyses were performed using JMP Version 10.0 (SAS Institute, Cary, NC, USA).

Results

The original data used for this study were obtained from 4,539 ICU patients. Of these, 157 (3.5 %) were identified as ARDS cases; 8 patients (5.1 %) fulfilled the exclusion criteria, leaving 149 patients (94.9 %) for analysis. Barotrauma was

Table 1 Patient background characteristics and outcomes

ARDS patients as defined by Berlin Definition criteria	Barotrauma ($n = 16$)	Non-barotrauma ($n = 133$)	P value
Patient background			
Age (years)	67.6 ± 11.6	67.2 ± 11.6	0.89
Gender (male, %)	56.3	66.2	0.42
APACHE II score	30 (23–35)	29 (23.5–33)	0.69
SOFA score (without CNS score)	6.5 (5.3–8.8)	8 (6–10)	0.13
Charlson comorbidity index score (%)			
0	12.5	15.9	
1	18.8	12.1	
2	31.3	22.7	
3	12.5	15.2	0.92
4	12.5	11.4	
5	12.5	10.6	
≥6	0	12.1	
Diagnostic categories of Charlson comorbidity index (%)			
Acute myocardial infarction	0	2.3	1.00
Congestive heart failure	18.8	4.5	0.06
Peripheral vascular disease	12.5	5.3	0.25
Cerebral vascular accident	0	7.5	0.60
Dementia	0	0.8	1.00
Pulmonary disease	12.5	11.3	1.0
Connective tissue disorder	12.5	4.5	0.21
Peptic ulcer	6.3	7.5	1.00
Liver disease	6.3	6.8	1.00
Diabetes	25.0	18.1	0.50
Diabetes complications	6.3	3.8	0.50
Paraplegia	0	0	1.00
Renal disease	12.5	12.0	1.00
Cancer	43.8	55.6	0.43
Metastatic cancer	0	15.8	0.13
Severe liver disease	0	0	1.00
HIV	0	0	1.00
Airway pressure release ventilation (%)	93.8	92.5	1.00
Peak pressure during mechanical ventilation (%)			
<30 cmH_2O	6.3	44.4	
≥30 cmH_2O, <35 cmH_2O	31.3	34.6	<0.001
≥35 cmH_2O	62.5	21.1	
PaO_2/F_IO_2 ratio	174.2 ± 50.0	169.2 ± 69.4	0.78
ARDS class (%)			
Mild	31.3	33.8	1.00
Moderate to severe	68.8	66.2	
Low-dose hydrocortisone (%)	43.8	37.6	0.71
Steroid pulse therapy (%)	18.8	5.3	0.08
Steroid medication before hospital admission (%)	25.0	10.5	0.11
Barotrauma (%)			
Pneumothorax	25.0	–	
Subcutaneous emphysema	56.3	–	
Mediastinal emphysema	6.3	–	
Subcutaneous and mediastinal emphysema	12.5	–	
Outcome measures			
Duration of mechanical ventilation (days)	31.8 ± 23.5	16.7 ± 15.7	<0.01
Length of ICU stay (days)	32.0 ± 23.1	16.0 ± 12.7	<0.01
Hospital mortality (%)	62.5	45.9	0.29

Continuous variable: mean ± SD; categorical variable: percentage

ARDS acute respiratory distress syndrome, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* sequential organ failure assessment, *CNS* central nervous system; *ICU* intensive care unit

observed to occur in 16 patients: 4 (22.2 %) of 18 patients using steroid medication before hospital admission and 12 (9.2 %) of 131 patients without this medication ($P = 0.11$).

Patient background characteristics are shown in Table 1. In ARDS patients identified according to the Berlin Definition criteria, there were no significant differences between the barotrauma and non-barotrauma groups except for congestive heart failure, peak pressure during mechanical ventilation, and steroid pulse therapy ($P = 0.06$, $P < 0.001$, and $P = 0.08$, respectively). In both groups, men comprised more than half of all patients. Illness severity scores were similar for both groups: APACHE II score of 30 in the barotrauma group and 29 in the non-barotrauma group, and SOFA score (without CNS score) of 6.5 in the barotrauma group and 8 in the non-barotrauma group. The most common diagnostic category of the Charlson comorbidity index was cancer, followed by diabetes. Pulmonary diseases such as emphysema and asthma were not significantly different between the barotrauma and non-barotrauma groups. The most common form of barotrauma was subcutaneous emphysema ($n = 9$, 6.0 % of 149 ARDS cases), followed by pneumothorax ($n = 4$, 2.7 % of 149 ARDS cases).

Outcome measures

For the ARDS cases identified according to the new definition, there was no significant difference in hospital

mortality between the barotrauma and non-barotrauma groups (62.5 % and 45.9 %, respectively; $P = 0.29$). However, the duration of mechanical ventilation and length of ICU stay were nearly twice longer in the barotrauma group than those of the non-barotrauma group ($P < 0.01$ for both variables).

Multiple logistic regression model for barotrauma incidence

We used the explanatory variables described in Table 2 for the multiple logistic regression analysis. After adjusting for these variables, the odds ratios (OR) for the risk factors were calculated (Table 3). Steroid medication before hospital admission was not significantly associated with barotrauma during mechanical ventilation [OR, 1.63; 95 % confidence interval (CI), 0.35–6.44; $P = 0.51$]. The only significant risk factor of barotrauma was peak pressure ≥35 cmH_2O during mechanical ventilation (OR, 17.34; 95 % CI, 3.00–329.47; $P < 0.01$). The C statistic for this regression model was 0.82, indicating a moderately high level of discrimination.

Table 2 Explanatory variables used in multiple regression analysis of barotrauma incidence

Explanatory variables	Format
Peak pressure during mechanical ventilation	
<30 cmH_2O (Reference)	YES = "C"
≥30 cmH_2O, <35 cmH_2O	YES = "B"
≥35 cmH_2O	YES = "A"
Steroid medication before hospital admission	YES = 0, NO = 1
Congestive heart failure	YES = 0, NO = 1
Steroid pulse therapy	YES = 0, NO = 1

Table 3 Results of multiple regression analysis of barotrauma incidence ($n = 149$)

Explanatory variable	Odds ratio	95 % CI	P value
Peak pressure during mechanical ventilation[a]			
≥30 cmH_2O, <35 cmH_2O	6.60	0.99–130.40	0.05
≥35 cmH_2O	17.34	3.00–329.47	<0.01
Steroid medication before index hospital admission	1.63	0.35–6.44	0.51
Congestive heart failure	3.23	0.51–18.53	0.20
Steroid pulse therapy	2.73	0.47–13.67	0.25

ARDS patients identified according to the Berlin Definition

CI confidence interval

[a] Reference category: <30 mmHg

Discussion

This study showed that steroid medication before hospital admission was not statistically associated with barotrauma during mechanical ventilation in patients with ARDS. The findings that pulmonary diseases (including chronic pulmonary disease and asthma) and connective tissue diseases (including systemic lupus erythematosus and rheumatoid arthritis) were not risk factors of barotrauma were surprising. A previous study identified the risk factors for barotrauma in mechanically ventilated patients as asthma, chronic interstitial lung disease, previous ARDS, pneumonia, and ARDS that developed during mechanical ventilation [13]. In this study, however, the Charlson comorbidity index was used to identify underlying diseases, so it is possible that we may have overlooked diseases not included in this index.

Patients with barotrauma have been shown to have no differences compared with non-barotrauma patients in ventilator parameters such as peak pressure, positive end-expiratory pressure (PEEP), and tidal volume [13]. Weg et al. [14] observed no relationship with either high airway pressures or high tidal volumes and the development of barotrauma in a prospective trial of patients with ARDS. In contrast, some researchers have suggested that high PEEP levels are associated with the development of barotrauma [15–18]. However, a recent review comparing high and low PEEP levels in mechanically ventilated ARDS patients showed no significant difference in barotrauma incidence [19]. Although we did not investigate mean airway pressure and PEEP levels because of the airway pressure release ventilation mode used in the majority of our participants, our results indicate that a high peak airway pressure (≥35 cmH_2O) was associated with barotrauma in mechanically ventilated ARDS patients. This finding is consistent with the findings of Boussarsar et al. [20], who have also shown that the peak airway pressure ≥35 cmH_2O is a risk factor of barotrauma. The incidence of pneumothorax in our study was approximately 2.6 %, which was a better outcome when compared with the incidence of a previous study (6.9 %) [14].

Long-term systemic steroid therapy has several documented adverse effects, such as cosmetic changes, impaired glucose tolerance, gastroduodenal ulceration, hypertension, osteonecrosis, and myopathy [21–23]. A previous case report noted that chest wall emphysema in a patient was likely caused by corticosteroid therapy for rheumatoid arthritis [24]. In addition, chronic obstructive pulmonary disease patients taking chronic systemic corticosteroids had a higher incidence of emphysema compared with patients not taking corticosteroids [8]. Our results, however, showed that patients with ARDS taking chronic corticosteroids did not show any statistical association with barotrauma expression.

The Charlson comorbidity index has been used as a robust tool for observational studies [12]. In critical care patients, Christensen et al. [25] suggested that this index can predict short- and long-term mortality as well as physiology-based scores such as APACHE II, simplified acute physiology score (SAPS) II, and SAPS III. For this reason, we included the Charlson comorbidity index in the severity scores.

We applied airway pressure release ventilation (APRV) for the majority of ARDS patients in this study. The APRV mode, which is characterized by achieving lower peak airway pressure and higher mean airway pressure compared with pressure support ventilation, has been shown to result in more effective gas exchange [26, 27]. Accordingly, we have introduced the APRV mode for ARDS patients to achieve open lung conditions and reduce differences between peak airway pressure and plateau airway pressure. The barotrauma incidence rate in the ARDS patients of this study was similar to those of previous studies [28]. Our study has several limitations. First, we cannot determine the accuracy of comorbidity coding in the patients. These coding diagnoses can be input by doctors and nurses at the point of diagnosis, rather than at or after discharge, which improves the reliability of the data. Therefore, this may reduce cases of miscoding or upcoding of comorbidities. We also attempted to reduce coding errors by using a combination of clinical records and administrative data.

Second, the relatively small number of patients with barotrauma in this study may affect the calibration of the regression model. However, we minimized the number of explanatory variables to four variables in the regression model. In addition, the model showed a moderately high level of discrimination. Therefore, we believe that the OR of steroidal medication estimated from the regression model has validity.

Finally, the present study was a single-center study and therefore had a relatively small population of cases with barotrauma and ARDS. This study included 18 cases that had been administered steroid therapy before hospital admission and 131 cases without this medication, and the difference in incidence of barotrauma between the two groups was 13.1 %. The β value was calculated to be 0.63, and type II error may therefore have occurred to some extent. External validation using a large population database and the use of multiple institutions are necessary to further investigate the results of this study.

In conclusion, this study is significant in that it is the first to investigate the influence of long-term therapy with systemic corticosteroids for ARDS patients. Steroid medication before hospital admission was not a significant risk factor for barotrauma in mechanically ventilated patients with ARDS. Instead, the results showed that the peak pressure during mechanical ventilation is an important predictor of barotrauma incidence.

Conflict of interest The authors declare no conflicts of interest.

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