RESPIRATORY CARE Paper in Press. Published on August 28, 2018 as DOI: 10.4187/respcare.06289

Continuous Neuromuscular Blockade and Mortality in Subjects With Exacerbation of Idiopathic Interstitial Pneumonias

Hideyuki Mouri MD, Taisuke Jo MD PhD, Nobuaki Michihata MD MPH, Hiroki Matsui MPH, Kiyohide Fushimi MD PhD, and Hideo Yasunaga MD PhD

BACKGROUND: Exacerbation of idiopathic interstitial pneumonias (IIPs) requiring mechanical ventilation is associated with high mortality. However, evidence for the optimal management strategy in patients on mechanical ventilation for exacerbation of IIPs is scarce. This study aimed to evaluate the association between continuous rocuronium infusion and in-hospital mortality in patients with exacerbation of IIPs requiring mechanical ventilation. METHODS: The effect of continuous rocuronium infusion was retrospectively analyzed using data in the Japanese Diagnosis Procedure Combination in-patient database from July 2010 to March 2016. We compared 28-d mortality between the continuous rocuronium infusion group (intravenous doses of ≥ 150 mg/d) and the control group using 1:4 propensity score matching. RESULTS: We enrolled 4,925 subjects. Propensity score matching yielded 66 subjects in the rocuronium group and 264 subjects in the control group. There was no significant difference in 28-d mortality (rocuronium vs control, 52% vs 44%, *P* = .31) or in-hospital mortality (68% vs 61%, *P* = .28) between the 2 groups. CONCLUSIONS: Continuous rocuronium infusion was not significantly associated with decreased mortality in patients with exacerbation of IIPs requiring mechanical ventilation. *Key words: idiopathic interstitial pneumonias; neuromuscular nondepolarizing agents; ventilator-induced lung injury; intensive care unit; positive-pressure respiration; mortality; pneumothorax.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Idiopathic interstitial pneumonias (IIPs) are a group of acute and chronic, progressive, diffuse parenchymal lung diseases with unknown etiology. A multidisciplinary approach is taken to classify IIPs into 6 major types that include 2 fibrosing IIPs (idiopathic pulmonary fibrosis and idiopathic nonspecific interstitial pneumonia), as well as 2 rare IIPs and unclassifiable IIPs. Acute interstitial pneumonia and exacerbation of the 2 fibrosing IIPs represent rapid progression. The pathological findings of rapidly progressive IIPs involve diffuse alveolar damage, which is also found in ARDS.[1] Exacerbation of idiopathic pulmonary fibrosis requiring mechanical ventilation is associated with high mortality.[2] Therefore, recent guidelines recommend that the majority of these patients should not receive mechanical ventilation.[3]

Several ventilation strategies for patients with ARDS are advocated to avoid ventilation-induced lung injury (VILI). In particular, adjunct treatment with neuromuscular blocking agents (NMBAs) in patients with severe ARDS has been shown to improve oxygenation and survival rate.[4,5]

Drs Mouri and Yasunaga and Mr Matsui are affiliated with the Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan. Drs Jo and Michihata are affiliated with the Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. Dr Fushimi is affiliated with the Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan.

The authors disclose relationships with the Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports, Science and Technology, and the Japan Agency for Medical Research and Development.

Correspondence: Hideyuki Mouri MD, Department of Clinical Epidemiology and Health Economics, School of Public Health, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: hmouri-tky@umin.ac.jp.

DOI: 10.4187/respcare.06289

RESPIRATORY CARE Paper in Press. Published on August 28, 2018 as DOI: 10.4187/respcare.06289

In one study, continuous infusion of cisatracurium for 48 h improved 90-d survival and decreased the incidence of barotrauma without increasing ICU-acquired weakness in subjects with ARDS.[4] Recently, NMBAs have been commonly used in patients with severe ARDS to alleviate ventilation asynchrony.[6,7]

However, there is little evidence regarding mechanical ventilation strategies for patients with IIPs. The strategies for ARDS are extrapolated to management of IIPs without critical evaluation, even though the pathophysiology of IIPs is different from that of ARDS. Patients with IIPs requiring mechanical ventilation should be managed cautiously because VILI is more likely to occur in IIPs than in ARDS. The respiratory system elastance is generally high in patients with IIPs, and high alveolar pressure is required during mechanical ventilation.[8] NMBAs can possibly control the plateau pressure to avoid overdistention of alveoli. However, to our knowledge, there are no published data on the effect of NMBAs during mechanical ventilation for mortality reduction in patients with IIPs.

This study aimed to examine the association between NMBAs and mortality in patients with exacerbation of IIPs requiring mechanical ventilation using data from a national in-patient database in Japan.

QUICK LOOK

Current knowledge

Respiratory care professionals may need to intubate patients with idiopathic interstitial pneumonias when exacerbated without a definitive diagnosis of idiopathic pulmonary fibrosis. Continuous infusion of neuromuscular blocking agents in patients with severe ARDS was shown to improve oxygenation and survival rate.

What this paper contributes to our knowledge

In this retrospective cohort study, we evaluated whether the use of continuous rocuronium infusion may provide therapeutic benefits in patients mechanically ventilated for exacerbation of idiopathic interstitial pneumonias. Continuous rocuronium infusion was not significantly associated with decreased mortality in these patients and therefore may not be recommended.

Methods

Data Source

We conducted a retrospective cohort study using data in the Japanese Diagnosis Procedure Combination database from July 1, 2010, to March 31, 2016.[9] The database is a nationwide in-patient administrative claims and discharge database for all in-patients discharged from > 1,000 participating hospitals, representing 50% of acute-care hospitalizations in Japan. The database includes the following information: age; sex; primary diagnosis, comorbidities on admission, and post-admission complications encoded with International Classification of Diseases-10th Revision (ICD-10) codes[10] and written in Japanese; dates of hospital admission, discharge, surgery, bedside procedures, and drugs administered; daily dosages of drugs; and discharge status. All interventional or surgical procedures are coded with original Japanese codes. The Institutional Review Board of The University of Tokyo approved this study. Informed consent was waived because of the anonymous nature of the data.

Subject Selection

We selected subjects age ≥ 18 y who were diagnosed with IIPs (ICD-10 codes: J841, J849) and required mechanical ventilation (ICD-10 code: J045) in the ICU. The following patients were excluded: those who were intubated for ≥ 8 d after admission; those who received lung transplantation during hospitalization; those who were discharged or died within 3 d after initiation of mechanical ventilation to avoid immortal time bias[11]; those who had rheumatic diseases or connective tissue diseases (ICD-10 codes: M05, M06, M30–M36); those who received surgery under general anesthesia before intubation; those who received cyclophosphamide; and those who received plasma exchange. We divided the subjects into 2 groups: subjects who received continuous rocuronium infusion (rocuronium group) and those who received only a single shot of rocuronium at intubation or did not receive rocuronium (control group). We defined the rocuronium group as subjects who received intravenous doses of ≥ 150 mg/d.

Baseline Characteristics and Outcomes

Subject baseline characteristics included age, sex, body mass index, Charlson comorbidity index, Japan Coma Scale score, smoking status (never, former, or current smoker), type of hospital (academic, non-academic), underlying malignancy, continuous renal replacement therapy, plasma exchange, hemoadsorption, extracorporeal membrane oxygenation, pulse steroid, sivelestat, cyclophosphamide, fentanyl, morphine, midazolam, dexmedetomidine, and propofol. Body mass index was classified into 4 categories (< 18.5, 18.5–24.9, 25.0–29.9, and ≥ 30 kg/m^2). The Japan Coma Scale correlates with the Glasgow Coma Scale[12,13]: 0, alert; 1, not fully alert but awake without stimulation; 2, aroused by stimulation; 3, coma. The primary outcome was 28-d

RESPIRATORY CARE Paper in Press. Published on August 28, 2018 as DOI: 10.4187/respcare.06289

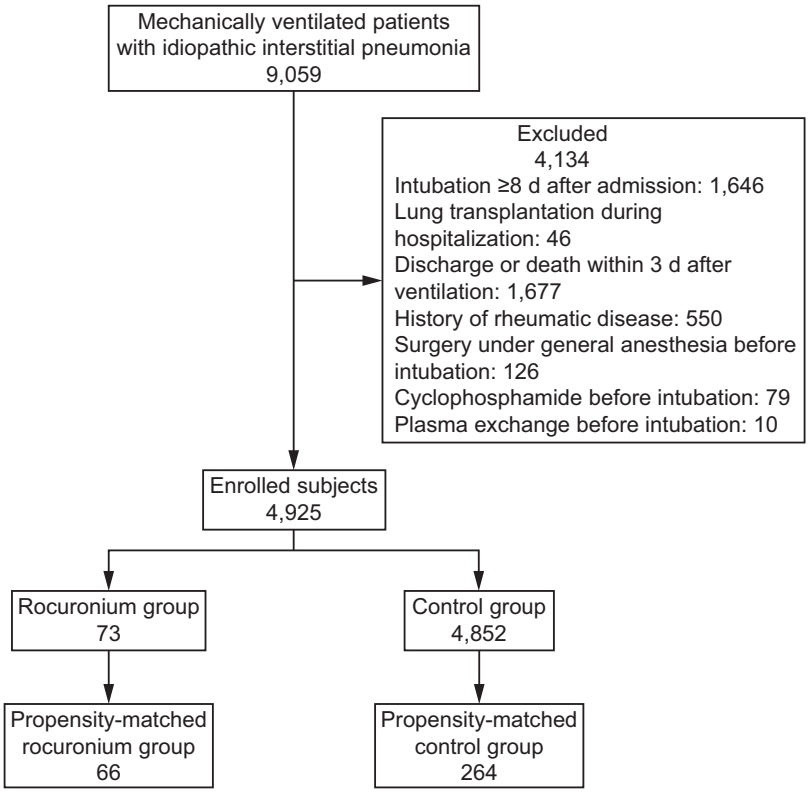

Fig. 1. Flow chart.

mortality. The secondary outcomes were in-hospital mortality and occurrence of pneumothorax requiring chest tube drainage.

Statistical Analysis

We compared subjects' background characteristics, and in-hospital treatments, procedures, and outcomes between the rocuronium and control groups. We performed a propensity-matched analysis to adjust for measured confounding factors. To estimate the propensity score, a logistic regression model was used with the baseline independent variables. The factors that could potentially affect the decision to use continuous rocuronium infusion were included as independent variables. The covariates introduced in the logistic regression model were age; sex; Charlson comorbidity index; smoking index; body mass index; cancer; sepsis; and use of pulse methylprednisolone, sivelestat, fentanyl, morphine, midazolam, dexmedetomidine, propofol, continuous renal replacement therapy, hemoadsorption, and extracorporeal membrane oxygenation. The C-statistic for evaluating the discrimination of the model was calculated. We performed 1:4 propensity-score matching between those with and without continuous rocuronium infusion using nearest-neighbor matching with replacement. Propensity scores were matched using a caliper with a width of 0.25 SD. We examined the balance in baseline variables using standardized differences, with differences of $> 10\%$ regarded as imbalanced. We estimated the relative risk using a modified Poisson regression model combined with generalized estimating equations to account for the correlation of repeated measurements.[14] Two-tailed values of $P < .05$ were considered significant. The statistical analyses were performed using IBM SPSS Statistics for Windows version 23.0 (IBM, Armonk, New York) and Stata statistical software version 15 (Stata, College Station, Texas).

Results

Figure 1 shows the flow chart for subject selection. We identified 9,059 patients with IIPs in the database. Of these, 4,925 subjects were enrolled (73 in the rocuronium group and 4,852 controls). We then generated 66 and 264 propensity score-matched pairs, respectively. The C-statistic was 0.83.

Table 1 shows the baseline demographics, preexisting medical conditions, and procedures in the unmatched and propensity score-matched groups. In the unmatched groups, subjects were more likely to receive continuous rocuronium infusion if they were younger or male, had a higher Japan Coma Scale score, were treated at an academic hos-

RESPIRATORY CARE Paper in Press. Published on August 28, 2018 as DOI: 10.4187/respcare.06289

Table 1. Baseline Characteristics of the Subjects in the Unmatched and Propensity Score-Matched Groups

	Unmatched Groups			Propensity-Score Matched Groups		
	Rocuronium	Control	Standardized Difference (%)	Rocuronium	Control	Standardized Difference (%)
Age, mean (SD)	68.6 (12.1)	74.5 (9.5)	5.4	70.0 (11.0)	70.7 (11.6)	5.5
Male, *n* (%)	59 (81)	3408 (70)	24.7	53 (80)	205 (78)	6.5
Body mass index, *n* (%)						
< 18.5 kg/m^2	9 (12)	541 (11)	3.7	7 (11)	27 (10)	1.2
18.5–24.9 kg/m^2	35 (48)	2632 (54)	12.3	34 (51)	123 (47)	0.9
25–29.9 kg/m^2	13 (18)	794 (16)	3.4	13 (20)	53 (20)	0.9
≥ 30 kg/m^2	5 (6.8)	168 (3.5)	15.4	4 (6.1)	16 (6.1)	0
Missing	11 (15)	717 (15)	0.8	9 (14)	45 (17)	9.5
Charlson comorbidity index, *n* (%)						
0	44 (60)	2460 (51)	18.4	39 (58)	144 (55)	6.1
1	7 (9.6)	591 (12)	8.0	7 (11)	34 (13)	7.1
2	15 (21)	1232 (25)	11.0	15 (23)	67 (25)	6.2
≥ 3	7 (9.6)	569 (12)	6.5	6 (9.1)	19 (7.2)	6.9
Japan Coma Scale score, *n* (%)						
Alertness	53 (73)	3465 (71)	2.1	48 (71)	189 (72)	0.8
Dizziness	5 (6.8)	845 (17)	32.3	5 (7.6)	25 (9.5)	6.8
Somnolence	2 (2.7)	233 (4.8)	10.6	2 (3)	4 (1.5)	10.2
Coma	13 (18)	309 (6.4)	35.8	12 (18)	46 (17)	2.0
Smoking, *n* (%)						
Nonsmoker	29 (40)	2152 (44)	9.2	28 (42)	117 (44)	3.8
Former or current smoker	26 (36)	1964 (44)	10.1	24 (36)	90 (34)	4.8
Unspecified	18 (25)	736 (15)	23.9	14 (21)	57 (22)	0.9
Academic hospital, *n* (%)	21 (29)	806 (17)	29.2	16 (24)	52 (20)	10.9
Underlying malignancy, *n* (%)	6 (8.2)	621 (13)	14.8	6 (9.1)	21 (8.0)	4.1
Sepsis, *n* (%)	4 (5.5)	186 (3.8)	8.0	3 (4.5)	11 (4.2)	1.8
Continuous renal replacement therapy, *n* (%)	1 (1.4)	75 (1.5)	1.9	0 (0)	0 (0)	0
Hemoadsorption, *n* (%)	4 (5.5)	109 (2.2)	15.6	4 (6.1)	12 (4.5)	6.7
Extracorporeal membrane oxygenation, *n* (%)	7 (9.6)	15 (0.3)	43.8	1 (1.5)	4 (1.5)	0
Pulse steroid, *n* (%)	23 (32)	1814 (37)	13.4	23 (35)	94 (36)	1.6
Sivelestat, *n* (%)	23 (32)	1141 (24)	17.4	18 (27)	88 (33)	13.2
Fentanyl, *n* (%)	31 (43)	871 (18)	54.8	25 (38)	101 (39)	1.6
Midazolam, *n* (%)	39 (53)	1437 (30)	49.5	37 (55)	138 (53)	3.8
Dexmedetomidine, *n* (%)	19 (26)	769 (16)	25.3	16 (24)	59 (22)	4.5
Propofol, *n* (%)	35 (48)	1040 (21)	57.6	29 (44)	122 (46)	3.8

In the unmatched groups, $n = 73$ subjects received rocuronium, whereas $n = 4,852$ subjects served as control. In the propensity-score matched groups, $n = 66$ subjects received rocuronium, whereas $n = 264$ subjects served as control.

pital, or required more extracorporeal membrane oxygenation, fentanyl, midazolam, dexmedetomidine, or propofol. After 1:4 matching, the baseline subject characteristics were well balanced between the 2 groups.

In the propensity score-matched groups, the overall 28-d mortality and in-hospital mortality were 46% (151 of 330 subjects) and 62% (206 of 330 subjects), respectively. Table 2 shows the 28-day mortality, in-hospital mortality, and proportion of pneumothorax, as well as the relative risks. There was no significant difference in 28-d mortality (rocuronium vs control, 52% vs 44%, $P = .31$), in-hospital mortality (68% vs 61%, $P = .28$), or the proportion of pneumothorax (7.6% vs 3.4%, $P = .23$).

Discussion

We did not find any significant difference in 28-d mortality, in-hospital mortality, or proportion of pneumothorax between the continuous rocuronium infusion group and the control group in subjects with exacerbation of IIPs in our propensity score analysis using data from a nationwide database. To our knowledge, this study is the first to examine the effects of continuous rocuronium infusion during invasive mechanical ventilation in patients with exacerbation of IIPs. In the study, subjects with exacerbation of IIPs requiring mechanical ventilation had high mor-

Table 2. Outcomes in the Propensity-Matched Groups

	Rocuronium	Control	Relative Risk (95% CI)	*P*
28-d mortality, *n* (%)	34 (52)	117 (44)	1.07 (0.94–1.23)	.31
In-hospital mortality, *n* (%)	45 (68)	161 (61)	1.07 (0.94–1.23)	.28
Pneumothorax, *n* (%)	5 (7.6)	9 (3.4)	1.04 (0.97–1.12)	.23

Rocuronium, $n = 66$; Control, $n = 264$.

tality. This finding is consistent with results from a previous study.[15]

A previous randomized control trial in subjects with moderate to severe ARDS revealed that cisatracurium infusion for a 48-h period improved 90-d adjusted mortality.[5] In other randomized control trials, the use of cisatracurium had anti-inflammatory effects in subjects with ARDS.[16,17] A recent propensity score-matched analysis showed that cisatracurium was not associated with a difference in mortality compared with vecuronium in subjects at risk for and with ARDS.[18] Taken together, it remains unknown whether cisatracurium alone is associated with decreased mortality, or whether aminosteroid NMBAs such as vecuronium have identical effects to cisatracurium in ARDS patients in terms of mortality reduction.

Our study revealed that continuous rocuronium infusion was not associated with reductions in mortality in subjects with exacerbation of IIPs. Furthermore, the results suggested that continuous rocuronium infusion may not prevent VILI, and there was no significant difference in occurrence of pneumothorax between subjects with and without continuous rocuronium infusion. Occurrence of pneumothorax can be regarded as an indicator of VILI. Even if ventilator asynchrony occurs in patients with exacerbation of IIPs, continuous rocuronium infusion may not be useful for inhibiting VILI. Recent guidelines recommend maintaining a light, rather than deep, level of sedation in ICU patients.[19] However, deep sedation was required during continuous rocuronium infusion. The necessity for deep sedation may have had an effect on the insignificant association between continuous rocuronium infusion and mortality.

The strength of our study was the relatively large number of subjects with IIPs. However, the study has several limitations. First, it was a retrospective study. Unmeasured confounders remained even after adjustment for measured confounders by propensity score-matching analysis. Second, the issue of how to identify interstitial lung disease patients remains a matter of debate. In idiopathic pulmonary fibrosis, exacerbation is defined as acute, clinically important deterioration of unidentifiable cause in patients with underlying idiopathic pulmonary fibrosis.[20] The clinical course of exacerbation in patients with idiopathic pulmonary fibrosis may differ from that in patients with other IIPs. However, we could not obtain detailed information about preceding clinical conditions, as well as time since diagnosis of underlying IIPs. In addition, we could not control for the severity of previous exacerbation states, such as pulmonary function test and 6-min walk test data. Third, we could not obtain information on P_{aO_2}/F_{IO_2} ratios, Acute Physiology and Chronic Health Evaluation scores, and mechanical ventilation management such as ventilator settings, fluid management, and other mechanical ventilation strategies.

Conclusions

This study did not show a significant association between continuous rocuronium infusion and decreased mortality in subjects with IIPs requiring mechanical ventilation. Continuous rocuronium infusion may not be recommended for these patients.

ACKNOWLEDGMENT

We thank Dr Tomohiro Shinozaki, Assistant Professor, Department of Biostatistics, The University of Tokyo, for his helpful advice on statistical analyses.

REFERENCES

1. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188(6):733-748.
2. Mallick S. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. Respir Med 2008; 102(10):1355-1359.
3. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788-824.
4. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107-1116.
5. Gainnier M, Roch A, Forel JM, Thirion X, Arnal JM, Donati S, Papazian L. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004;32(1):113-119.
6. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute

respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315(8):788-800.
7. Torbic H, Bauer SR, Personett HA, Dzierba AL, Stollings JL, Ryder LP, et al. Perceived safety and efficacy of neuromuscular blockers for acute respiratory distress syndrome among medical intensive care unit practitioners: a multicenter survey. J Crit Care 2017;38:278-283.
8. Nava S, Rubini F. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. Thorax 1999; 54(5):390-395.
9. Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Matsuda S. Clinical epidemiology and health services research using the Diagnosis Procedure Combination Database in Japan. Asian Pacific J Dis Manag 2015; 7(1-2):19-24.
10. Bramer GR. International statistical classification of diseases and related health problems. Tenth revision. World Health Stat Q 1988; 41(1):32-36.
11. Ravi B, Croxford R, Austin PC, Lipscombe L, Bierman AS, Harvey PJ, et al. The relation between total joint arthroplasty and risk for serious cardiovascular events in patients with moderate-severe osteoarthritis: propensity score matched landmark analysis. BMJ 2013; 347:f6187.
12. Ono K, Wada K, Takahara T, Shirotani T. Indications for computed tomography in patients with mild head injury. Neurol Med Chir (Tokyo) 2007;47(7):291-297.
13. Shigemori M, Abe T, Aruga T, Ogawa T, Okudera H, Ono J, et al. Guidelines for the management of severe head injury, 2nd edition guidelines from the guidelines committee on the management of severe head injury, the Japan Society of Neurotraumatology. Neurol Med Chir (Tokyo) 2012;52(1):1-30.
14. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159(7):702-706.
15. Rush B, Wiskar K, Berger L, Griesdale D. The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: a nationwide retrospective cohort analysis. Respir Med 2016; 111:72-76.
16. Forel JM, Roch A, Marin V, Michelet P, Demory D, Blache JL, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34(11):2749-2757.
17. Fanelli V, Morita Y, Cappello P, Ghazarian M, Sugumar B, Delsedime L, et al. Neuromuscular blocking agent cisatracurium attenuates lung injury by inhibition of nicotinic acetylcholine receptor-alpha1. Anesthesiology 2016;124(1):132-140.
18. Sottile PD, Kiser TH, Burnham EL, Ho PM, Allen RR, Vandivier RW, Moss M. An observational study of the efficacy of cisatracurium compared with vecuronium in patients with or at risk for acute respiratory distress syndrome. Am J Respir Crit Care Med 2018; 197(7):897-904.
19. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263-306.
20. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176(7):636-643.