Enteral Nutrition Is a Risk Factor for Airway Complications in Subjects Undergoing Noninvasive Ventilation for Acute Respiratory Failure

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BACKGROUND: Early enteral nutrition is recommended for mechanically ventilated patients in several studies and guidelines. In contrast, the effects of early enteral nutrition on noninvasive ventilation (NIV) have not been investigated extensively. The lack of an established method of airway protection suggests that enteral nutrition administration to these patients could increase airway complications and worsen outcomes. METHODS: Between January 2007 and January 2015, 150 patients were admitted to our respiratory department for acute respiratory failure and received NIV for >48 h. Of these, 107 subjects incapable of oral intake were retrospectively analyzed. Clinical background and complications were compared in subjects who did and did not receive enteral nutrition. RESULTS: Sixty of the 107 subjects (56%) incapable of oral intake who received NIV also received enteral nutrition. Serum albumin concentration was significantly lower in subjects who received enteral nutrition than in those who did not (mean 2.7 ± 0.68 mg/dL vs 3.0 ± 0.75 mg/dL, *P* = .048). The rate of airway complications was significantly higher (53% [32/60] vs 32% [15/47], *P* = .03), and median NIV duration was significantly longer (16 [interquartile range 7–43] d vs 8 [5–20] d, *P* = .02) in subjects who received enteral nutrition than in those who did not. Multivariate analysis showed that enteral nutrition was unrelated to in-hospital mortality. CONCLUSIONS: Among subjects receiving NIV, enteral nutrition was associated with increased risk of airway complications but did not affect mortality. Enteral nutrition should be carefully considered in these patients. *Key words: noninvasive ventilation; enteral nutrition; critical care; airway management; respiratory failure; respiratory care units.* [Respir Care 2017;62(4):459–467. © 2017 Daedalus Enterprises]

Introduction

Early enteral nutrition is recommended for mechanically ventilated patients in several studies and guidelines.[1-5] Enteral nutrition reportedly reduces the duration of mechanical ventilation and hospitalization and enhances patient survival.[6-12] However, the effects of early enteral nutrition on noninvasive ventilation (NIV) have not been investigated extensively. In addition, enteral nutrition has shown adverse effects, including critical ones.

Patients receiving NIV may experience various complications, including airway problems (vomiting, increased

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sputum, mucus plugging, and atelectasis) and other problems (discomfort, pneumothorax, hypotension, cardiac rhythm disturbances, and anxiety). Enteral nutrition may worsen these complications, especially airway complications, possibly leading to critical problems, such as pneumonia and airway obstruction. Moreover, unlike for invasive ventilation, no methods of airway protection have been established for NIV.[13,14] Despite the advantages of enteral nutrition in patients with acute respiratory failure, the effects of enteral nutrition in patients receiving NIV have not been clarified.

Aspiration and mucus plugging are considered to be major complications of NIV, although only a few studies have evaluated its actual incidence and influence on clinical outcomes. Gay[15] reported that aspiration occurred in 5% of subjects undergoing NIV and recommended careful patient selection and gastric drainage when appropriate, despite the fact that gastric drainage completely opposes the goals of enteral nutrition. Gay[15] also described the importance of mucus plugging, while acknowledging that its incidence, effect on clinical outcomes, and effective strategies for prevention remain unclear. This study hypothesized that administration of enteral nutrition to subjects receiving NIV would increase airway complications and worsen outcomes by causing severe hypoxia and/or pneumonia.

QUICK LOOK

Current knowledge

The adverse effects of enteral nutrition related to the airway, including vomiting, mucus plug, and pneumonia, may cause critical complications. Although consensus guidelines recommend early enteral nutrition for mechanically ventilated patients, the effect on patients receiving noninvasive ventilation (NIV), without the existence of a precise airway protection method, is unknown.

What this paper contributes to our knowledge

Enteral nutrition caused more airway complications in subjects receiving NIV for acute respiratory failure than in those receiving nutrition by other routes. However, enteral nutrition did not affect the mortality or rate of NIV failure.

Methods

Study Design and Population

This historical cohort study included subjects admitted to the ICU or intermediate care unit of the respiratory department at our institution, a community teaching hospital in Hyogo prefecture in Japan, from January 2007 through January 2015. Subjects were included in this study if they were admitted for acute respiratory failure and received NIV treatment for >48 h. Acute respiratory failure was defined as a P_{aO_2} <60 mm Hg, a S_{pO_2} ≤90%, or a P_{aCO_2} ≥45 mm Hg, along with signs and symptoms of respiratory distress.[16,17] Patients who needed urgent intubation were not included. Patients able to maintain sufficient nutrition by oral intake at the time of starting NIV treatment were excluded, as were patients who had previously undergone gastrostomy, jejunostomy, or percutaneous endoscopic gastrostomy. Patients were also excluded if they had been diagnosed with ileus; were receiving NIV during the daytime for a chronic disease; were started on NIV at another hospital before transfer to our hospital; were receiving NIV for a non-pulmonary diagnosis, such as seizure; or were pregnant. NIV was indicated in patients with one or more of the following criteria: breathing frequency >25 breaths/min, contraction of accessory inspiratory muscles, paradoxical abdominal motion, P_{aO_2} <60 mm Hg while breathing air, P_{aO_2}/F_{IO_2} <250 mm Hg while breathing supplemental oxygen, or P_{aCO_2} >45 mm Hg. Patients who required urgent intubation because of respiratory arrest, respiratory pauses, severe coma, copious tracheal secretion or hemodynamic instability were not started on NIV.

NIV was delivered in CPAP or spontaneous/timed mode via a well-fitting full-face mask. The inspiratory positive airway pressure when applying the spontaneous/timed mode and the PEEP were initially set at 8–12 and 4–10 cm H_2O, respectively, and were gradually changed depending on the subject's clinical response and tolerance.

The spontaneous/timed mode was selected when subjects developed hypercapnia with acute respiratory acidosis or signs of respiratory distress. The F_{IO_2} was adjusted to keep the S_{pO_2} at ≥90% with the aim of achieving a satisfactory P_{aO_2} level without increasing the degree of hypercapnia. NIV treatment was initially continuous, and attempts to withdraw the subjects were started when their conditions stabilized and they required ≤8 cm H_2O of support, had a PEEP of ≤6 cm H_2O, and had an F_{IO_2} of ≤0.4.

Sedatives were administered when subjects could not continue NIV due to agitation, and +1 or more on the Richmond Agitation-Sedation Scale was generally considered an indication to administer sedation.[17] Subjects were most often managed between −2 and 0 on the Richmond Agitation-Sedation Scale during sedation. Sedation was usually initiated intermittently, and if the target sedation level was not achieved, we began continuous administration. When dyspnea could not be con-

trolled despite sedation, we used opioids to alleviate the dyspnea.

Subjects unable to maintain volitional intake were classified into 2 groups, those who did and did not receive enteral feeding. Feeding was started in subjects considered incapable of oral intake for more than a few days. Because the purpose of feeding was to promote early recovery and reduce time to discharge, nutrition was not recommended for subjects thought to respond poorly to treatment and with little possibility of recovery. According to guidelines, enteral nutrition was usually preferred to parental nutrition. However, subjects in whom enteral nutrition was unfeasible for some reason (including high risk of aspiration, copious sputum, or episodes of vomiting) or those who refused to receive enteral nutrition were considered for parental nutrition.[1] Traditional nutrition indicators, such as the serum albumin level, did not affect the management because these are considered to be invalid in critical care. Most subjects in the enteral feeding group received a commercially available standard enteral nutrition preparation containing 1 kcal/mL, administered through a nasogastric tube. The initial rate was 10–20 mL/h and was increased after 8 h or a few days in the absence of significant gastric residuals (ie, >200 mL) or other problems, such as nausea, vomiting, severe diarrhea, or aspiration, until the target feeding was achieved. Gastric residual volumes were checked every 8 h. Target energy and protein were calculated by multiplying body weight by 25–30 kcal/kg and 1–2 g/kg, respectively. Actual body weight was used for underweight and normal weight subjects, whereas adjusted body weight, defined as weight at a body mass index of 22 kg/m^2, was used for overweight and obese subjects. Subjects were in a semi-recumbent position ($\geq$30°) during enteral feeding. Oral intake could be initiated if clinically indicated. Subjects who were at risk for airway complications were carefully monitored and received prompt care when needed. Nurses estimated the frequency of suctioning for each subject and conducted it regularly.

Because we used an approved database to obtain medical records of subjects, provision of informed consent was not required for this study. The study was approved by the institutional review board of Kobe City Medical Center General Hospital.

Data Collection

Subjects' baseline demographic and physiologic characteristics, as well as comorbidities, were determined at admission. Respiratory status and nutrition were evaluated on the date each subject started receiving NIV. Subject physical activity was assessed before the onset of disease and was classified into 3 groups: class 0, without restriction; class 1, activities restricted to the home; and class 2, requirement to be bedridden. Lung injury category and the decision to administer sedatives and/or opioids were obtained from subjects' medical charts. All data were collected and analyzed by the authors of this report.

Outcome Measures

The main outcomes were the frequency of airway complications during NIV treatment, NIV failure, NIV days, hospital days, in-hospital mortality, and the type of discharge. Airway complications were defined as the total number of episodes of vomiting, followed by desaturation, mucus plug, and aspiration pneumonia. Subjects were defined as having a mucus plug if they required frequent sputum suction (>2 times/h) and had episodes of temporal desaturation that could only be caused by sputum obstruction of the airways. Aspiration pneumonia was diagnosed by the physician in charge, and subjects were administered antibiotic treatment. Discontinuation of NIV was defined as not requiring NIV during the daytime. Mask leak of up to 30–40% was allowed as long as it was compensated by ventilation. Criteria for NIV failure included loss of consciousness or persistent hypercapnic coma while receiving NIV, psychomotor agitation making nursing care impossible and requiring continuous sedation, pronounced worsening in signs of respiratory distress with a breathing frequency >40 breaths/min under NIV, S_{pO_2} <90% despite F_{IO_2} of 1.0, and requiring intubation. When NIV failure was considered to have occurred, the patients were intubated unless they had do-not-intubate orders. Types of discharge were categorized as discharge to home, transfer, or death.

Statistical Methods

Subject demographic and clinical characteristics, as well as complications and outcomes, were compared between the group with enteral feeding and that without enteral feeding. Data are presented as medians with interquartile ranges for ordinal data and as mean with SD for continuous data. Continuous variables were compared with the Wilcoxon rank-sum test, and categorical variables were compared with the Pearson chi-square test. Durations of NIV, hospitalization, and the ICU/intermediate care unit stay were determined by the Kaplan-Meier method and compared by log-rank tests, with censoring at the time of death or transfer. End points included discontinuation of NIV and discharge. Subgroup analyses were also performed among subjects with and without airway complications.

To determine the factors associated with airway complications, possible predictors of airway complications were tested by univariate and multivariate logistic regression

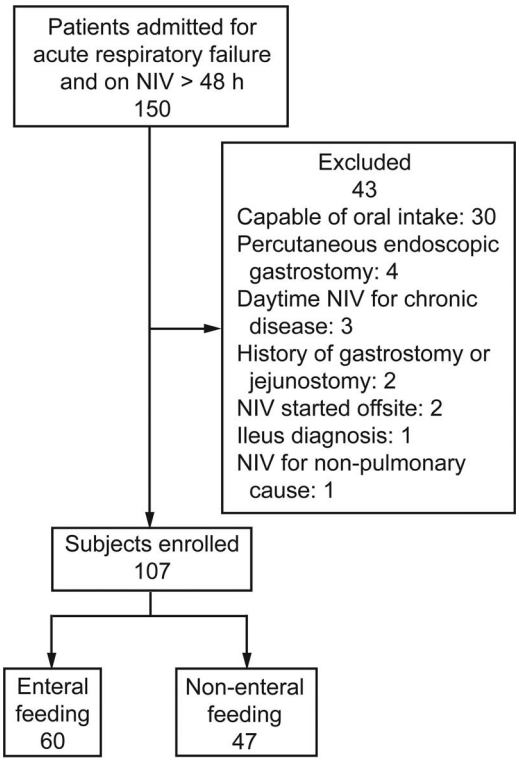

Fig. 1. Flow chart. NIV = noninvasive ventilation.

analyses. Cut-off values were either the median of that parameter (eg, age ≥75 y) or based on a clinically relevant threshold (eg, P_{aO_2}/F_{IO_2} ratio <200, P_{aCO_2} ≥45 mm Hg, or serum albumin concentration >3 g/dL). Variables with $P < .05$ on univariate analysis were entered into the multivariate model. The results were expressed as odds ratios and 95% CIs.

Survival of subjects with and without enteral feeding was also assessed by the Kaplan-Meier method and compared by log-rank tests. To evaluate the effect of enteral feeding, low albumin level, and other factors, Cox proportional hazard models were constructed to estimate the hazard ratio. Multivariate analysis included factors with $P < .05$ by univariate analysis, enteral feeding and serum albumin concentration. The results were expressed as hazard ratios and 95% CIs. $P < .05$ was considered statistically significant. All statistical analyses were performed using JMP 8.0 for Windows (SAS Institute, Cary, North Carolina). The physician (MK) conducted all statistical analyses with the supervision of a statistician (TM).

Results

Subject Characteristics

During the study period, 150 subjects received NIV for >48 h; of these, 43 were excluded from analysis (Fig. 1). The reasons for exclusion were capability of oral intake ($n = 30$), treatment with percutaneous endoscopic gastrostomy ($n = 4$), treatment with NIV during the daytime for a chronic disease ($n = 3$), history of gastrostomy or jejunostomy ($n = 2$), starting NIV at another hospital before transfer to our hospital ($n = 2$), diagnosis of ileus ($n = 1$), and treatment with NIV for a non-pulmonary cause ($n = 1$). Of the 107 included subjects, 60 received enteral nutrition, and 47 did not. None of the included subjects were in postoperative status. Their clinical features are summarized in Table 1. There were no significant between-group differences, except that the initial serum albumin concentration was lower in subjects with than without enteral feeding (2.7 ± 0.68 mg/dL vs 3.0 ± 0.75 mg/dL, $P = .048$). Of the 60 subjects in the enteral feeding group, 26 started enteral feeding within 48 h after NIV initiation (median 3 [interquartile range 1–4] d); the median duration of enteral feeding in this group was 10 d (interquartile range 5–23 d). All subjects in the enteral feeding group continued enteral feeding until they began oral intake or were discharged (died or transferred).

Outcomes

Rates of mucus plug (50% [30/60] vs 30% [14/47]), aspiration pneumonia (17% [10/60] vs 4% [2/47]), and airway complications (53% [32/60] vs 32% [15/47]) were higher in the enteral feeding than in the non-enteral feeding group (Table 2). Vomiting was observed only in the enteral feeding group. The durations of NIV and hospitalization were significantly longer in the enteral feeding group ($P < .05$ each). Survivors in the enteral feeding group tended to stay longer in the ICU/intermediate care unit ($P = .01$) and were less likely to be discharged home (8% vs 36%), but there was no significant between-group difference in NIV failure ($P = .59$) and in-hospital mortality rate ($P = .17$). In the subgroup analyses, the durations of NIV and hospitalization were significantly longer in the enteral feeding group only among subjects without airway complications. However, there was a tendency to prolonged hospitalization in the enteral feeding group, particularly among subjects with airway complications (Table 3).

Logistic Regression Analysis for Airway Complications

Of the 107 subjects included in this study, 47 (44%) experienced airway complications. Univariate analysis showed that age ($P = .02$), enteral feeding ($P = .03$), serum albumin concentration ($P = .03$), admission for pneumonia ($P = .03$), and underlying neurological disease ($P = .033$) were significantly associated with airway

Table 1. Baseline Characteristics of Subjects in the Groups That Did and Did Not Receive Enteral Feeding

Characteristics	Non-Enteral Feeding (n = 47)	Enteral Feeding (n = 60)	P
Age, median (IQR) y	73 (64–81)	77 (68–83)	.71
Male sex, *n* (%)	33 (70)	47 (78)	.33
Physical activity, *n* (%)*			.96
0	25 (53)	33 (55)	
1	14 (30)	18 (30)	
2	8 (17)	9 (15)	
Underlying disease, *n* (%)			
Pulmonary	30 (64)	39 (65)	.90
Cardiac	8 (17)	15 (25)	.32
Renal	8 (17)	11 (18)	.86
Neural	7 (15)	11 (18)	.63
Malignant	9 (19)	9 (15)	.57
Lung injury category, *n* (%)			
Pneumonia	24 (51)	27 (45)	.53
COPD exacerbation	5 (11)	7 (12)	.87
IP exacerbation	2 (10)	12 (20)	.19
Cardiac failure	6 (13)	2 (3)	.065
Others	9 (19)	13 (22)	.75
Weight, mean ± SD kg	52 ± 13	51 ± 12	.55
BMI, mean ± SD kg/m^2	20 ± 4	20 ± 5	.71
Diabetes, *n* (%)	13 (28)	16 (27)	.90
LTOT before admission, *n* (%)	13 (28)	9 (15)	.11
EPAP, median (IQR) cm H_2O	6 (4–8)	6 (4–8)	.93
IPAP, median (IQR) cm H_2O	10 (8–14)	10 (8–12)	.93
P_{aO_2}/F_{IO_2} ratio, mean ± SD	118 ± 43	124 ± 49	.51
P_{aCO_2}, mean ± SD mm Hg	59 ± 30	53 ± 25	.31
Opioids, *n* (%)	12 (26)	24 (40)	.13
Sedatives, *n* (%)	15 (33)	29 (48)	.10
Opioids or sedatives, *n* (%)	17 (34)	33 (66)	.065
Hemoglobin, mean ± SD mg/dL	11.6 ± 2.3	11.6 ± 2.6	.56
Creatinine, mean ± SD mg/dL	0.99 ± 0.81	1.34 ± 1.6	.55
Glucose, mean ± SD mg/dL	158 ± 60	163 ± 76	.88
Albumin, mean ± SD mg/dL	3.0 ± 0.75	2.7 ± 0.68	.048
Total protein, mean ± SD g/dL	6.4 ± 0.89	6.1 ± 1.0	.49
Nutrition type, *n* (%)			
EN	0	60 (100)	
TPN	3 (6)	0 (0)	
PPN	16 (34)	0 (0)	
Fluid replacement	28 (60)	0 (0)	

* Physical activity was categorized as follows: class 0, without restriction; class 1, activities restricted to the home; and class 2, requirement to be bedridden.
IQR = interquartile range
IP = interstitial pneumonia
BMI, body mass index
LTOT = long-term oxygen therapy
EPAP = expiratory positive airway pressure
IPAP = inspiratory positive airway pressure
EN = enteral nutrition
TPN = total parental nutrition
PPN = peripheral parental nutrition

complications (Table 4). Multivariate analysis showed that enteral feeding (odds ratio 2.46, 95% CI 1.03–6.13) and serum albumin concentration (odds ratio 0.26, 95% CI 0.09–0.68) were significant risk factors for airway complications.

Survival Analysis

Kaplan-Meier analysis showed similar survival curves for the enteral feeding and non-enteral feeding groups (P = .62) (Fig. 2). Both univariate and multivariate analyses revealed

Table 2. Outcomes of Subjects in the Groups That Did and Did Not Receive Enteral Feeding

Outcomes	Non-Enteral Feeding (n = 47)	Enteral Feeding (n = 60)	P
Vomiting, n (%)	0 (0)	2 (3)	.21
Mucus plug, n (%)	14 (30)	30 (50)	.035
Aspiration pneumonia, n (%)	2 (4)	10 (17)	.044
Airway complications, n (%)	15 (32)	32 (53)	.03
NIV failure, n (%)	29 (63)	40 (67)	.59
NIV days, median (IQR) d	8 (5–20)	16 (7–43)	.02
Hospital days, median (IQR) d	37 (21–55)	48 (34–88)	<.001
In-hospital mortality, n (%)	22 (46)	36 (60)	.17
ICU/IMCU days, median (IQR) d	7 (3–17)	14 (5–25)	.01
Type of discharge, n (%)			.001
To home	17 (36)	5 (8)	
Transfer	8 (17)	19 (32)	
Death	22 (46)	36 (60)	

NIV = noninvasive ventilation
IQR = interquartile range
IMCU = intermediate care unit

Table 3. Subgroup Analysis of Subjects With and Without Airway Complications

Outcomes	Non-Enteral Feeding* (n = 15)	Enteral Feeding (n = 32)	P
With airway complications			
NIV failure, n (%)	9 (60)	23 (71)	.41
NIV days, median (IQR) d	13 (9–29)	15 (7–43)	.76
Hospital days, median (IQR) d	24 (7–39)	37 (24–48)	.061
Discharge home, n (%)	2 (13)	2 (6)	.43
In-hospital mortality, n (%)	8 (53)	19 (57)	.30
Without airway complications			
NIV failure, n (%)	20 (54)	17 (46)	.88
NIV days, median (IQR) d	7 (4–12)	19 (6–43)	.02
Hospital days, median (IQR) d	21 (15–31)	26 (11–32)	.02
Discharge home, n (%)	15 (46)	3 (10)	<.001
In-hospital mortality, n (%)	14 (43)	16 (57)	.30

* For non-enteral feeding, n = 15 with airway complications, and n = 32 without airway complications.
† For enteral feeding, n = 32 with airway complications, and n = 28 without airway complications.
NIV = noninvasive ventilation
IQR = interquartile range

that neither the serum albumin concentration nor enteral feeding was associated with subject survival (Table 5).

Discussion

To our knowledge, this is the first study to evaluate the effects of enteral nutrition in subjects receiving NIV for acute respiratory failure. The present study results indicated that enteral nutrition is an independent factor associated with airway complications and longer duration of NIV and hospitalization.

Increased rates of vomiting and aspiration and increased amounts of sputum are complications of enteral nutrition.[13,14] The presence of a feeding tube crossing the lower esophageal sphincter and gastroduodenal hypomotility also contribute to reflux and aspiration in mechanically ventilated patients.[18] These complications can be minimized, however, by careful monitoring and preventive measures, such that these complications do not affect clinical outcomes.[19,20]

Many studies have shown the benefits of early enteral nutrition, including reduced risks of infection,[10,21,22] shorter duration of hospital stay and mechanical ventilation,[23-25] and lower mortality rates.[12] This study found, however, that enteral feeding increased airway complications in subjects receiving NIV and may be associated with longer duration of NIV and hospitalization. Moreover, enteral nutrition was not associated with better outcomes in this population.

Airway management is important in preventing ventilator-associated pneumonia and choking. Two randomized studies reported that improvements in secretion management could reduce the risk of ventilator-associated pneumonia.[26] Although subjects receiving NIV received frequent oral suctioning in this study, reliable airway protection is impossible for them. This may increase the risk of pneumonia as well as of mucus plugs.

Because the purpose of this study was to understand the effects of enteral nutrition on clinical outcomes, we evaluated the number of clinical events, including vomiting and aspiration pneumonia, which have been suggested as major complications for NIV, instead of measuring the gastric pepsin concentration in tracheal secretions.[15] However, neither the true incidence of these events nor the utility of the interventions for prevention is known. Because each airway complication is related to other factors (eg, vomiting and mucus plugging might cause aspiration pneumonia), it was difficult to individually separate the complications; when compared with other airway complications, however, the incidence of vomiting was very small (0 subjects in the non-enteral feeding group and 2 subjects in the enteral feeding group), and neither patient's condition was critical. This might suggest the importance of the nutrition protocol; however, further studies are needed.

Early nutrition has been shown to benefit intubated patients with acute respiratory failure, but no study to date has evaluated the risks or benefits of enteral nutrition among NIV patients. Although guidelines recommend enteral over parental feeding,[1-3] the results presented here suggest that enteral nutrition in patients receiving NIV increases the

Table 4. Univariate and Multivariate Analyses of Factors Related to Airway Complications

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex (male vs female)	2.26 (0.89–5.76)	.08		
Age (≥75 y vs <75 y)	2.47 (1.13–5.42)	.02	1.98 (0.82–4.8)	.12
P_{aO_2}/F_{IO_2} (<200 vs ≥200)	0.77 (0.18–3.25)	.72		
P_{aCO_2} (≥45 vs <45 mm Hg)	1.39 (0.64–2.99)	.40		
Enteral feeding	2.43 (1.1–5.4)	.03	2.46 (1.03–6.13)	.043
Opioids	0.60 (0.26–1.37)	.22		
Sedatives	0.57 (0.26–1.26)	.16		
Opioids or sedatives	0.52 (0.24–1.14)	.10		
Albumin (>3 vs ≤3 g/dL)	0.25 (0.1–0.63)	.002	0.26 (0.09–0.68)	.005
Physical activity (class 2 vs 0/1)	0.87 (0.31–2.50)	.80		
Pneumonia	2.37 (1.09–5.18)	.03	2.36 (0.99–5.78)	.051
Underlying neurological disease	3.09 (1.06–8.98)	.033	1.14 (0.77–8.63)	.13

OR = odds ratio

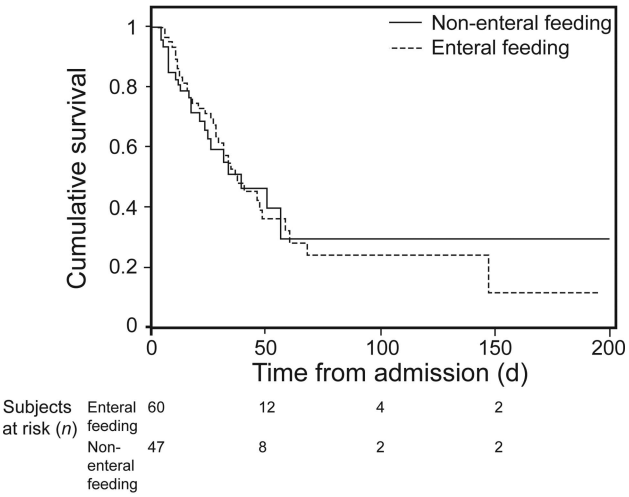

Fig. 2. Kaplan-Meier analysis of cumulative survival in the enteral feeding and non-enteral feeding groups. $P = .62$.

risk of airway complications. The route of nutrition should therefore be considered carefully in NIV patients.

In subgroup analyses, even among subjects without airway complications, both the duration of NIV and hospitalization length were prolonged, and fewer subjects in the enteral feeding group were discharged home. This result suggests that there might be factors, other than airway complications, associated with prolonged NIV, hospitalization, time to recover to discharge home such as rehabilitation programs and incidence of delirium. Unfortunately, we did not collect data on those factors and could not clarify their influence on NIV outcomes. Because this was a retrospective study with a small sample size, there is the possibility that other factors we did not identify or could not evaluate might have an influence on these results. Although we must recognize that airway complications are one of the significant and critical problems of patients undergoing NIV, further study is needed to confirm the effects of enteral nutrition on NIV outcomes.

This study had several limitations. First, it was retrospective in design, making it impossible to control for subject characteristics. This resulted in lower serum albumin concentration in the enteral feeding group. Because the sample size was overly small for subgroup analyses, we performed a multivariate analysis, which showed that enteral feeding was independently associated with airway complications. Univariate analysis showed that enteral nutrition was not significantly associated with survival. Additionally, multivariate analysis confirmed that serum albumin concentration was also not associated with survival. Second, as in other retrospective studies, decisions on the use of NIV and enteral nutrition were made by attending clinicians, although they were recommended to follow our institutional protocol. Third, not all of the exact gastric residual volumes of subjects in the enteral group were recorded in a chart, and the possibility remained that the gastric residues had an influence on the rate of airway complications. However, enteral nutrition was withheld when the gastric residual volume was >200 mL; thus, gastric residual volume was kept under clinically important values to avoid complications. Fourth, it was impossible to compare subjects with and without NIV, because they had very different baseline characteristics, including code status, illness severity, indication for ventilation, and consciousness level. These differences could mask any effect of enteral nutrition on NIV. Fifth, many of the subjects lacked spirometric data, and the baseline respiratory status was unclear. Sixth, there was a wide variation among subjects in terms of illness severity, nutrition status, and lung injury, although the only significant difference be-

Table 5. Cox Regression Model for Risk of In-Hospital Mortality

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥75 y vs <75 y)	0.88 (0.52–1.48)	.64		
P_{aO_2}/F_{IO_2} (<200 vs ≥200)	1.3 (0.47–5.34)	.65		
P_{aCO_2} (≥45 vs <45 mm Hg)	0.4 (0.23–0.69)	<.001	0.4 (0.21–0.73)	.003
Enteral feeding	0.96 (0.58–1.71)	.95	0.97 (0.57–1.69)	.92
Airway complications	0.81 (0.47–1.37)	.43		
Albumin (>3 vs ≤3g/dL)	0.89 (0.47–1.6)	.71	1.36 (0.68–2.58)	.37
Physical activity (class 2 vs 0/1)	1.0 (0.99–1.95)	.99		
IP exacerbation	1.88 (1.01–3.33)	.047	1.36 (0.7–2.54)	.34
Number of underlying diseases (≥2 vs <2)	1.38 (0.81–2.35)	.23		

IP = interstitial pneumonia
HR = hazard ratio

tween the groups of subjects who did and did not receive enteral nutrition was their mean serum albumin concentration. Because this study was retrospective in design, performed at a single center, and included a small number of subjects, there was potential for selection bias. Finally, the sample size for the study was not calculated in advance; thus, these findings should be interpreted as exploratory results. Although we went back in time as far as possible for inclusion (unless we managed subjects in the same protocol), it is possible that the sample size was too small to detect differences in the clinical outcomes between the groups.

There is no consensus regarding nutrition, especially in patients receiving NIV. Our study showed the risks of enteral nutrition in these patients. Although many previous studies have reported the benefits of enteral nutrition for patients with acute respiratory failure, prospective randomized controlled studies are needed to evaluate the advantages and disadvantages of enteral nutrition specific to patients receiving NIV.

Conclusions

Enteral feeding in subjects receiving NIV for acute respiratory failure was independently associated with airway complications and associated with longer durations of NIV and hospitalization. Enteral nutrition should be carefully considered in these patients, because its benefits may be offset by its disadvantages.

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REFERENCES

1. Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. Crit Care Med 2009;37(5):1757-1761.
2. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2009;33(3):277-316.
3. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 2003;27(5):355-373.
4. Heyland DK, Dhaliwal R, Day A, Jain M, Drover J. Validation of the Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients: results of a prospective observational study. Crit Care Med 2004;32(11):2260-2266.
5. Dhaliwal R, Heyland DK. Nutrition and infection in the intensive care unit: what does the evidence show? Curr Opin Crit Care 2005;11(5):461-467.
6. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med 2011;39(5):967-974.
7. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med 2009;35(12):2018-2027.
8. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma–a prospective, randomized study. J Trauma 1986;26(10):874-881.
9. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 1999;27(11):2525-2531.
10. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg 1992;216(2):172-183.

11. Windsor AC, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998;42(3):431-435.
12. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. Am J Crit Care 2010;19(3):261-268.
13. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study: the Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med 1999;27(8):1447-1453.
14. Blaser AR, Starkopf J, Kirsimägi Ü, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. Acta Anaesthesiol Scand 2014; 58(8):914-922.
15. Gay PC. Complications of noninvasive ventilation in acute care. Respir Care 2009;54(2):246-257, discussion 257-258.
16. Lemiale V, Lambert J, Canet E, Mokart D, Pène F, Rabbat A, et al. Identifying cancer subjects with acute respiratory failure at high risk for intubation and mechanical ventilation. Respir Care 2014;59(10): 1517-1523.
17. Matsumoto T, Tomii K, Tachikawa R, Otsuka K, Nagata K, Otsuka K, et al. Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital. BMC Pulm Med 2015;15:71.
18. Bosscha K, Nieuwenhuijs VB, Vos A, Samsom M, Roelofs JM, Akkermans LM. Gastrointestinal motility and gastric tube feeding in mechanically ventilated patients. Crit Care Med 1998;26(9):1510-1517.
19. Mizock BA. Risk of aspiration in patients on enteral nutrition: frequency, relevance, relation to pneumonia, risk factors, and strategies for risk reduction. Curr Gastroenterol Rep 2007;9(4):338-344.
20. Mullan H, Roubenoff RA, Roubenoff R. Risk of pulmonary aspiration among patients receiving enteral nutrition support. JPEN J Parenter Enteral Nutr 1992;16(2):160-164.
21. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med 2005;33(1):213-220, discussion 260-211.
22. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr 2001; 74(4):534-542.
23. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 2001;29(12):2264-2270.
24. Elke G, Kuhnt E, Ragaller M, Schädler D, Frerichs I, Brunkhorst FM, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis: a secondary analysis of the VISEP trial. Med Klin Intensivmed Notfmed 2013;108(3):223-233.
25. Altintas ND, Aydin K, Türkoğlu MA, Abbasoğlu O, Topeli A. Effect of enteral versus parenteral nutrition on outcome of medical patients requiring mechanical ventilation. Nutr Clin Pract 2011;26(3):322-329.
26. Cook D, De Jonghe B, Brochard L, Brun-Buisson C. Influence of airway management on ventilator-associated pneumonia: evidence from randomized trials. JAMA 1998;279(10):781-787.