Early nutritional support is associated with improved outcomes in respiratory failure

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Objective. To evaluate early feeding as a predictor of outcome in critically ill patients receiving prolonged mechanical ventilation. **Patients and methods.** A retrospective cohort study in four medical, surgical and multidisciplinary intensive care units (ICU) in a tertiary referral center of adult patients requiring at least 48 hours of mechanical ventilation. Early feeding was defined as any nutritional support (enteral or parenteral) for at least 6 hours, started within 48 hours of mechanical ventilation. The primary endpoint was hospital mortality. The secondary endpoints were length of stay, and duration of mechanical ventilation. Univariate and multivariate analysis were used as appropriate. **Results.** 394 out of 4,546 patients admitted to the ICU were studied. Age (mean: 95% confidence interval was 62 (60-63); female gender 43%; APACHE III 72 (70-75); APACHE III predicted hospital mortality 36 % (33-39); ICU mortality 19%, hospital mortality 28%, ventilation –free days 41 (39-44). Only 11% (3% enteral, 8% parenteral) were fed on day 1, 55% (30% enteral, 25% parenteral) on day 4, and 88% (51% enteral, 37% parenteral) on day 7. Early feeding was associated with a reduced Standardized Mortality Ratio (number of observed hospital deaths/number of expected hospital deaths) of 0.53. When adjusted for various confounding factors such as severity of illness, trauma, route of feeding, post-operative state or the use of vasopressors, early feeding remained independently associated with decreased hospital mortality (Odd Ratio 0.51; 95% confidence interval 0.26-0.98; p = 0.042). **Conclusion.** Early nutrition is associated with decreased hospital mortality in patients receiving prolonged (more than 48 hours) invasive mechanical ventilation.

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Introduction

Malnutrition is common in hospitalized patients (1) and contributes to increased morbidity and mortality (2). A low body mass index in critically ill patients is associated with a poor outcome (3). Early nutritional support is essential for malnourished patients, and may also be beneficial in those who are well nourished (4). Indications for nutritional support of well-nourished patients include inability to eat for more than seven days because of a critical illness, a major surgical procedure or a major trauma (5). Basic requirements include fluids, electrolytes, protein, lipids, carbohydrates, vitamins, and minerals. The tight control of glucose remains controversial (6, 7). The ultimate goal of nutritional support is to improve outcome (8, 9).

A delay in feeding, with or without preexisting malnutrition, may compound the debt patients have to pay (10). In addition, early enteral nutrition (11) may preserve gut integrity, barrier and immune function, reduce infectious complications and ultimately affect outcome (12). The benefit of early nutrition on ventilation days, hospital stay, and hospital mortality however is still not well established (13, 14). Therefore individual practices, including nutrition practice, at Mayo Clinic vary. This variability allowed us to assess the predicting character of early feeding on outcome in critically ill patients who required prolonged invasive mechanical ventilation. Our hypothesis was that early feeding in the critically ill is associated with a higher survival rate.

Patients and methods

The Institutional Review Board of Mayo Clinic College of Medicine approved the study. Subjects or their legal representatives have given written authorization to have their chart reviewed for research purposes. The medical records of all adult patients requiring 48 hours or more of mechanical ventilation in four medical, surgical and multidisciplinary intensive care units (ICU) between January 1, 2001 and December 31, 2001 were reviewed. Patients ventilated for less than 48 hours, those using a ventilator at home; those with neuromuscular disease, pneumonectomy or a terminal illness were excluded. The data of this cohort has been reported elsewhere to study the relationship between mechanical ventilation and ventilator-associated lung injury (15). The relationship between mechanical ventilation and nutrition has not been addressed so far.

Data were collected daily from the first day of mechanical ventilation and included age, gender, body mass index, the presence of acute lung injury, Acute Physiology, Age, Chronic Health Evaluation (APACHE III) score from the day of ICU admission and APACHE III derived predicted hospital mortality. Preexisting conditions included a history of lung, heart, liver, kidney or brain disease, active cancer, and alcohol and tobacco abuse. The reason for admission to the ICU included exacerbation of a chronic lung condition, coma, post-operative state, trauma, congestive heart failure, and sepsis. Postoperative state distinguishes surgically (postoperative) and medically critically ill patients.

Nutritional support was defined as enteral and or parenteral nutrition provided for at least six hours each day and initiated from day 1 to day 7. Early feeding was defined as any nutritional support (enteral or parenteral) started on day 1 or day 2, i.e. within 48 hours of mechanical ventilation. Late feeding was defined as any nutritional support (enteral or parenteral) started on day 3, 4, 5, 6 or 7, i.e. after more than 48 hours of mechanical ventilation. Outcome was evaluated by the mortality rate in the ICU, the mortality rate in hospital, Standardized Mortality Ratio (SMR) defined as the ratio of actual hospital mortality over predicted hospital mortality, the length of stay in the ICU, the length of stay in hospital, the duration of mechanical ventilation and the number of ventilation-free days.

Statistical analysis

Statistical analysis used univariate analysis (Wilcoxon test, Chi-Square) and multivariate logistic regression as appropriate (JMP® 8.0, 2008 SAS Institute Inc., Cary, NC, 27513). The population was divided between patients who were fed early (less than 48 hours after initiation of the mechanical ventilation) and those fed late (more than 48 hours) without distinction between enteral and parenteral nutrition, usual care at that time being that any patient was started on enteral support whenever feasible, otherwise given parenteral nutrition. Factors that were different by univariate analysis were subsequently plotted together in a multivariate analysis to study their relationship.

Results

Among 4,546 patients admitted to the four ICUs, 441 patients met the study inclusion criteria and 394 patients had complete nutrition data for study purposes. Baseline characteristics are shown in Table 1. In this study, 11% (3% enteral, 8% parenteral) were fed on day 1, 55% (30% enteral, 25% parenteral) on day 4, and 88% (51% enteral, 37% parenteral) on day 7 (Figure 1). The studied population was divided into two groups: those who were fed early, within 48 hours after initiation of mechanical ventilation, and those who where fed late, more than 48 hours after initiation of mechanical ventilation (Table 2). Patients, who were fed early had similar APACHE III scores and predicted hospital mortality rates, were younger, needed fewer vasopressors, more often received parenteral nutrition, and had lower hospital mortality (Figure 2). There was no difference in the number of days of mechanical ventilation or the number of ventilation-free days. When adjusted for confounding factors such as APACHE III, trauma, post-operative state, route of feeding, and vasopressor use, early feeding

Table 1 Baseline characteristics and subgroups of patients fed early (less than 48 hours) and late (more than 48 hours); univariate analysis, mean (95% confidence interval) or number and percent as appropriat

Baseline characteristics	Total N = 394	Early (<48 hours) N = 105	Late (>48 hours) N = 289	P value
Age (years)	62 (60-63)	57 (54-61)	62 (60-64)	0.009
Female gender (%)	170 (43%)	44 (42%)	126 (44%)	0.764
Body Mass Index	27 (27-28)	28 (27-30)	27 (26-28)	0.132
APACHE III*	72 (70-75)	69 (64-74)	73 (69-76)	0.392
APACHE III predicted hospital mortality (%)	36 (33-39)	38 (32-44)	36 (32-39)	0.721
Any vasopressor use (%)	226 (57%)	47 (45%)	179 (62%)	0.002
Post operative state (%)	215 (55%)	53 (51%)	162 (56%)	0.326
Trauma (%)	50 (13%)	18 (17%)	32(11%)	0.110
Route of feeding[§]				P<0.001
Enteral only	246 (62%)	39 (37%)	207 (72%)	
Parenteral	148 (38%)	66 (63%)	82 (28%	
ICU[†] length of stay (days)	14 (13-16)	15 (13-18)	14 (13-15)	0.807
ICU mortality (%)	77 (20%)	14 (14%)	63 (22%)	0.066
Hospital length of stay (days)	28 (25-32)	40 (30-50)	26 (23-30)	0.008
Hospital mortality (%)	112 (28%)	21 (20%)	91 (32%)	0.025
Ventilation days	8 (8-9)	9 (7-11)	8 (7-9)	0.674
Ventilation-free days	41 (39-44)	46 (41-51)	40 (37-43)	0.066

*APACHE III: Acute Physiology, Age, Chronic Health Evaluation; [†]ICU: Intensive Care Unit, [§] During the first 7 days after ICU admission

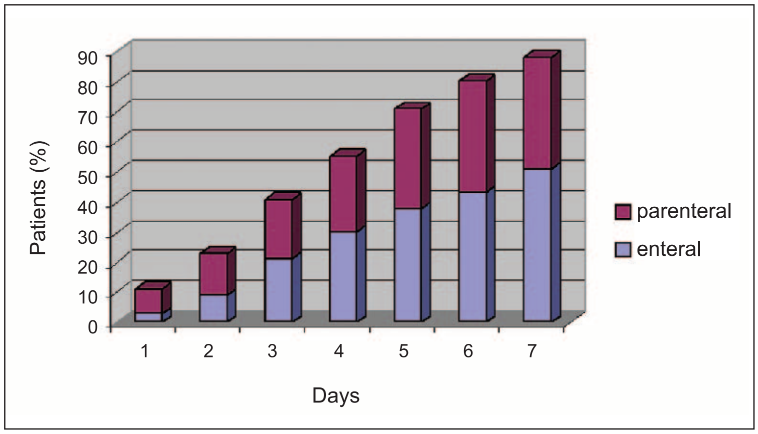

Figure 1 Timing of initiation of nutritional support in mechanically ventilated patients.

Table 2 Comparison between groups of patients fed early (less than 48 hours) and late (more than 48 hours) by multivariate analysis after adjustments for other confounders, early feeding remains a prognostic factor for hospital mortality in mechanically ventilated patients

Variables	Odd ratio (95% confidence interval)	P value
Early feeding	0.51 (0.26-0.98)	0.042
Feeding route*	1.55 (0.87-2.79)	0.135
APACHE III† predicted hospital mortality	1.36[§] (1.24-1.49)	<0.001
Any vasopressor use	1.37 (0.79-2.40)	0.262
Post operative state	0.68 (0.39-1.17)	0.162
Trauma	0.33 (0.09-0.94)	0.038

* Enteral or parenteral, during the first 7 days after ICU admission; †APACHE III: Acute Physiology, Age, Chronic Health Evaluation; § by 10th percentile increment

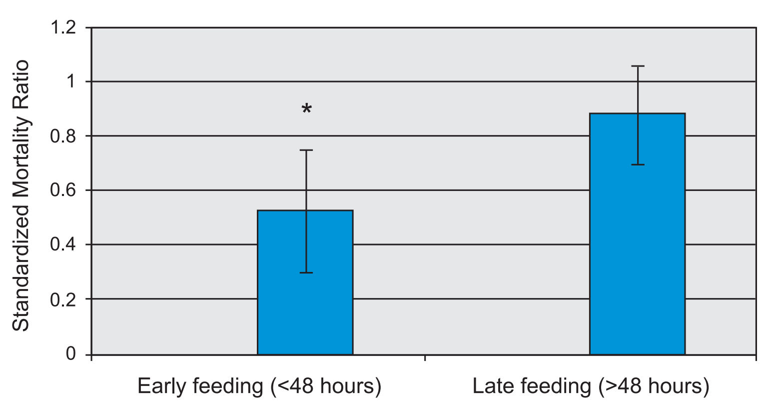

Figure 2 Standardized mortality ratio with 95% confidence interval between groups of patients fed early (less than 48 hours) and late (more than 48 hours): early feeding is associated with significantly less hospital deaths than expected (*), whereas, there is no significant difference between the number of observed hospital deaths and the number of expected hospital deaths in the late feeding group.

remained associated with decreased hospital mortality (Odd Ratio 0.51; 95% confidence interval 0.26-0.98; p = 0.042).

Discussion

The main finding of this retrospective observational study is that initiating feeding within the first 48 hours of mechanical ventilation is associated with lower hospital mortality when compared with delayed initiation of nutritional support. Limitations of this study include its retrospective aspect, the small number of patients initiated with nutritional support (10%) and the heterogeneity of different ICUs.

The large variability of our nutrition practice at a time before the most recent nutrition guidelines were published allowed us to test the association between the timing of nutrition support and the outcome of critically ill patients. In the following sections we will discuss our findings in the context of the evidence based nutrition literature and explore alternative interpretations of the data.

Does the literature support early feeding of critically ill patients?

Current guidelines recommend initiating nutritional support within 24 to 48 hours after admission to ICU, to promote earlier feeding, greater nutritional adequacy, and improve clinical outcome (13) including in well nourished, but critically ill patients. This supports the pretest probability that our observations are valid and should drive a change in practice. In a heterogeneous ICU population, outcome was not different when patients were provided with a full nutritional support from day 1, but this study lacked power (16). In a group of patients requiring prolonged mechanical ventilation, early feeding significantly reduced ICU and hospital mortality; this was true mainly in the sickest patients, and despite an increased risk of ventilator-associated pneumonia (17). When evidence-based recommendations were implemented, stressing early institution of nutritional support, preferably enteral, there were more days of enteral nutrition, a significantly shorter mean stay in hospital and a trend toward reduced mortality when compared to a control arm (18). In other instances however, an excessive intake was associated with excess morbidity and mortality (19). Thus not only the timing but also the amount and likely the composition of nutritional support will determine whether nutrition influences the outcome of critically ill patients. The present study indicates that early feeding is associated with a lower hospital mortality rate than predicted.

Was the decision to initiate feeding within 48 hours of intubation an APACHE III independent predictor of a patient's severity of illness and hence outcome?

Erroneous conclusions due to uncontrolled variables and underappreciated confounders are an inherent danger of all retrospective research. The preceding section dealt with the pretest probability that our findings are real and deserves to shape future nutrition practice. In this section we will examine the alternative, namely, that patient outcomes were independent of nutrition support and reflect variable(s) we did not adjust for. To weigh this possibility we need to examine other aspects of our practice in 2001.

During the year 2001, nearly 10% of patients in four ICU's received invasive mechanical ventilation for at least 48 hours. With the notable exception of trauma patients who required prolonged mechanical ventilation were not fed early. Only half of the patients were given some nutritional support on day 4, either through enteral or parenteral routes. At our Institution, during the study period, nutritional support was implemented at the discretion of the team in charge. Some patients were fed early, other not, according to the practice of the consultant on duty. There was also no clear indication whether a patient needed to be started on parenteral instead of enteral nutrition. No trial of enteral feed was systematically implemented before considering parenteral support. There was no consideration for combining enteral and parenteral support. Furthermore, glucose management was not intensive since the now controversial tight glucose control recommendation had not yet been published (6, 7). The nutritional service was readily available, with fairly uniform care processes, but was not systematically and/or independently activated.

The reason for the variability in nutrition practice at the time in part reflects the lack of convincing evidence that early feeding was beneficial. The statement of the American College of Chest Physicians from 1997 (8) was vague as when to start nutritional support in well nourished patients. The primary team may have been more focused on stabilizing the patient than feeding him, influenced by the 'seven-day' rule according to which fasting a patient for the first week was not considered harmful (5). There may have been some concern that the adverse effects of lipids or the hyperglycemia induced by the total parenteral nutrition negate any beneficial effect of nonlipid supplementation (12).

Two additional confounders need to be considered: physician preferences and outcome predictors not taken into account by the APACHE III score. In term of physician preferences, there was no link between the propensity to feed and outcome. The situations that would influence a physician to feed or not to feed a patient include the type of patient (medical, post operative or trauma), and the severity of the underlying illness (APACHE III, need for vasopressors). Although trauma patients were fed early more often, they did not bias the result. There was no link between the type of ICU (medical, surgical) and outcome. The APACHE III score is a well-established outcome prediction tool in critically ill patients. The expected hospital mortality rate is usually within 3 percent of the actually observed hospital mortality rate (20). Glucose control is not incorporated into the APACHE III scoring system. Glucose level on day 1 was identical in survivors and non-survivors at hospital discharge as was the albumin level. Ongoing large ARDS-net clinical trial of early full versus trophic nutritional support in mechanically ventilated patients with acute lung injury will further improve our understanding of this important issue.

Conclusion

In a cohort of ventilator dependent patients we observed an association between early nutrition and outcome. Having considered the pretest probability of such a result, and eliminated bias from confounders as far as is possible post hoc, we believe that nutritional support should not be delayed in critically ill patients who require invasive mechanical ventilation.

Conflict of interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organisation.

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