Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients*

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Objectives: **Delay in initiating enteral nutrition has been reported to disrupt intestinal mucosal integrity in animals and to prolong the duration of mechanical ventilation in humans. However, its impact on intestinal absorptive function in critically ill patients is unknown. The aim of this study was to examine the impact of delayed enteral nutrition on small intestinal absorption of 3-O-methyl-glucose.**

Design: **Prospective, randomized study.**

Setting: **Tertiary critical care unit.**

Patients: **Studies were performed in 28 critically ill patients.**

Interventions: **Patients were randomized to either enteral nutrition within 24 hrs of admission (14 "early feeding": 8 males, 6 females, age 54.9 ± 3.3 yrs) or no enteral nutrition during the first 4 days of admission (14 "delayed feeding": 10 males, 4 females, age 56.1 ± 4.2 yrs).**

Measurements and Main Results: **Gastric emptying (scintigraphy, 100 mL of Ensure (Abbott Australia, Kurnell, Australia) with 20 MBq ^{99m}Tc-suphur colloid), intestinal absorption of glucose (3 g of 3-O-methyl-glucose), and clinical outcomes were assessed 4 days after intensive care unit admission. Although there was no difference in gastric emptying, plasma 3-O-methyl-glucose concentrations were less in the patients with delayed feeding compared to those who were fed earlier (peak: 0.24 ± 0.04 mmol/L vs. 0.37 ± 0.04 mmol/L, $p < .02$) and integrated (area under the curve at 240 mins: 38.5 ± 7.0 mmol/min/L vs. 63.4 ± 8.3 mmol/min/L, $p < .04$). There was an inverse correlation between integrated plasma concentrations of 3-O-methyl-glucose (area under the curve at 240 mins) and the duration of ventilation ($r = -.51$; $p = .006$). In the delayed feeding group, both the duration of mechanical ventilation (13.7 ± 1.9 days vs. 9.2 ± 0.9 days; $p = .049$) and length of stay in the intensive care unit (15.9 ± 1.9 days vs. 11.3 ± 0.8 days; $p = .048$) were greater.**

Conclusions: **In critical illness, delaying enteral feeding is associated with a reduction in small intestinal glucose absorption, consistent with the reduction in mucosal integrity after nutrient deprivation evident in animal models. The duration of both mechanical ventilation and length of stay in the intensive care unit are prolonged. These observations support recommendations for "early" enteral nutrition in critically ill patients. (Crit Care Med 2012; 40:50–54)**

KEY WORDS: critical illness; delayed feeding; enteral nutrition; intestinal absorption

It is estimated that up to 45% of critically ill patients receive no feeding during the first 3 to 5 days after admission to the intensive care unit (ICU). In addition, only 50% to 68% of energy requirements are delivered over the ICU stay, resulting in a marked calorie deficit in some patients (1–5). The provision of nasogastric feeding is frequently compromised by delayed gastric emptying (6). In healthy and obese subjects, gastric emptying is slowed after 4 days of fasting (7). We accordingly evaluated the impact of nutritional deprivation on gastrointestinal function and clinical outcomes in critically ill patients (8). Although delaying enteral feeds for 4 days had no apparent effect on either gastric emptying or enterogastric feedback hormones, it was associated with a prolonged requirement for mechanical ventilation and length of stay in ICU (8), suggesting that these outcomes are attributable to other factors. This finding is consistent with reports of critically ill surgical patients indicating that nutritional deprivation increases septic complications (9, 10), duration of mechanical ventilation, and length of stay in ICU (8–10).

Although the association between delayed initiation of feeding and poor clinical outcomes solely may be attributable to a cumulative energy or protein delivery deficit, it is possible that a period of fasting will have other effects on gastrointestinal function that may further compound the resulting poor nutritional status. In animals, delaying enteral nutrition for 3 days leads to a reduction in villous height and crypt depth as well as increased intestinal permeability (11, 12). A similar mechanism has been proposed in patients deprived of intraluminal nutrients, thereby predisposing to bacterial translocation and subsequent infectious morbidity (13, 14). Critical illness is known to be associated with disruption of small intestinal mucosal integrity, dysmotility, and reduced absorptive function (15, 16), which may be attributable to a period of reduced or absent delivery of enteral nutrition. Furthermore, in healthy subjects and critically ill

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patients, impaired carbohydrate absorption and intestinal permeability associated with total parenteral nutrition can normalize after the institution of enteral nutrition (17–19). Hence, delayed initiation of enteral nutrition may result in subsequent impaired nutrient absorption that further exacerbates the poor nutritional status attributable to reduced nutrient administration and may be pivotal to the prolongation of both the duration of mechanical ventilation and ICU stay. The impact of delayed enteral feeding on small intestinal absorptive function, however, has not been examined in critically ill patients. Given the major component of enteral feed formulas administered to these patients are carbohydrates, assessment of glucose absorption is important. Thus, the aim of the current study was to evaluate the effects of delayed enteral feeding on small intestinal absorption of the simple sugar glucose. The relationship between clinical outcomes with glucose absorption was also evaluated.

MATERIALS AND METHODS

Subjects. All critically ill patients (aged between 17 and 80 yrs) who were admitted to a level 3 mixed medical and surgical ICU, able to receive enteral nutrition, and likely to receive mechanical ventilation for at least 4 days were considered for recruitment in this study. The impact of delayed feeding on gastric emptying and enterogastric hormone response in this group of critically ill patients has been previously reported (8). Exclusion criteria were patients who: were transferred from other ICUs or were recently (within 14 days) admitted to an ICU; were receiving parenteral nutrition; had recent (<4 wks) major surgery that involved opening the abdominal cavity or gastrointestinal tract or previous surgery of the esophagus or stomach; receiving prokinetic therapy within 24 hrs before the study; and (v) pregnant or breastfeeding. Written informed consent was obtained from the next of kin of the critically ill patients. The study had been approved by the Research Ethics Committee of the Royal Adelaide Hospital, South Australia, and was performed according to the Australian National Health and Medical Research Committee Guidelines for the conduct of research on unconscious patients.

Protocol. Within 10 hrs of their admission to the ICU, recruited patients were randomized to receive either "early enteral feeding" within 24 hrs of admission or "delayed feeding" in which the patient did not receive any form of nutritional support, including parenteral nutrition for the first 4 days in ICU. Randomization was generated using computer software (GraphPad Prism, La Jolla, CA) and the list was maintained by an independent research coordinator.

On admission, a nasogastric tube was inserted in all patients and the correct position of the tube was confirmed by routine radiograph. In the early feeding group, enteral nutrition was commenced at a rate of 40 mL/hr. Gastric aspirates were collected every 6 hrs, as per clinical practice. If feeding was tolerated (aspirate volume <250 mL), then the rate was increased by 20 mL/hr until the prescribed maximum was reached. In accordance with usual practice in our ICU (3), nutritional requirements were determined by a dietician and based on the patient's body mass index (20), with feeding prescribed by an intensive care physician. If an aspirate >250 mL occurred, then the feeding rate was reduced by half or to the minimum rate of 20 mL/hr. Prokinetic therapy was not administered throughout the study period. For patients in the "late feeding" group, the nasogastric tube was placed on free drainage. Parenteral nutrition was not administered in either group.

On day 4 of admission to ICU, gastric scintigraphy (mobile γ camera Starcam 3200iXCT; General Electric, Milwaukee, WI) and intestinal absorption of 3-O-methyl-glucose (3-OMG) were assessed in all subjects. In the early feeding group, feeding was ceased 6 hrs before the study. A test meal consisting of 100 mL of Ensure (Abbott Australia, Kurnell, Australia) (1 kcal/mL; Abbott Australasia), containing 20 MBq ^{99m}Tc-sulfur colloid and 3 g of 3-OMG, was instilled into the stomach over 5 mins via the nasogastric tube. Patients were studied supine at 30-deg head elevation and scintigraphic images were acquired for 240 mins (3-min frames). Gastric emptying was analyzed as previously described (7). Arterial blood samples were collected at predetermined intervals immediately before and after the meal for assessment of plasma 3-OMG concentrations. Plasma 3-OMG concentrations were assayed using high-performance exchange chromatography (21). Data were assessed for peak and time to peak 3-OMG concentration and areas under the curve at 240 mins.

Enteral feeding was continued in all patients after the study and in each individual; the daily requirement was determined by a dedicated ICU dietitian. Decision relating to the necessity for ventilation and the timing of its cessation were made independently by the intensive care physicians responsible for the patient's care and were not influenced in any way by the investigators. All details of the patient's demographics, admission diagnosis, Acute Physiology and Chronic Health Evaluation II score, and sedation score were collected prospectively. Secondary clinical outcomes including the duration of mechanical ventilation, mechanical ventilation-free days, occurrence of ventilatior-associated pneumonia, length of stay in ICU, and ICU mortality were also collected as secondary measures. The diagnosis of ventilator-associated pneumonia was made by the treating ICU specialist. The length of ICU stay was defined as the duration of stay from the time of admission to ICU to the time of discharge out of ICU. The ventilator-free days were calculated as previously reported (22) by subtracting the number of days receiving mechanical ventilation from the lesser of 28 days or the number of days to death. Suitability for discharge was determined by the treating ICU clinician. Discharge was not delayed by lack of availability of ward beds.

Data Analysis. The primary outcome measure was plasma 3-OMG levels. Power calculations were based on previous data derived from a study that examined the impact of fasting on gastric emptying in healthy subjects (7) and suggested that a sample size of 28 was required to show a 10% difference in gastric emptying and carbohydrate absorption at a 5% significance level and 80% power. Although secondary outcomes including the duration of mechanical ventilation, prevalence of ventilator-associated pneumonia, and mortality are reported, the power calculation was not based on these outcomes.

Data are presented as mean ± SEM. Student unpaired *t* test, Fisher exact test, two-way repeated measures analysis of variance, and Pearson linear correlation were used to analyze the results. Significance was accepted at $p < .05$.

RESULTS

The demographics, disease severity, admission diagnosis, and the use of medications that potentially affect gastrointestinal function were comparable between patients who received early and delayed feeding (Table 1). The early feeding group received a mean of 2894 ± 198 kcal (72% ± 4% prescribed caloric requirement) in the first 4 days.

As reported, there was no difference in gastric emptying between patients who received early, compared to delayed, feeding (8). Patients who received delayed feeding, however, had lower absolute (Fig. 1), peak (0.24 ± 0.04 mmol/L vs. 0.37 ± 0.04 mmol/L; $p < .02$), and integrated (area under the curve at 240 mins: 38.5 ± 7.0 mmol/min/L vs. 63.4 ± 8.3 mmol/min/L; $p < .04$) plasma 3-OMG concentrations than those who received early feeding, respectively. The time taken for plasma 3-OMG concentration to peak was similar between patients who received early and delayed feeding (152 ± 18 min vs. 163 ± 21 min; $p > .05$, respectively).

There was a positive correlation between both the peak ($r = .54$; $p = .002$) and integrated ($r = .62$, $p = .0004$) plasma 3-OMG concentrations with the

Table 1. Demographic Data and Characteristics of Critically Ill Patients Who Received Early and Delayed Enteral Feeding

	Early Feeding (n = 14)	Delayed Feeding (n = 14)
Age (yrs)	54.9 ± 3.3	56.3 ± 3.4
Gender (M:F)	8:6	10:4
Body mass index (kg/m^2)	28.3 ± 1.7	27.4 ± 1.9
Acute Physiology and Chronic Health Evaluation II score		
Admission	24.0 ± 1.7	22.9 ± 1.7
Study day	22.5 ± 1.7	21.2 ± 1.7
Diagnosis[a] n (%)		
Head injury	6 (42)	7 (50)
Sepsis	6 (42)	6 (42)
Respiratory failure	5 (36)	4 (29)
Trauma	4 (29)	6 (42)
Dissecting aortic aneurysm	1 (7)	2 (14)
Burns	1 (7)	0 (0)
Baseline blood glucose level (mmol/L)	7.3 ± 0.2	7.8 ± 0.2
Sedation data		
Opioid ± benzodiazepine, n (%)	8 (58)	10 (71)
Propofol, n (%)	6 (42)	4 (29)
Sedation-Agitation Scale score on study day	2.0 ± 0.2	1.9 ± 0.2
Inotrope data, n (%)	6 (42)	7 (50)
Sequential Organ Failure Assessment score on study day	5.3 ± 0.9	4.8 ± 0.8
Calories received before study (kcal)	2894 ± 198	0
Administered-to-prescribed calorie ratio (%)	72 ± 4	0

Data are mean ± SEM.

[a]More than one diagnosis possible in any patient.

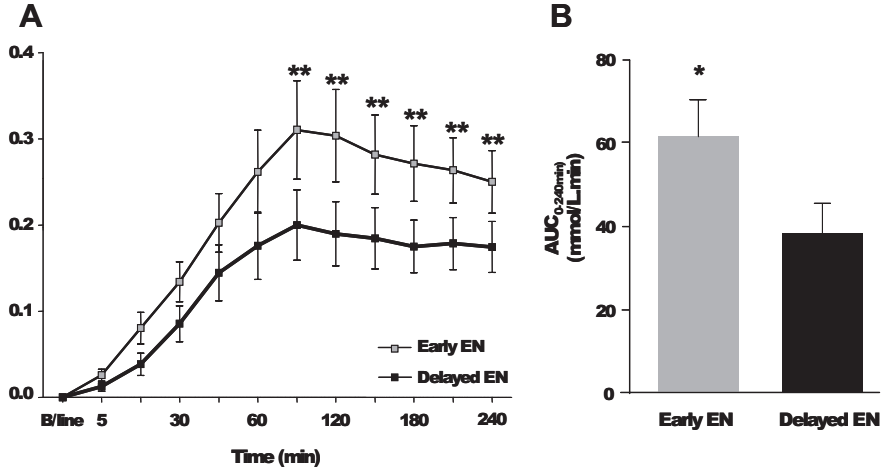

Figure 1. Comparison of (*A*) absolute and (*B*) integrated (area under the curve [*AUC*]) plasma 3-O-methyl-glucose concentrations in patients who received early and delayed enteral feeding. *p = .05 vs. delayed enteral nutrition (*EN*) patients, **p < .001 vs. delayed EN patients.

amount of calories received in the first 4 days. There was also an inverse correlation between integrated plasma 3-OMG concentrations with the duration of ventilation (r = −.51; p = .006; Fig. 2). The length of both mechanical ventilation (13.7 ± 1.9 days vs. 9.2 ± 0.9 days; p = .049) and ICU stay (15.9 ± 1.9 days vs. 11.3 ± 0.8 days; p = .048) were longer in the delayed feeding group. There were fewer ventilator-free days in the delayed feeding groups as compared to the early feeding groups (15.60 ± 1.6 days vs. 20.30 ± 1.1 days; p = .03). Although the number of patients (n = 6) who had ventilator-associated pneumonia in the delayed feeding group was twice the number of patients who received early feeding (n = 3), the difference did not reach statistical significance (p = .22). The mortality rate was identical between the groups (4/14 vs. 4/14).

DISCUSSION

This is the first randomized controlled study to examine the impact of delaying enteral feeding on small intestinal absorption of nutrient. Despite the comparable demographics, underlying diseases, illness severity scores, and gastric emptying rate in the two groups, intestinal glucose absorption (as assessed by 3-OMG) was substantially less in critically ill patients in whom the initiation of enteral feeding was delayed for 4 days after ICU admission. There was also a direct relationship between both the number of calories received over 4 days and the duration of mechanical ventilation with the plasma 3-OMG concentrations. These findings are consistent with those reported in animal models and support the concept that enteral nutrition has an important role in small intestinal absorptive function in critically ill patients.

In health, there are close relationships between luminal nutrients, growth, and differentiation of enterocytes, nutrient absorption, and intestinal permeability (11, 12). Luminal nutrients, such as carbohydrates, are an important source of energy to maintain enterocyte function. In rats and piglets, short-term nutrient deprivation (for 3 days) leads to reduced villous height and crypt depth as well as increased intestinal permeability (23–25). These changes result in an appreciable decrease in absorption of nutrients as part of the end stage of digestion and transport. As a result of decreased energy available for normal enterocytes turnover, migration, and maturation, the intestine can no longer operate optimally as either a digestive organ or an organ of protection (23, 26). Although the turnover rate of gastrointestinal tract in rodents is much more rapid than that of the humans (27), a similar relationship between nutritional deprivation and loss of intestinal mass and function has also been observed in humans (11, 12). Thus, our observations are not surprising.

Physiologically, the absorption of glucose or 3-OMG occurs in the proximal small intestine via sodium-glucose cotransporters at the luminal membrane and glucose transporters at the basolateral membrane (11). Absorption is influenced by the rate of gastric emptying, intestinal transit time, surface area, and integrity, and, to a lesser extent, the presence of pancreatic enzymes (12). In the current study, the time taken for plasma 3-OMG to peak was similar between the groups. This indicates the rate of absorption and most likely reflects the comparable rates of gastric emptying. We have previously shown that the rate of glucose absorption is markedly reduced in ICU

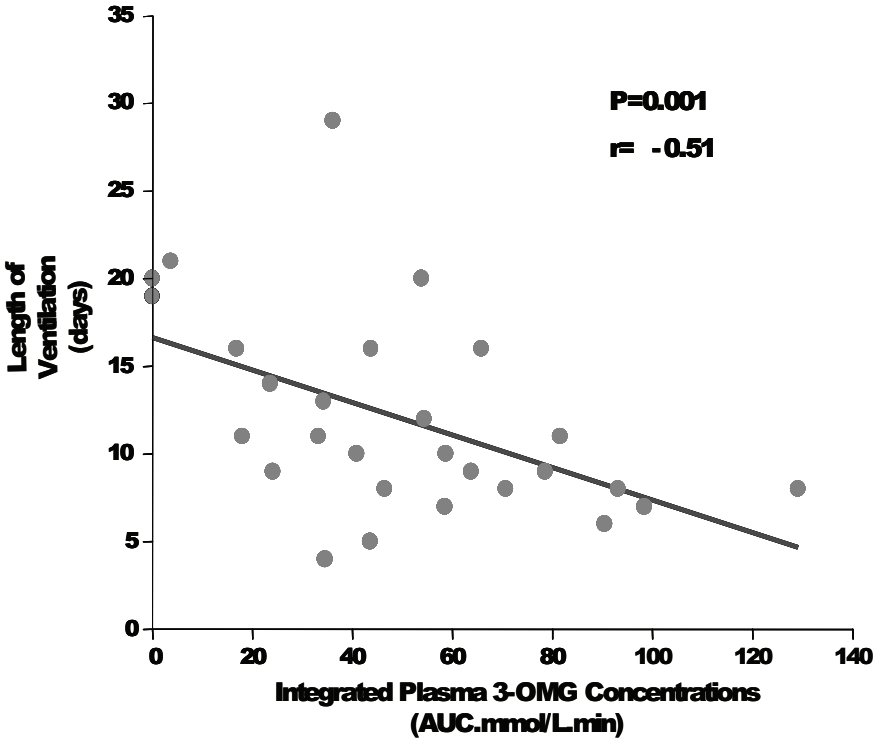

Figure 2. Relationship between length of mechanical ventilation with small intestinal glucose absorption (expressed as integrated plasma 3-O-methyl-glucose [*3-OMG*] concentrations) and in critically ill patients. *AUC*, area under the curve.

patients (compared to healthy subjects) and is closely related to gastric emptying (28). The reason for increased total 3-OMG absorption in patients who were fed earlier (greater peak and integrated plasma 3-OMG concentrations) is unclear but is likely to be related to better mucosal function and integrity. Structurally, critical illness or excessive stress (which often accompanies prolonged fasting) (2) has been associated with small intestinal mucosal atrophy and ulceration, leading to disruption in the amount and function of digestive enzymes (16). The presence of luminal nutrients in patients who received earlier feeding may prevent these effects on the intestinal mucosa. This luminal source of energy for enterocytes may be critical for their survival and function, particularly when splanchnic blood flow is often reduced during critical illness (16, 29). In rats, intestinal mucosal change correlates best with deprivation of luminal nutrition rather than overall nutritional state (23, 26).

The reasons for the prolonged mechanical ventilation and ICU stay in patients with delayed feeding are unclear, and our study was not powered adequately to address this. Poor clinical outcomes may be related to reduced calorie delivery and malnutrition. Reduced intestinal absorption could theoretically relate to disruption of intestinal integrity and lead to higher occurrence of infective complications, such as ventilator-associated pneumonia (16). In animals, prolonged fasting is associated with a disruption of intestinal mucosal integrity, which may predispose to bacterial translocation and subsequent infectious complications (13, 14). Although the number of patients who had ventilator-associated pneumonia develop was numerically higher in the delayed feeding group, the difference did not reach statistical significance and is likely to be related to the small sample size. Numerically, our observations are consistent with earlier data that suggest that delaying enteral feeding in critically ill patients is associated with a higher rate of infectious complications (9). As with the clinical outcome of ventilator-associated pneumonia, our sample size was not powered to examine mortality.

It is possible that better overall nutritional support was associated with improved clinical outcomes, whereas the enteral route of feeding provided a luminal source of energy for the gut to maintain its absorptive integrity. This study was not designed to determine the differences between these two positive outcomes. Further studies are now warranted to compare the impact of early supplementary parenteral nutrition to enteral nutrition on gut function and clinical outcomes.

In conclusion, delaying enteral feeding during critical illness impairs small intestinal glucose absorption and is associated with prolonged mechanical ventilation and length of stay in the ICU, consistent with the adverse impact of nutrient deprivation on small intestinal mucosal integrity evident in animal studies. These observations support current recommendations that in patients without contraindications to enteral nutrition, this should be initiated within 24–48 hrs of admission (9).

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