Effect on mortality of early enteral nutrition in critically ill patients with COVID-19

Efecto de la nutrición enteral precoz en la mortalidad de pacientes críticos con COVID-19

Efeito da nutrição enteral precoce na mortalidade em doentes críticos com COVID-19

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Summary

Background: Early enteral nutrition (EEN) has shown favorable clinical outcomes, such as lower risk of death, fewer frequency of infection and lower health care costs. Different societies recommend the provision of enteral nutrition within the first 24 to 48 hours of admission to the Intensive Care Unit in patients with COVID-19.

Methods: Retrospective cohort study including adult patients with severe COVID-19 and orotracheal intubation. Demographic and clinical characteristics, as well as use of drugs with nutritional relevance, as well as biochemical results (serum electrolytes) were registered. EEN was defined as the provision of enteral feeding within the first 24-48 hours of invasive mechanical ventilation (IMV). The primary outcome was in-hospital all-cause mortality.

Results: Overall, 404 patients were included in the study. EEN was achieved in 74% of all patients. EEN significantly reduced mortality in the bivariate model (RR 0.88, 95% CI 0.80 - 0.95) and in the multivariate model (adjusted OR 0.42, 95% CI 0.19 – 0.90). No differences in hospital length of stay and days on IMV in survivors were found.

Conclusions: EEN was associated with a lower risk of death in critically ill patients with COVID-19. Additional studies are needed to confirm these findings.

Resumen

Antecedentes: la nutrición enteral temprana ha demostrado resultados clínicos favorables, tales como menor riesgo de mortalidad, menor frecuencia de infecciones y menores costos en salud. Diferentes sociedades reco na el inicio de la nutrición enteral temprana como beneficioso. La nutrición enteral temprana se define como la provisión de alimentación enteral en las primeras 24-48 horas post-ingreso en UCI. El principal resultado fue la mortalidad hospitalaria por todas las causas.

Resultados: se incluyeron en el análisis a 404 pacientes. El 74 % de los casos recibió nutrición enteral temprana. La nutrición enteral temprana se asoció con una reducción estadísticamente significativa en la mortalidad por todas las causas en el modelo bivariado (riesgo relativo [RR]: 0,88; intervalo de confianza [IC] del 95 %: 0,19 – 0,90).

Conclusión: la nutrición enteral temprana se asoció con una menor mortalidad. Se requieren estudios adicionales para confirmar estos hallazgos.

Resumo

Introdução: a nutrição enteral precoce (NEP) tem mostrado resultados clínicos favoráveis, como menor risco de morte, menor frequência de infecção e menores custos de saúde. Diferentes sociedades recomendam o fornecimento de nutrição enteral nas primeiras 24 a 48 horas após a administração na Unidade de Terapia Intensiva em pacientes com COVID-19.

Métodos: estudo de coorte retrospectivo incluindo pacientes adultos com COVID-19 grave e intubação orortraqueal. Foram registradas as características demográficas e clínicas, bem como o uso de medicamentos com relevância nutricional, assim como o uso de fármacos de relevância nutricional, como os resultados bioquímicos (eletrólitos séricos). A NEP foi definida como o fornecimento de alimentação enteral nas primeiras 24-48 horas após intubação mecânica invasiva (VMI). O desfecho primário foi a mortalidade de intra-hospitalar por todas as causas.

Resultados: quatrocentos e quatro pacientes foram incluídos no estudo. A NEP foi alcançada em 74% de todos os pacientes. A NEP reduziu significativamente a mortalidade no modelo bivariado (RR 0,88, 95% IC 0,80 a 0,95) e no modelo multivariado (OR ajustado 0,42, 95% IC 0,19 – 0,90). Não foram encontradas diferenças no tempo de internação e nos dias de VMI sobreviventes.
INTRODUCTION

Different societies recommend the provision of enteral nutrition within the first 24 to 48 hours of admission to the Intensive Care Unit (ICU) in patients with COVID-19. Early enteral nutrition (EEN) has shown favorable clinical outcomes, such as lower risk of death, fewer frequency of infection and less healthcare costs. Benefits of early enteral nutrition are summarized in Table 1. On the other hand, delayed enteral nutrition (DEN), started after day 4 of invasive mechanical ventilation (IMV), is associated with longer hospital stay, longer stay in the ICU and more days on IMV. It is reported that the most common reasons for the delay in enteral feeding in critically ill patients with COVID-19 are hemodynamic instability (requiring high vasopressor doses) and provider fear of aspiration, particularly with the patient in prone position. Current guidelines suggest that critically ill patients in prone position or with gastric residual volume within the suggested thresholds can and should be fed. There is evidence to suggest that dietitian involvement in the multidisciplinary team providing care to critically ill patients improves the achievement of protein and energy targets, development and implementation of nutrition algorithms and, most importantly, early initiation of enteral nutrition.

Patients infected with SARS-CoV-2 often develop acute respiratory distress syndrome (ARDS) and around 5% of all confirmed COVID-19 cases will require critical care and IMV. We conducted a retrospective cohort study to evaluate the effect of EEN on mortality in patients with COVID-19 who required IMV.

METHODS

For this single-center cohort study, data were retrospectively collected using medical records of adult patients (>18 years) admitted with confirmed SARS-CoV-2 infection between June 2021 and January 2022 to a referral center in Mexico City. All consecutive patients admitted with laboratory confirmed COVID-19 who were under IMV for more than 72 hours were included. Patients transferred from other units, who had previously been on IMV, or who had been started on IMV before transfer were excluded.

Out of a total of 455 patients, a sample size of 293 patients was considered statistically significant. Sample size was calculated using the formula for finite population, a confidence level of 95%, an acceptable margin of error of 0.05, an occurrence probability of 0.95 and a non-occurrence probability of 0.05.
Data collection

Demographic and clinical characteristics (comorbidities, in-hospital length of stay [LOS], days on IMV and survival) as well as biochemical parameters (serum electrolytes) were registered. Data on the use of drugs with nutritional relevance, such as vasopressors and steroids were also collected. Gastrointestinal intolerance was defined as the presence of gastric residual volume >500 mL every six hours in supine position, and >300 mL every four hours in prone position, the presence of emesis or diarrhea (defined as more than 3 stool or a total stool volume of more than 750 mL in 24 hours)\(^{(8,9)}\).

Table 1. Early Enteral Nutrition Benefits

<table>
<thead>
<tr>
<th>Early Enteral Nutrition Benefits</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>Attenuate oxidative stress by decreasing the systemic inflammatory response syndrome.</td>
</tr>
<tr>
<td>Respiratory system</td>
</tr>
<tr>
<td>Reduce lung axis of inflammation by maintaining the mucosal associated lymphoid tissue and increasing the production of secretory A immunoglobulin at epithelial surfaces.</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
</tr>
<tr>
<td>Help maintaining muscle reserve, function, mobility and return to baseline function.</td>
</tr>
<tr>
<td>Gut</td>
</tr>
<tr>
<td>Maintain gut integrity by decreasing gut permeability, supporting commensal bacteria and stimulating oral tolerance. Increase butyrate production and promote insulin sensitivity by decreasing hyperglycemia.</td>
</tr>
<tr>
<td>Immune system</td>
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<tr>
<td>Increase dominance of anti-inflammatory Th2 over pro-inflammatory Th1 responses; modulate adhesion molecules to decrease transendothelial migration of macrophages and neutrophils.</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
</tr>
<tr>
<td>Provide antioxidants, micro and macronutrients. Maintain lean body mass, decrease muscle and tissue glycosylation, increase mitochondrial function and protein synthesis to meet metabolic demands, increase absorptive capacity, decrease virulence of pathogenic organism and favors motility and contractility.</td>
</tr>
</tbody>
</table>


Nutritional parameters

Data on nutritional intake (energy and protein) during the first 72 hours after orotracheal intubation were collected. Causes of interruptions in enteral feeding were collected from medical charts. Prone position and the presence of gastric residual volumes lower than those previously stated were considered unjustified reasons for delaying enteral feeding. EEN was defined as the provision of enteral feeding in the first 24-48 hours of IMV. Weight and height were estimated using Rabito formulas in patients who could not be weighed before orotracheal intubation\(^{(10,11)}\). Refeeding syndrome risk was defined as patients with a BMI <18.5 kg/m\(^2\), unintentional weight loss >10% in the past 3 to 6 months, little or no nutritional intake for >5 days at the moment of admission, history of alcohol or drug abuse (including insulin, chemotherapy, antacids, or diuretics), low baseline levels of potassium, phosphate or magnesium before feeding\(^{(11)}\), as well as refeeding hypophosphatemia (phosphate <2 mg/dl or a drop of >0.5 mg/dl after the first 72 hours of enteral nutrition initiation or increase)\(^{(8)}\).

Study endpoints

The primary outcome was in-hospital all-cause mortality. Secondary outcomes included hospital LOS and days on IMV in survivors.

Statistical analysis

Categorical variables were reported in absolute and relative frequencies. Quantitative variables were reported using mean and standard deviation or median and interquartile range, according to each variable distribution as assessed by the Shapiro-Wilk test. Comparisons between groups were made using Chi-squared, Fisher exact test and Student’s t test for variables with normal distribution, or the two-sample rank sum test for variables with no normal distribution. A bivariate analysis was performed in order to find associations between in-hospital all-cause mortality and baseline characteristics. Relative risk and 95% confidence intervals were
calculated. A logistic regression model was constructed to find independent associations between in-hospital all-cause mortality and the variables of interest. Interactions were assessed using the Cochran-Mantel-Haenszel Chi. A two tailed p value of less than 0.05 was considered significant. The STATA version 14 software package (Texas, USA) was used.

**Ethical approval**

This study complies with the Declaration of Helsinki and with the General Health Law of Mexico.

**RESULTS**

During the study period, 455 patients were considered eligible for inclusion. We excluded 78 patients for the reasons described in Figure 1. Overall, 404 patients were included in the study. The demographic characteristics and clinical features are shown in Table 2.

EEN was achieved in 74% of all patients. The mean age was 59 (48-71) years, 65.8% were male and 42% were obese. Significant differences were observed between the EEN and DEN groups for chronic kidney disease on renal replacement therapy (CKD-RRT) and vasopressor or steroid use. A total of 332 patients (82%) died. Surviving patients were ventilated for 15 (10-24) days. Surviving patients who received EEN (62) were ventilated for 17 (10-24) days and had a LOS of 39 (28-50) days. Surviving patients in the DEN group (10) were ventilated for 13 (7-19) days and had a LOS of 30 (13-35) days.

![Figure 1. Study design. IMV: Invasive Mechanical Ventilation.](image-url)
### Table 2. Patient’s characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total n= 404 (100%)</th>
<th>EEN n= 299 (74%)</th>
<th>DEN n= 105 (26%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n (%)</td>
<td>266 (65.8)</td>
<td>197 (65.8)</td>
<td>69 (65.7)</td>
<td>0.97</td>
</tr>
<tr>
<td>Age ≥60 years n (%)</td>
<td>195 (48.2)</td>
<td>143 (47.8)</td>
<td>52 (49.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Body mass index, median (IQR) - (kg/m²)</td>
<td>28.2 (24.9–32.9)</td>
<td>29.6 (28.9–30.4)</td>
<td>28.9 (27.5–30.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Obesity n (%)</td>
<td>170 (42%)</td>
<td>122 (40.8%)</td>
<td>41 (39%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>156 (38.6%)</td>
<td>117 (39.1%)</td>
<td>39 (37.1%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus n (%)</td>
<td>168 (41.6%)</td>
<td>126 (42.1%)</td>
<td>42 (40%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Chronic Kidney Disease – Renal Replacement Therapy n (%)</td>
<td>13 (3.22%)</td>
<td>5 (1.67%)</td>
<td>8 (7.6%)</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Refeeding syndrome risk n (%)</td>
<td>50 (12.4%)</td>
<td>33 (11.0%)</td>
<td>17 (16.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease n (%)</td>
<td>8 (2.0%)</td>
<td>6 (2.0%)</td>
<td>2 (1.9%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Stroke n (%)</td>
<td>9 (2.2%)</td>
<td>7 (2.3%)</td>
<td>2 (1.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Malignancy n (%)</td>
<td>6 (1.5%)</td>
<td>4 (1.3%)</td>
<td>2 (1.9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Human Immunodeficiency Virus n (%)</td>
<td>3 (0.7%)</td>
<td>1 (0.3%)</td>
<td>2 (1.9%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Heart Disease n (%)</td>
<td>19 (4.7%)</td>
<td>11 (3.7%)</td>
<td>8 (7.6%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Liver Disease n (%)</td>
<td>9 (2.2%)</td>
<td>3 (1.0%)</td>
<td>6 (5.7%)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Connective Tissue Disease n (%)</td>
<td>4 (1.0%)</td>
<td>4 (1.3%)</td>
<td>0 (0.0%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

### Drugs
- Vasopressors n (%) | 365 (90.3%) | 264 (88.2%) | 101 (96.1%) | **0.018** |
- Steroids n (%)     | 338 (83.7%) | 254 (84.9%) | 84 (80%)   | 0.23  |

### Outcomes
- In-hospital death n (%) | 332 (82.2%) | 237 (71%) | 95 (28%) | **0.010** |
- Median Length of stay (IQR)
  n= 72 | 37 (26-49) | 39 (28-50) | 30 (13-35) | 0.096 |
  n=62 | 15 (10-24) | 17 (10-24) | 13 (7-19) | 0.173 |

DEN: Delayed Enteral Nutrition; EEN: Early Enteral Nutrition; IQR: Interquartile range.

Our results are consistent with those of Ortiz-Martinez et al., who found positive effects on mortality. Their retrospective cohort study in 242 Mexican patients showed an OR of 0.21 (0.087-0.509) in favor of patients receiving EEN\(^{(14)}\). Chawla et al., in a retrospective review in 515 adults, found that EEN was associated with a lower risk of hospital mortality (adjusted HR 0.79, 95% CI, 0.63-1.0)\(^{(15)}\). Furthermore, late enteral nutrition has been associated with higher hospital mortality (RR 9.00, 95% CI, 2.25-35.99)\(^{(16)}\).

Beneficial effects in terms of LOS, days on IMV and costs, but not so on mortality, have been previously described in patients who received EEN. These differences may be explained by the definition used for EEN. Definitions are as broad as feeding within the first 24 hours or up to 72 hours of IMV. Farina et al., for exam-
ple, defined EEN as the provision of enteral nutrition within the first 24 hours of IMV. On the other hand, Haines defined EEN as initiating nutrition feeding within the first 3 days of IMV. ASPEN guidelines define EEN as the provision of enteral feeding in the first 12 hours of IMV or within 36 hours of admission to the ICU.

Benefits of enteral nutrition in critically ill patients with COVID-19 may be due to maintenance of gut integrity, stress modulation, and disease severity attenuation. Similar evidence has been found in critically ill patients who did not have COVID-19. Minnelli et al. hypothesized that timing of nutrition delivery may be crucial as enteral nutrition not only provides macro and micronutrients, but also helps to sustain gut integrity through blood flow stimulation in intraepithelial cells. Also, enteral nutrition, even at a trophic rate, maintains gut integrity in the intestinal villi by preserving tight junctions. Nutrient interaction with mucosal cells and with gut-associated lymphoid tissue (GALT) may play a role in immune functions.

Pardo et al. found an increase in mortality when EEN was used in critically ill patients. They included in their study patients with multiple organ failure, a factor that has been found to be associated with worse prognosis. In studies that have not found differences in mortality with EEN, medical-nutrition therapy (MNT) was not guided by a nutritional support team.

We found an independent association between age 60 or greater and in-hospital mortality. These results are consistent with previously published research. Association between mortality and male sex, obesity, T2DM or HTN was not found in this cohort, even...
though these characteristics have been previously reported as risk factors for mortality. Nevertheless, all our patients already presented severe COVID-19.

Similar to our findings, reports show that 60% to 70% of all patients receive EEN\(^{3,4,6,13,17,23}\). Causes of DEN include the use of vasopressor agents, even at low doses, provider fear of aspiration in prone position, and obesity\(^{3,4,9,14}\). However, evidence suggests that EEN is possible and should be started at stable or decreasing doses of vasopressors and in prone position\(^{1,8,24}\).

One of the main strengths in this study is the large sample size. Also, MNT was guided by a dietitian specialized in clinical nutrition. However, this study has some limitations, including the fact that no information on vaccination was collected. As evidence shows, the benefit of the vaccine relies on preventing disease transmission and, above all, severe forms of COVID-19. Given that this study included critically ill ventilated patients, it is to be expected that the effect of vaccination would not be as reported in literature. There are also limitations inherent to the retrospective nature of this study. Additionally, steroid use was not associated with increased mortality in this cohort. This could be explained by the fact that patients with refractory shock were treated with hydrocortisone. Finally, we did not consider outcomes that could worsen risk of death, such as acute kidney injury and secondary infections. Additional research is needed.

In conclusion, EEN is associated with a lower mortality risk in critically ill patients with COVID-19. Additional studies are necessary to further clarify the effects of early enteral feeding on patient outcomes.

**KEY POINTS**

- Early enteral nutrition was associated with reduced mortality in critically ill patients with COVID-19.
- Early enteral nutrition was achieved in 74% of our patients.
- Most common causes for delayed enteral nutrition in critically ill patients with COVID-19 were hemodynamic instability, metabolic acidosis, and lack of feeding access.

**Acknowledgments**

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**Authorship declaration**

All authors participated equally in the design, acquisition, analysis, and interpretation of the data and drafting and critical review of the manuscript, and agreed with the final version of the project.

**Conflict of interest**

The authors had no disclosures to declare.

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