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Background: Enteral nutrition (EN) in critically ill patients requiring vasoactive drug (VAD) support is controversial. This study assesses the tolerability and safety of EN in such patients.

Methods: This prospective observational study was conducted in 23 ICUs over 30 months. Inclusion criteria were a need for VAD and/or mechanic circulatory support (MCS) over a minimum of 48 h, a need for at least 48 h of mechanical ventilation, an estimated life expectancy longer than 72 h, and at least 72 h of ICU stay. Patients with refractory shock were excluded. EN was performed according to established protocols

during which descriptive, daily hemodynamic and efficacy and safety data were collected. An independent research group conducted the statistical analysis.

Results: Of 200 patients included, 30 (15%) required MCS and 145 (73%) met early multiorgan dysfunction criteria. Mortality was 24%. Patients needed a mean dose of norepinephrine in the first 48 h of 0.71 μg/kg/min (95%CI: 0.63-0.8) targeting a mean arterial pressure of 68 mmHg (95%CI: 67-70) during the first 48 h. EN was started 34 h (95%CI: 31-37) after ICU admission. Mean energy and protein delivered by EN/patient/day were 1159 Kcal (95%CI: 1098-1220) and 55.6 g (52.4-58.7) respectively. Daily energy balance during EN/patient/day was -432 (95%CI: -496 to -368). 154 (77%) patients experienced EN-related complications. However, severe complications such as mesenteric ischemia were recorded in only 1 patient (0.5%).

Conclusions: EN in these patients seems feasible, safe and unrelated to serious complications. Reaching the energy target only through EN is difficult.

**CLINICAL RELEVANCY STATEMENT**

Enteral nutrition (EN) in critically ill patients requiring vasoactive drugs (VAD) is currently a subject of controversy. Factors such as when to start EN, dosing, monitoring, or whether to avoid EN altogether are a real challenge because of its link to a risk of bowel ischemia. We describe our experience with EN in 200 critically ill patients on mechanical ventilation and requiring VAD. Under adequate supervision, EN proved feasible and safe. Our findings require confirmation in clinical intervention trials.

**INTRODUCTION**

In the critically ill patient on mechanical ventilation, enteral nutrition (EN) has shown several clinical benefits such as a reduced risk of infection, shorter ICU stay, and a

possible mortality reduction [1]. Hemodynamic instability affecting a large proportion of critical patients triggers a series of changes in the splanchnic circulation that give rise to diminished splanchnic blood flow in relation to cardiac output (especially in situations of hypovolemic or cardiogenic shock). This is accompanied by arteriolar constriction which persists even when hemodyamic measures such as mean arterial pressure (MAP) have normalized and leads to what is known as occult intestinal hypoperfusion [2]. Additional factors such as a loss of intestinal barrier integrity, or dysbiosis perpetuate the proinflammatory state these patients feature, promoting progression to multi-organ dysfunction syndrome (MODS) [3]. The presence of nutrients in the gut lumen sets off a postprandial hyperemic response which may offset the splanchnic vasoconstriction described above. However, if metabolic demands outstrip the required increase in blood flow, this could aggravate the setting of intestinal hypoperfusion and lead to a risk of non-occlusive mesenteric ischemia (NOMI) or non-occlusive bowel necrosis (NOBN), both with a high associated mortality [4, 5]. Hence, the decision to start EN in a critically sick patient under treatment with vasoactive drugs (VAD) who requires or not mechanical circulatory support (MCS), is highly controversial and a challenge for the medical support team because of the safety issues attributed to a greater risk of NOMI/NOBN [6, 7]. According to the available scientific evidence, the American Society for Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) recommend withholding EN until the patient is "fully resuscitated and/or stable" [8]. The Surviving Sepsis Campaign guidelines of 2021 suggest "early initiation of EN for adult patients with sepsis or septic shock who can be fed enterally (weak recommendation; very low quality of evidence)" [9]. In contraposition, the 2019 guidelines of the European Society of Parenteral and Enteral Nutrition (ESPEN) highlight current limitations in the

evidence supporting the use of EN in septic shock [10]. According to the recently published recommendations of the Metabolism and Nutrition Working Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC), adequately resuscitated patients with hemodynamic compromise, even when in a situation of low cardiac output and requiring one or several VAD, can be started on EN accompanied by appropriate clinical monitoring [11]. However, the data available to date concerning the use of EN in this patient profile, on which the cited recommendations are based, are those arising from case reports, retrospective observational studies or studies with historical controls and from the only recent intervention trial published [12]. Thus, few prospective studies have assessed the benefits of EN in these patients.

The present study was designed to prospectively address the tolerability and safety of EN in critically ill patients on mechanical ventilation and on VAD in 23 Spanish ICUs.

**METHODS**

This prospective observational study was conducted over the period January 2018 to July 2020 in 23 ICUs across Spain (ClinicalTrials.gov Identifier: NCT03401632). Inclusion criteria were: a need for VAD (norepinephrine, dopamine, dobutamine, epinephrine) and/or MCS (extracorporeal membrane oxygenation (ECMO), intraaortic balloon pump (IABP) or ventricular assistance device) over a minimum of 48 h since ICU admission, need for invasive mechanical ventilation during at least 48 h, estimated life expectancy longer than 72 h, and at least 72 h of ICU stay. Candidate patients were excluded if they suffered refractory shock. This entity was defined as a need for progressive VAD dose elevation and/or persistently high or increasing tissue hypoperfusion markers (eg, base excess or blood lactate concentration), and/or a MAP

≤60 mmHg despite stabilization attempts. Remaining exclusion criteria were refusal to participate, a history of significant abdominal vascular disease (ischemic colitis, chronic mesenteric ischemia, abdominal aortic aneurysm, aortic dissection involving mesenteric vessels, etc), an absolute contraindication for EN (active digestive hemorrhage, intestinal obstruction, etc) or non-functional gastrointestinal tract (Fig. 1). All potential candidates were screened for compliance with inclusion and exclusion criteria by the participanting ICUs. Data were prospectively compiled from the clinical records of each patient and entered in a database using the platform REDCap®, which was established and centralized at the Health Research Institute of the Hospital Universitario 12 de Octubre, Madrid, Spain.

Hemodynamic monitoring

From the time of ICU admission, patients were subjected to invasive arterial pressure monitoring to calculate MAP using the equation: $MAP = \frac{\int_{t_1}^{t_2} AP\ dt}{t_2 - t_1}$. The integral was calculated of arterial pressure values recorded over 2 periods of time ($t_2$ and $t_1$), and the area under the curve obtained [13]. Cardiac index (CI) was measured using a Swan-Ganz catheter, pulse contour analysis of arterial waveform, or echocardiography, according to the recommendations established in clinical practice guidelines [14, 15]. Using these data and following a procedure used in prior work [16, 17], we determined minimum daily MAP/CI. After the stage of invasive arterial pressure monitoring, MAP was non-invasively measured every hour and calculated using the equation: MAP= systolic arterial pressure + (2 x diastolic arterial pressure)/3. As for the invasive measurements, we calculated minimum daily non-invasive MAP. Doses of VAD and inotropic agents (norepinephrine, dopamine, dobutamine, epinephrine) were calculated hourly in µg/kg/min. Using these data, daily maximum values were

estimated for each patient. Maximum blood lactate concentrations in mmol/L in arterial or central venous blood samples were recorded in each patient. Data on the MCS used in each patient throughout the course of follow up were also collected (ECMO, both venoarterial and venovenous, IABP, ventricular assistance or other device).

Nutritional therapy and EN protocols

Nutritional therapy in the form of EN was administered according to the protocol established at each participating ICU. As a guide, the reader is referred to the protocol used in prior reports from the SEMICYUC's Metabolism and Nutrition Working Group [18]. Enteral access was mainly nasogastric. Based on the findings of studies in critically ill patients with hemodynamic instability, the energy target was set at 25 kcal/kg of weight per day, to be reached within 72 h of the onset of nutritional therapy. For patients with a body mass index (BMI) of less than 20 kg/m$^2$, the energy target was 25 kcal/kg of ideal body weight. For obese patients with a BMI greater than 30 kg/m$^2$, the target was (25 kcal/kg of ideal weight) + 30% [19]. The timing of EN onset and feed increases was set by each participating ICU. No prokinetic agents or complementary parenteral nutrition were routinely used unless indicated by the responsible physician. The enteral formulas prescribed were: standard, pharmaconutrition, hyperproteic, fermentable fiber-enriched, diabetes-specific or other. Feeding solutions were delivered over 23 h by continuous pumping. The patient's head rest was elevated by more than 30º to minimize the risk of bronchoaspiration or ventilator-associated pneumonia. Gastric residual volume was measured every 6 h on the first day of EN, every 12 h on the second day, and daily thereafter. The complications related to EN recorded were: an increase in gastric residual volume recorded at each time point greater than 500 mL [18]; abdominal

distention, defined as a change in abdominal cavity size detected in a physical examination relative to that recorded before EN onset; regurgitation, defined as the presence of EN feed in the oral cavity or oropharynx and its spontaneous drainage through the mouth or nose; diarrhea, defined as five or more liquid stools in 24 h, or more than two 1000 mL stool volumes, each over a 24-h period; constipation, defined as a lack of bowel movements in 7 days from the onset of EN or for 3 days after the first week of admission; and bronchoaspiration, defined as the presence of respiratory secretions of similar characteristics to the prescribed EN feed, as confirmed by the glucose-oxidase technique in tracheal secretions. Clinical, analytical and radiological warning signs of mesenteric ischemia, as described in Table 1S, were meticulously monitored [5]. In cases of suspected mesenteric ischemia, EN was suspended and it was decided whether to conduct an abdominal-pelvic computerized tomography (CT) with intravenous contrast as the first-choice diagnostic method. The definitive diagnosis was performed by arteriography or exploratory laparotomy/laparoscopy. All described complications were assessed daily by the responsible physician. Patient follow-up

Patients were prospectively followed for 14 days from ICU admission or until switching to oral diet, ICU discharge or death. The variables determined are indicated in Table 1. Mesenteric ischemia was checked for during the entire hospital stay.

The study protocol (Ref. "NE-INEST HD-16") was approved by the Ethics Committee for Clinical Research of the Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain and the review boards of the remaining participating hospitals. Written informed consent was obtained from the patients' closest relatives or, if possible, from the patients themselves.

**Statistical analysis**

Data are provided as means and their corresponding 95% confidence intervals (CI) for continuous variables, and as absolute and relative frequencies for categorical variables. Mean energy delivered, energy balance, blood lactate levels and norepinephrine dose during the course of EN are graphically represented for the entire study sample. Qualitative variables in contingency tables were compared using the chi-squared or Fisher's exact tests. The Wilcoxon-Mann-Witney test or Student's t-test, as appropriate, were used to compare ordinal and continuous measurement distributions. Associations between continuous variables were assessed through Pearson's correlation coefficient. Following a previously described method [16], subject effects on repeated measurements that could lead to bias (e.g., blood lactate, cardiac index or SOFA score), were accounted for through a mixed effects regression model constructed using two level data for observations repeated over time (level 1) nested within patients (level 2). A multivariate analysis of risk factors proving significant as well as those considered clinically relevant was performed using a mixed effects regression model. The effect of covariables on the response variable was determined as the estimated fixed coefficient and 95% CI. We estimated the mean and 95% CI of the dependent variable (eg, SOFA score or blood lactate) measured over time, using the model with or without correction for patient characteristics (patient subset, need for MCS, high norepinephrine requirement/blood lactate in the first 48 h, and EN-related complications). All statistical tests were performed using SAS software (SAS Institute Inc., Cary, NC, USA). Our hospital's Unit of Research Support was responsible for the statistical treatment of data.

**RESULTS**

Patient characteristics (Table 2)

Of an initial 216 patients assessed for inclusion, 16 were excluded (13 fulfilled an exclusion criterion and 3 were lost to follow up) leaving a study population of 200 patients (Figure 1). Participant characteristics were: a high SAPS 3 or SOFA severity score (means 64 and 12, respectively), a high incidence of early MODS (defined as failure of 2 or more organs within 48 h [16]), and elevated mean ICU stay and mortality (25 days and 23.6%, respectively). The most frequent patient profile was medical (49%), followed by cardiac surgery patients (20%), those with severe trauma (13%), and non-surgical cardiology patients (10%).

Hemodynamic status (Table 3)

All participants required at least one VAD during at least 48 h since their ICU admission: norepinephrine in 100%, followed by dobutamine in 39.5% of the patients. A significant proportion of patients showed more hemodynamic instability and 38% required 2 VAD, and 7% 3 VAD; 15% required MCS. Values of MAP were always above 65 mmHg regardless of VAD dose within 48 h of ICU admission. In most participants, blood lactate levels fell significantly after 48 h in the ICU.

Efficacy of EN therapy (Table 4, Figure 2 and Figure 1S)

Two-thousand-and-one days of EN were prospectively monitored. The most frequently prescribed formula was hyperproteic (44.8% of EN days), followed by pharmaconutrition (19.2%) and diabetes-specific (13%). In most patients (n=198), the administration route was gastric (99%). A nasojejunal tube was used in only 2 patients (1%). In 146 patients (73%), EN was the only nutritional support given. In 54 patients (27%), complementary or full parenteral nutrition was required at some time point. Owing to the need to stabilize the hemodynamic situation of each patient, EN was started on average within 34 h of ICU admission. Mean calories and proteins delivered

by the enteral route were 1159kcal/patient/day and 55.6 g/patient/day. This meant that energy balances, both daily and cumulative, were negative (Table 4).

Safety of EN therapy (Table 5)

Nine patients (4.5%) showed warning signs of mesenteric ischemia, yet this complication was only confirmed in 1 patient. The affected patient was a 75-year-old woman with 4 cardiovascular risk factors who had undergone coronary bypass surgery; her EUROSCORE was 23 points. Immediately after surgery, she had suffered cardiogenic shock and required 3 VAD (norepinephrine, dopamine and dobutamine) and mechanical support with IABP. The mean norepinephrine dose this patient received was 0.11 μg/kg/min in the first 48h of ICU stay and 0.15 throughout the course of follow-up. Enteral nutrition was started at a dose of 760 mL/24 h at 22 h post-ICU admission and increased over days 3 and 4. While the caloric target was reached on Day 5, she had vomiting and, on Day 6, she presented with abdominal distention and hemodynamic decline. Enteral feeding was suspended. In an abdominal angio-CT, data were obtained suggestive of non-occlusive ischemia of the right and transverse colon with pneumatosis intestinalis. After an urgent laparotomy confirming ischemia of the right descending transverse colon and a hypoperfused sigmoid colon, a total colectomy and ileostomy were performed. The patient recovered well and was discharged from the ICU. In the remaining 8 patients with warning signs of mesenteric ischemia, an abdominal angio-CT was performed. In 5 cases, mesenteric ischemia was excluded in this way, but in 3 patients pathological findings prompted surgical exploration to rule out this complication. Only 1 patient died, but the CT was performed before death.

EN-related complications were observed in 154 patients (77%), and it was necessary to suspend EN in 77 patients (38.5%). The most frequent complication, increased gastric residual volume, affected 69 patients (34.5%).

Patient subgroup analysis

*Critically ill patient profiles (Table 2S).* Patients with severe trauma were significantly younger, had a significantly lower SAPS 3/SOFA score, lower rate of hospital-acquired infection and lower ICU mortality. Cardiology patients, both medical and surgical, showed a significantly higher mortality than the remaining subsets along with greater continuous renal replacement therapy requirements and hospital-acquired infection. With regard to the hemodynamic situation in the first 48 h of ICU stay, cardiac surgery patients showed significantly higher blood lactate levels 48 h post-ICU admission along with lower CI values and greater MCS requirements, although MAP did not differ from that recorded in other patients, except those with severe trauma who showed significantly higher values. No significant differences were detected in norepinephrine doses between the patient subsets, although cardiology patients required a significantly higher dobutamine dose. With regard to EN efficacy/feasibility, EN was initiated significantly earlier in the trauma patients than remaining patients. In addition, they received a significantly greater calorie/protein supply especially when compared with the medical and surgical cardiology patients. In terms of safety, no differences emerged among the different subsets except for the case of increased residual gastric volume (greater frequency in trauma patients) and diarrhea (greater frequency in non-surgical cardiology patients).

*Patients with a need for MCS (Table 3S).* These patients showed a significantly longer ICU stay, greater SOFA score, greater need for CRRT, along with a tendency for greater mortality. Regarding the hemodynamic situation in the first 48 h of stay,

patients requiring MCS showed significantly higher blood lactate levels, significantly lower CI and MAP, and a need for more VAD. These patients also showed a significantly lower tolerance to EN than the remaining patients requiring vasoactive support in terms of both calories and proteins delivered. Energy balance was significantly lower. No differences between the patient subsets were produced in EN safety-related variables.

*Patients with EN-related complications (Table 4S)*. No significant differences were detected in severity scores on ICU admission, or SOFA, between patients with and without EN-related complications. However, patients with EN-related complications showed a significantly greater incidence of early MODS, longer ICU stay and higher ICU mortality. They also showed a greater tendency toward hospital-acquired infections. In terms of the hemodynamic situation in the first 48 h of hospital stay, patients with EN-related complications needed a significantly greater norepinephrine dose, although no differences in the remaining variables were observed. The presence of EN complications was associated with fewer calories/proteins delivered and a more negative energy balance than those recorded in the subset of patients without these complications.

*Patients with high norepinephrine requirements (>0.5 ug/kg/min) and/or high blood lactate levels (>3 mmol/l) in the first 48 h of ICU stay (Table 5S).* The subset of patients showing greater hemodynamic instability had a significantly higher SOFA score and incidence of early MODS, along with a need for CRRT, MCS and more than one VAD during their ICU stay. Mortality was significantly greater. In these patients, the time elapsed until the start of EN was significantly longer. In terms of EN efficacy variables, this patient subset received a significantly lower calorie/protein supply and energy balance. In terms of safety, while no differences were detected in

the overall incidence of complications, a greater yet not significant proportion of patients required temporary EN interruption.

Multivariate analysis (Tables 6S, 7S and 8S)

In our efficacy analysis, a higher SOFA score, norepinephrine dose and blood lactate concentration were independently associated with a lower EN calorie and protein supply. The subset of cardiac surgery patients was independently associated with a lower EN calorie supply, while the difference in the protein supplied by EN did not quite reach significance.

In terms of EN safety, only SOFA score was found significantly associated with a greater risk of EN-related complications requiring its interruption. The remaining variables examined showed no independent association with the presence of these complications.

**DISCUSSION**

Our results indicate that the use of EN in the mechanically-ventilated critically ill patient under VAD treatment (mean norepinephrine dose more than 0.5 μg/kg/min in the first 48 h of ICU stay) is feasible and safe, provided a set EN protocol is followed. This protocol should include close surveillance of intestinal ischemia warning signs, and EN onset once the initial resuscitation/stabilization stage is complete. This form of nutritional therapy is feasible even in hemodynamically complex patients such as cardiology patients requiring MCS. Patient stabilization in the initial ICU hours (mean 34 h) was essential to safely initiate EN. Moreover, it was gradually implemented with careful monitoring of warning signs of intestinal ischemia (Table 1S) targeting an early diagnosis. The presence of these signs meant we had to temporarily interrupt EN (until this serious complication could be confirmed or ruled out) in up to 4.5% of

patients. This probably explained the low incidence of intestinal ischemia observed here (0.5%), in agreement with reported rates [12].

The present study differs with respect to the recent clinical trial NUTRIREA-2, in which early EN did not reduce mortality or secondary infection risk but was associated with a significantly higher incidence of digestive complications (including intestinal ischemia) compared with early parenteral nutrition [26]. As main differences, we should highlight that in that study, EN was started as early as possible (within 24 h of intubation), that full doses were used from the start without limiting its onset to after hemodynamically stabilizing the patient, and there was no routine monitoring of gastric residual volume. Our findings support the conclusions of NUTRIREA-2 in that the use of EN in the critically ill patient on VAD could increase the risk of intestinal ischemia but they do not, nevertheless, concur with regard to the best timing of feeding onset, which should always be dependent on controlling the situation of shock, or with regard to the administration protocol, which should be gradually started with monitoring of intestinal ischemia warning signs.

While the VAD dose received by the patient at the time of EN onset is an important factor to consider [27], more important factors are the gradual tapering of this dose and stabilization of tissue hypoperfusion variables. Once these conditions are met, EN can be safely started at trophic doses [5,11]. This rationale has been recently confirmed as feasible in a pilot phase III clinical trial including 31 patients with septic shock [28].

It should be noted that both calorie and protein levels delivered by EN were overall insufficient to attain our theoretical goals. This gave rise to negative energy balances and a need for complementary parenteral feeding in 27% of our patients. This finding has been described by others, especially in hemodynamically unstable patients undergoing heart surgery or patients on ECMO [16, 29-30]. Adequate calorie intake as

from the second week could be a good marker of survival [31], but the net clinical impact of these negative cumulative energy balances is difficult to establish. The reasons justifying these results are multiple: slow cautious start of enteral feeding, significant incidence of complications requiring transient interruption of EN in up to 38% of the patients, interruptions for procedures, transport, etc. These data point to an essential need to optimize EN and the individualized complementary use of parenteral nutrition [1, 32].

Among the safety variables recorded (Table 5), besides a low incidence of intestinal ischemia, we should mention the high incidence of EN-related complications (77%), greater than that reported by the SEMICYUC's Metabolism and Nutrition Working Group of 62.8% [33]. Most of these complications were resolved by transiently interrupting EN and/or reducing the EN infusion rate. Acute mesenteric ischemia among critically ill patients is mainly related to low flow states leading to the phenomenon of NOMI. It is likely that low cardiac output is a strong risk factor for the development of NOMI. Interestingly, in Table 2S it may be seen that the cardiac surgery group patients had the lowest cardiac output, the highest dobutamine dose, and that the patient developing acute mesenteric ischemia was in this group. This suggests that not only the catecholamine dose matters, but that a low cardiac output is also an important factor.

Our patient subgroup analysis revealed that patients with severe trauma, despite receiving similar norepinephrine doses, had significantly higher levels of calories/proteins delivered and were started on EN significantly earlier than the remaining subsets. In contrast, adequate calorie/protein intake was more difficult in cardiology patients. These patients showed a higher ICU mortality, a greater need for organ support systems and returned higher organ dysfunction scores. Collectively

these factors may explain the particular challenge of enteral feeding in such patients. Similarly, the subset of patients requiring MCS who had a more compromised hemodynamic situation in the first 48 h of ICU stay, received a significantly lower calorie/protein supply than the remaining subgroups. However, in terms of safety, no differences were detected in the overall frequency of EN-related complications among the different subsets. The exceptions to this were increased gastric residual volume (more frequent in trauma patients) and diarrhea (more frequent in non-surgical cardiology patients). Finally, we should mention that the subset of patients with EN-related complications showed a worse prognosis, including significantly longer ICU stay and higher mortality than the remaining patients. These results are comparable to reported figures [34] and may essentially be explained by two factors: a detrimental effect of fewer calories/proteins delivered and the consequence of acute gastrointestinal dysfunction, which leads to a worse prognosis in the critically sick patient, as described by others [35-37].

According to our results, cardiology patients and those requiring MCS could be considered subsets at special risk in terms of EN efficacy and safety. These patients would benefit from an especially strict surveillance protocol aimed at avoiding malnutrition and the appearance of potentially serious complications such as NOMI/NOBN.

Patients with high norepinephrine requirements and/or elevated blood lactate levels in the first 48 h showed special difficulty for enteral feeding, and this led to a lessened calorie/protein intake, a greater need for parenteral nutrition, and a greater severity of EN-related complications in terms of the need for its transient interruption. However, besides their greater norepinephrine requirement, these patients were clinically more severe in that they obtained higher SOFA organ dysfunction scores. This variable

should be considered along with the norepinephrine dose received by the patient to design the most appropriate nutrition strategy. The correlation coefficients obtained for different combinations of these variables were: norepinephrine dose received-calorie intake = -0.29; norepinephrine dose received-protein intake = -0.27; SOFA score-calorie intake = -0.28; and SOFA score-protein intake = -0.29 (p value <0.05 in all cases). Hence, although there is some relationship between these variables and the calories/proteins supplied by EN, this correlation is weak. It is therefore necessary to consider this whole set of variables individually in each patient.

Our multivariate analysis confirmed the importance of the norepinephrine dose, blood lactate level and SOFA score as predictors of calorie/protein supply through EN in these patients. Moreover, the special difficulty in attaining nutritional requirements was also confirmed in the subset of patients undergoing heart surgery, as was the important role of SOFA score as a predictor of the risk of EN-related complications.

According to the above findings, EN therapy in these patients is complex but possible. Besides the dose of norepinephrine the patient receives at a given time point, other factors need to be considered such as the temporal tendency, blood lactate concentration and SOFA score. The approach to patient management should therefore be dynamic, selecting the most appropriate nutrition administration route (enteral, parenteral and/or mixed) [19]. Our study also found that EN was safe in critically ill patients receiving high catecholamine doses, but the EN volume used was limited. In addition, trophic enteral nutrition emerged as safe in terms of avoiding a risk of acute mesenteric ischemia.

Study limitations

This was an observational study with no control group. Its findings should be therefore treated with caution and require confirmation in a clinical intervention trial.

Other limitations we should mention were the different nutritional protocols implemented at each center, the use of pharmaconutrition in some cases, the low number of patients included (compared to the NUTRIREA-2 trial), and the low number of patients per site (fewer than 1 patient included per 3 months in one center).

## CONCLUSIONS

Our findings indicate that EN in the critically ill patient requiring vasoactive agents and/or mechanical support may be feasible and safe, provided it is started once the resuscitation stage is complete and is conducted under adequate supervision. This strategy is even recommended for patients requiring high doses of norepinephrine within the first 48 h of ICU admission and in cardiology patients needing mechanical circulatory support. However, as a shortcoming, it is especially difficult via this route alone to meet calorie/protein requirements. The use of established EN protocols, daily monitoring of calories/proteins delivered, and active surveillance of warning signs of mesenteric ischemia are essential.

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## Statement of authorship

JL Flordelís and JC Montejo contributed to the conception and design of the research and interpretation and analysis of the data; JL Flordelís, JC López Delgado, P Zárate

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**Table 1.** Variables examined in 200 critically ill patients receiving enteral nutrition

| | |
|---|---|
| **PATIENT CHARACTERISTICS** | Demographic data, weight, height, body mass index (BMI), severity scores (SAPS 3 [20], ISS [21] and EUROSCORE [22]), patient subset (medical, trauma, cardiology (medical or surgical), other surgeries). |
| **HEMODYNAMIC** | Blood lactate (daily peak), cardiac index (CI) (daily lowest), dose of vasoactive drugs (highest daily), mechanical circulatory support (presence and type), mean arterial pressure (MAP) (lowest daily). |
| **OTHER** | Pre-ICU serum albumin, maximum daily SOFA [23], acute kidney failure (RIFLE criteria [24]), CRRT, infectious complications (ENVIN-HELICS criteria) [25], days of mechanical ventilation, ICU stay and mortality. |
| **EN EFFICACY-RELATED** | EN diet, days of EN, volume delivered, kilocalories (kcal) delivered by enteral/non enteral route*, energy balance (kcal delivered by EN – nutritional target in kcal), nutrition tolerance (kcal delivered by EN / nutritional target in kcal), daily GRV. Contribution of the oral route was not assessed. |
| **EN SAFETY-RELATED** | Mesenteric ischemia (suspected, confirmed), high GRV, abdominal distention, diarrhea, vomiting/regurgitation, bronchoaspiration, nasogastric tube complications (obstruction or misplacement/accidental extubation), need to interrupt or discontinue EN (and reasons). |

SAPS 3 = simplified acute physiology score 3 [20]; ISS = injury severity score [21]; EUROSCORE: European system for cardiac operative risk evaluation [22]; SOFA = sequential organ failure assessment [23]; RIFLE = risk, injury, failure and end stage model [24]; CRRT = continuous renal replacement therapy; ENVIN-HELICS = National study of nosocomial infection surveillance in ICU [25]; GRV = gastric

residual volume; EN = enteral nutrition; MV = mechanical ventilation; ICU = intensive care unit. *kcal delivered by the non-enteral route including parenteral nutrition and non-nutritional energy delivered to the patient as i.v infusions and fluids used to solubilize drugs (glucose, glucosaline, etc) including the lipid vehicle of the sedative propofol.

**Table 2.** Data recorded in the critically ill patients receiving enteral nutrition

| Variable | n=200 |
|---|---|
| Age (years) [a] | 60.8 (58.8-62.8) |
| Gender: male [b] | 128 (64%) |
| Body mass index (kg/m$^2$) [a] | 27.9 (27-28.7) |
| Pre-Intensive Care Unit albumin (g/dl) [a] | 3.3 (3.1-3.4) |
| Simplified Acute Physiology Score 3 (SAPS 3) (all patients, n=200) [a] | 64.4 (61.9-66.8) |
| Injury Severity Score (ISS) (trauma patients, n=26) [a] | 34 (27.5-40.6) |
| EUROSCORE (cardiac surgery patients, n=40) [a] | 9.6 (7.9-11.4) |
| Sequential Organ Failure Assessment (SOFA) [a] | 11.7 (11.2-12.1) |
| Medical patient [b] | 98 (49%) |
| Cardiac surgery patient [b] | 40 (20%) |
| Non surgical cardiology patient [b] | 20 (10%) |
| Trauma patient [b] | 26 (13%) |
| Other surgeries [b, *] | 16 (8%) |
| Energy target (kcal) [b] | 1824.5 (1781.9-1867.2) |
| Need for mechanical circulatory support [b, **] | 30 (15%) |
| Early Multiple Organ Dysfunction Syndrome (MODS) [b] | 145 (72.5%) |
| Acute renal failure (RIFLE criteria) without CRRT [b] | 151 (75.5%) |
| Acute renal failure (RIFLE criteria) with CRRT [b] | 60 (30.2%) |
| ICU acquiredinfection (ENVIN-HELICS criteria) [b, 25, ***] | 124 (62%) |
| Days of mechanical ventilation [a] | 19.4 (17.1-21.6) |
| Intensive Care Unit (ICU) stay (days) [a] | 25 (22.5-27.4) |
| Intensive Care Unit (ICU) mortality [b] | 47 (23.6%) |

Data expressed as means and the corresponding 95% confidence interval[a] or as the number of patients and the corresponding percentage[b] * "Other surgeries" refers to other surgical procedures: abdominal (n=9), orthopedic (non polytraumatized, n=3), neurosurgery (non polytraumatized, n=3), thoracic (n=1), ** Mechanical circulatory support = intra-aortic balloon pump (n=15), VA ECMO (n=13), VV ECMO (n=8), ventricular assist device (n=4) and other devices (n=2); *** ENVIN-HELICS = National study of nosocomial infection surveillance in ICU: ventilator associated pneumonia (n=45), bloodstream (n=27), urinary tract (n=16), surgical site (n=10) and other source infections (n=25); CRRT = continuous renal replacement therapy; RIFLE = risk, injury, failure and end stage model. Early MODS defined as failure of 2 or more organ systems in the first 48 hours.[16]

**Table 3. Hemodynamic data recorded in the first 48 h of ICU stay and over the study course**

| Variable | ICU first 48 h | ICU overall |
|---|---|---|
| Lactate (mmol/L) n=200 | 3.5 (3.1-3.9) | 1.8 (1.7-1.9) |
| Cardiac index (L/min/m$^2$) n=107 | 2.6 (2.4-2.8) | 2.8 (2.6-2.9) |
| MAP (mm Hg) | 68 (67-70) | 73 (72-74) |

| | | |
|---|---|---|
| NE dose (μg/kg/min) n=200 | 0.71 (0.63-0.8) | 0.29 (0.26-0.33) |
| DA dose (μg/kg/min) n=11 | 2.51 (0.62-4.4) | 0.84 (0.45-1.23) |
| DBT dose (μg/kg/min) n=79 | 5.18 (4.25-6.11) | 2.84 (2.33-3.36) |
| Ep dose (μg/kg/min) n=13 | 0.14 (0.02-0.26) | 0.04 (0.01-0.06) |

Results expressed as means and corresponding 95% confidence intervals; MAP = mean arterial pressure; NE = norepinephrine; DA= dopamine; DBT = dobutamine; Ep = epinephrine.

**Table 4. Feasibility/efficacy of enteral nutrition**

| Variable | n=200 |
|---|---|
| Time from ICU admission to the start of EN (hours) [a] | 34 (31.2-36.8) |
| Days of EN [a, *] | 12.8 (12.6-12.9) |
| Kcal of EN delivered/patient/day [a] | 1159.2 (1098.1-1220.3) |
| Protein delivered by EN/patient/day [a] | 55.6 (52.4-58.7) |
| Daily energy balance during EN (kcal/patient/day) [a] | -432.3 (-496.4 to –368.2) |
| Cumulative energy balance of EN (days 1-14) (kcal) [a] | -4568.8 (-5291.4 to -3846.2) |
| Nutrition tolerance (%) [b] | 76.2 (72.3-80.1) |
| Need for PN (total/supplementary) [b] | 54 (27%) |

Variables expressed as means and 95% confidence intervals[a] or as number of patients and corresponding percentage[b]; *Refers to the days of EN prospectively assessed over the study course. Nutrition tolerance (%) = kcal delivered by EN/nutritional target in kcal. Energy balance and nutritional tolerance represent the means and 95% confidence intervals recorded over the study. kcal = kilocalories; EN = enteral nutrition; PN = parenteral nutrition.

**Table 5. Safety of enteral nutrition**

| Variable | Number of patients (%) |
|---|---|
| Suspected mesenteric ischemia | 9 (4.5%) |
| Confirmed mesenteric ischemia | 1 (0.5%) |
| High GRV | 69 (34.5%) |
| Abdominal distention | 53 (26.5%) |
| Diarrhea | 49 (24.5%) |
| Constipation | 57 (28.5%) |
| Vomiting/Regurgitation | 45 (22.5%) |
| NGT complications | 11 (5.5%) |
| Bronchoaspiration | 2 (1%) |
| Patients with complications | 154 (77%) |
| Patients with complications requiring EN discontinuation | 77 (38.5%) |

GRV = gastric residual volume; NGT = nasogastric tube; EN = enteral nutrition.

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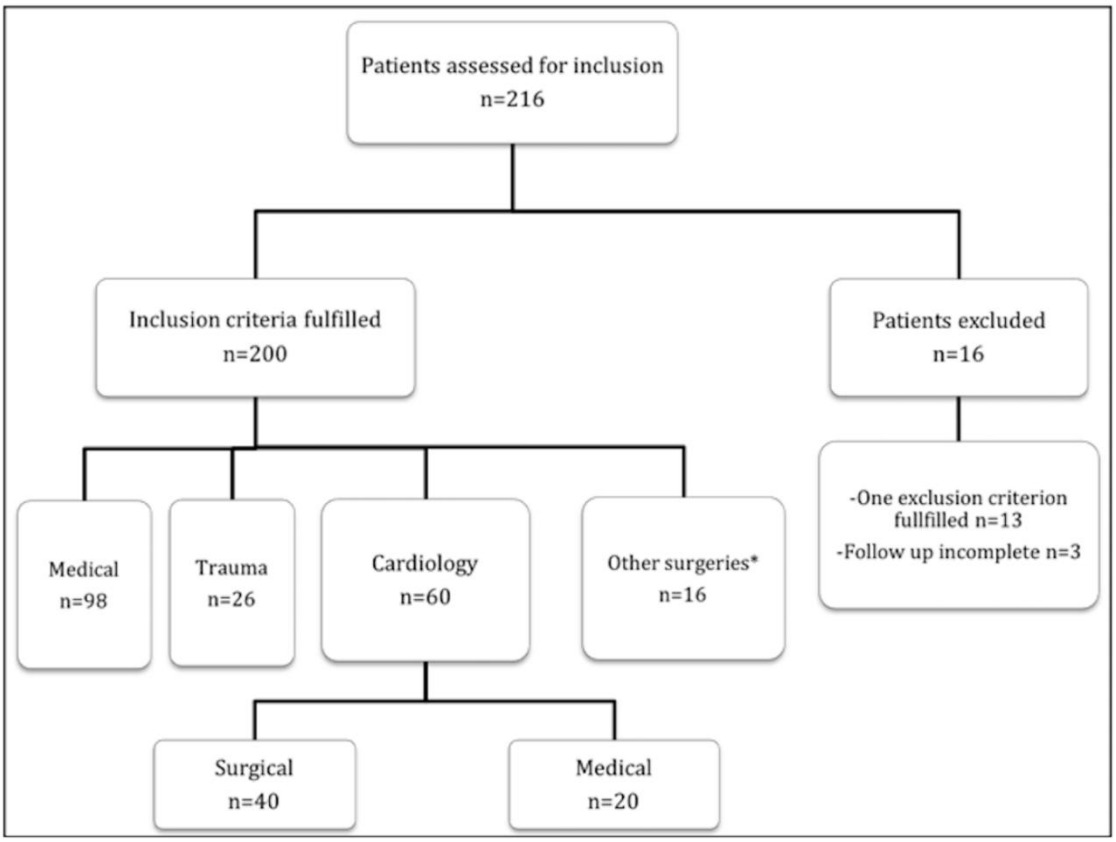


Figure 1 *Other surgeries: abdominal (n=9), orthopedic (non polytraumatized, n=3), neurosurgery (non polytraumatized, n=3), thoracic (n=1).

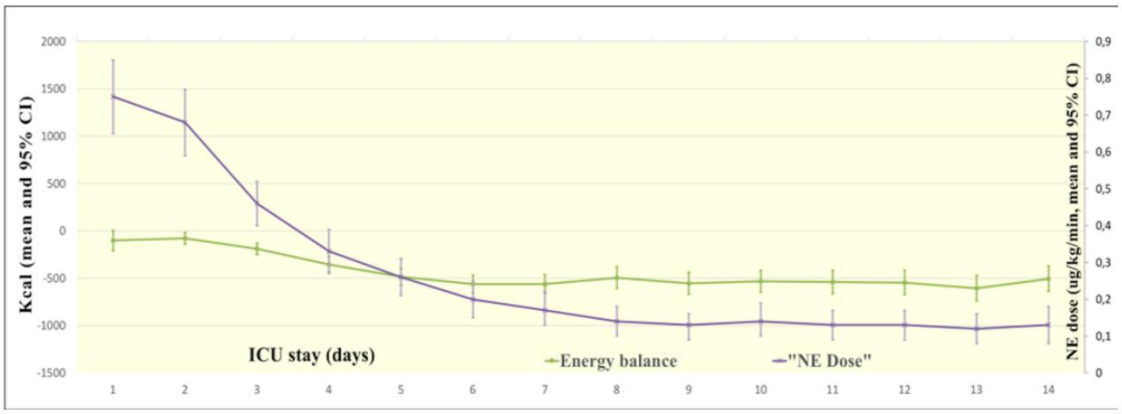


Figure 2 Energy delivery, energy balance, energy target and norepinephrine (NE) dose expressed as means and their corresponding 95% confidence intervals.