Nutrición Hospitalaria

Nutr Hosp 2011;26(Supl. 2):67-71
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198
CODEN NUHOEQ
S.V.R. 318

Chapter 15

Guidelines for specialized nutritional and metabolic support in the critically-ill patient. Update. Consensus SEMICYUC-SENPE: Septic patient

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Abstract

Nutritional metabolic management, together with other treatment and support measures used, is one of the mainstays of the treatment of septic patients. Nutritional support should be started early, after initial life support measures, to avoid the consequences of malnutrition, to provide adequate nutritional intake and to prevent the development of secondary complications such as superinfection or multiorgan failure.

As in other critically-ill patients, when the enteral route cannot be used to ensure calorie-protein requirements, the association of parenteral nutrition has been shown to be safe in this subgroup of patients. Studies evaluating the effect of specific pharmaconutrients in septic patients are scarce and are insufficient to allow recommendations to be made.

To date, enteral diets with a mixture of substrates with distinct pharmaconutrient properties do not seem to be superior to standard diets in altering the course of sepsis, although equally there is no evidence that these diets are harmful.

There is insufficient evidence to recommend the use of glutamine in septic patients receiving parenteral nutrition. However, given the good results and absence of glutamine-related adverse effects in the various studies performed in the general population of critically-ill patients , these patients could benefit from the use of this substance. Routine use of omega-3 fatty acids cannot be recommended until further evidence has been gathered, although the use of lipid emulsions with a high omega-6 fatty acid content should be avoided. Septic patients should receive an adequate supply of essential trace elements and vitamins. Further studies are required before the use of high-dose selenium can be recommended.

Nutr Hosp 2011; 26 (Supl. 2):67-71

Key words: *Sepsis. Septic shock. Glutamine. Arginine.*

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SEMICYUC: Spanish Society of Intensive Care Medicine and Coronary Units.
SENPE: Spanish Society of Parenteral and Enteral Nutrition.

RECOMENDACIONES PARA EL SOPORTE NUTRICIONAL Y METABÓLICO ESPECIALIZADO DEL PACIENTE CRÍTICO. ACTUALIZACIÓN. CONSENSO SEMICYUC-SENPE: PACIENTE SÉPTICO

Resumen

El manejo metabólico nutricional constituye, junto al resto de medidas de tratamiento y soporte, uno de los pilares del tratamiento del paciente séptico. Debe iniciarse precozmente, tras la resucitación inicial, con el objetivo de evitar las consecuencias de la desnutrición, proveer el adecuado aporte de nutrientes y prevenir el desarrollo de complicaciones secundarias como la sobreinfección y el fracaso multiorgánico.

Al igual que en el resto de pacientes críticos, cuando la ruta enteral es insuficiente para asegurar las necesidades caloricoproteicas, la asociación de nutrición parenteral ha demostrado ser segura en este subgrupo de pacientes. Los estudios que evalúan el efecto de farmaconutrientes específicos en el paciente séptico son escasos y no permiten establecer recomendaciones al respecto.

Respecto a las dietas enterales con mezcla de sustratos con diferente capacidad farmaconutriente, su uso no parece aportar, hasta el momento actual, beneficios claros sobre la evolución de la sepsis respecto a las dietas estándar, aunque tampoco hay clara evidencia de que sean perjudiciales.

A pesar de que no hay suficiente evidencia para recomendar el empleo de glutamina en el paciente séptico que recibe nutrición parenteral, éste podría beneficiarse de su uso, dados los buenos resultados y la ausencia de efectos adversos atribuible a la glutamina en los diferentes estudios llevados a cabo en el conjunto de pacientes críticos. No se puede recomendar el empleo rutinario de ácidos grasos ω-3 hasta que dispongamos de mayor evidencia, aunque debe evitarse en estos pacientes el empleo de emulsiones lipídicas con alto contenido en ácidos grasos ω-6. El paciente séptico debe recibir un adecuado aporte de oligoelementos y vitaminas. El empleo de selenio a dosis altas requiere de más estudios para poder recomendarlo.

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Palabras clave: *Sepsis. Shock séptico. Glutamina. Arginina.*

Introduction

Nutritional support in sepsis shows very important limitations in its indications and evaluation. On the one hand, the *Surviving Sepsis Campaign*[1] does not consider specialized nutrition as an issue that must be complied with, but, on the other hand, all reviews performed by experts claim the need for this nutritional support. In addition, the studies published on nutritional support in septic patients are very limited and the results of other populations of critically-ill patients or those suffering another aggression are usually extrapolated. The conclusions on the use of specialized nutritional support in sepsis are usually aimed at improving the hospital length of stay, organ function and other surrogate objectives, and only three studies have been published[2-4] that have reported a decreased mortality. An added difficulty is that most of studies on nutrition and sepsis were conducted with mixtures of nutrients, so it is difficult to allocate the results to one or the other substrate.

Therefore, in this scenario there is a common opinion about the need for feeding septic patients, but there is no definition yet of the quality, the amount, or the timelines for the requirements of substrates.

Is it safe to administer enteral nutrition to patients in septic shock?

As in all other critically-ill patients, provided the gastrointestinal tract is intact and the patient requires artificial nutrition, the enteral route is of choice over the parenteral. The start of enteral nutrition (EN) should be early, within 24-48 hour and after resuscitation of the patient. Splachnic infusion may be compromised in hypotensive patients with inadequate perfusion pressure and, although the reported incidence of intestinal ischemia associated with EN is low and particularly related to postpyloric nutrition[5] (III), [6,7] (IV), and there is no evidence contraindicating the administration of EN in early stages of the shock, it appears to be advisable to recommend, given the fatal consequences of intestinal ischemia, to start EN after patient resuscitation or at least when a stable shock stage has been reached, with an adequate perfusion pressure (doses of vasoactive drugs stabilized, metabolic acidosis and lactate stabilized and/or decreasing, mean blood pressure of ≥ 60 mmHg).

In any case, particularly in the early stages of shock, close monitoring for signs of intestinal intolerance (abdominal distension, increased gastric residue, etc.) is necessary to early identify signs of subclinical intestinal ischemia.

Is the use of parenteral nutrition harmful in sepsis?

In a 1-day observational prevalence study performed in 454 intensive care units (ICUs) in Germany[8] and in 415 patients with severe sepsis or septic shock, it was confirmed that patients with severe sepsis or septic shock receive in Germany a nutritional support preferably with parenteral nutrition (PN), alone or in combination with EN. After analyzing the results, it is concluded that the use of PN was associated with an increased risk of death[8] (III). However, in this study, for its limitations, no adjustment was made with other factors of treatment, for example if the antibiotic therapy was appropriate or resuscitation adequate, and the authors specified[9] that they do not refer to a causal relationship but to an association, and confirm that PN plays a role in patients with contraindications for EN or where the nutritional needs are not achieved by the enteral route.

In contrast, a randomized, controlled, prospective study on PN vs EN enriched with pharmaconutrients (mixture of arginine, ω-3 and antioxidants) in septic patients reported a greater intra-ICU mortality in the enteral group[10] (Ib).

Are diets with mixtures of pharmaconutrients indicated in sepsis?

Only one controlled study has been published on the effects of diets enriched with "immunomodulating" pharmaconutrients (arginine, ω-3, nucleotides, antioxidants) in septic patients in a critical condition. Its results indicate that the use of an enriched diet is associated with lower mortality compared with the use of a control diet[3] (Ib). In the study by Kieft et al.[11], in a group of critically-ill patients for various causes, no differences were seen in terms of mortality, infectious complications, length of stay in ICU and days on mechanical ventilation. An analysis of the patient subgroup with sepsis shows that this was so small (30 patients) that an efficacy study could not be considered in it[11] (Ib).

The metaanalyses published on studies comparing diets enriched with pharmaconutrients with non-enriched diets, do not include a specific analysis of the group of septic patients, because of the few studies available. However, there is a known controversy about the outcomes and recommendations of the different metaanalyses. Heyland et al.[12] suggested that the use of diets enriched with "immunomodulating" pharmaconutrients (IMD) may be associated with increased mortality. Montejo et al.[13], in contrast, concluded that there is sufficient evidence to use IMD in critically-ill patients, considering the benefits associated with their use and the lack of harmful effects. Marik and Zaloga[14], in the last metaanalysis published, concluded that only in the group of patients with sepsis, septic shock, or acute respiratory distress syndrome (ARDS), the use of IMD was associated with a significant decrease of mortality, secondary infections, and stay at the ICU, but provided this formula contained fish oil.

Other formulations enriched with pharmaconutrients, initially designed for acute lung injury (ALI) or ARDS, have been investigated in septic patients. A multicenter study in patients undergoing mechanical ventilation with severe sepsis and septic shock[4] (Ib) reported a 19.4% reduction in the absolute risk of mortality, improved oxygenation, more days free from mechanical ventilation, decreased stay at the ICU and less development of new organic dysfunctions in the group receiving the study diet. A more recent multicenter study[15] (Ib) showed a significant decrease in the mean length of stay in the ICU without affecting mortality or infectious complications in the intention to treat analysis.

Controversy about the use of diets enriched with pharmaconutrients (in the two modalities of arginine/ω-3/antioxidants or EPA/GLA/antioxidants) in septic patients persists. However, the results available do not seem to suffice for contraindicating the use of this type of diets in patients with severe sepsis. In contrast, administration may be followed by benefits.

Is the use of arginine harmful in sepsis?

It is known that sepsis is a condition associated with arginine deficit and arginine has been associated with benefits for sepsis, such as an increase in acute phase reactants, genesis of nitric oxide (NO) with antibacterial activity, action as bowel neurotransmitter and regulator of microcirculation, production of ornithine promoting cell growth and cell differentiation and activity in insulin stimulation, as well as modulation of cell signals from its metabolite, agmatin. However the use of arginine in sepsis is currently questioned in various clinical guides, unlike in other group of critically-ill patients. This is due to the fact that the results expressed in the above mentioned metaanalysis by Heyland et al.[12] on the use of pharmaconutrient formulations that contained arginine and where the authors concluded that the benefits were dependent on the amount of arginine (a higher supply was associated with lower mortality) but also on the target population, and therefore they suggested there was a trend towards increased mortality with arginine supply in critically-ill patients, particularly those with septic shock[12] (IV).

However, to enhance this controversy, in a later metaanalysis[14] the authors concluded that the action of IMD with arginine on the progress of patients with sepsis or systemic inflammatory response syndrome (SIRS) could not be evaluated using the studies reviewed in it[14] (Ia).

With regard to the results using arginine alone in sepsis, the small number of cases studied gives it a low level of evidence. Thus, in 2 studies of the same research group, supplements containing intravenous arginine did not evidence any hemodynamic adverse event, but these results have been only communications and have never been published[16,17] (III). Lorente et al.[18], with the administration of a bolus of 200 mg/kg of L-arginine in a group of 7 patients with septic shock, noticed immediate hemodynamic changes because of pulmonary and systemic vasodilation, though these changes were transient[18] (III).

The increased NO synthesis in sepsis is based on the evidence of the high plasma concentration of its degradation products, nitrates, nitrites (NOx). However, there are disagreements about the real changes in vivo in the genesis of NO and NOx. For the moment, there is only one study that has measured production in vivo of NO in septic patients via its conversion rate in NOx, and reporting slower NOx fractionated synthesis rates in septic patients (n = 6), while the absolute rate was identical to healthy controls (n = 10)[19] (IIb).

As arginine is an amino acid that is decreased in sepsis and it is considered necessary to restore its values, new pathways are under research to restore this deficit supplying citrulline[20].

Is glutamine administration of choice in sepsis?

Although no studies have been performed in humans to evaluate the effect of glutamine on septic patients receiving PN, there is sufficient evidence to the routine use of glutamine in all critically-ill patients receiving PN[21,22] (Ib). After aggression, glutamine plays a major role in inducing mechanisms of cell protection mainly through increasing production of heat shock proteins, as their expression protects against cell damage and against ischemia/reperfusion mechanisms[23] (IIa), which gives it a potential role to prevent progression to multiple organ failure.

With regard to glutamine by enteral route, currently there are insufficient data for recommending it in septic patients and to recommend its intravenous use, as a supplement, when the patient is receiving EN. In a randomized, controlled, prospective study in 55 patients with sepsis and comparing the administration of an enteral diet enriched with glutamine and antioxidants to a standard enteral diet, the intervention group had improved parameters of multiple organ failure versus the control group[24] (Ib), but these outcomes are, however, questioned because the intervention group received a significantly higher protein supply, which may have influenced the results.

What lipid emulsions must be used in sepsis?

The potential benefit of adding ω-3 to EN in critically-ill septic patients shows non-conclusive results, because it is based on studies with diets of different composition from other substrates, different amount and percentage of ω-3 and different comparative agents. Beneficial effects have been reported in terms of mortality, days on mechanical ventilation and days of stay at ICUs with administration of a diet rich in

EPA, with GLA and antioxidants[4], while in other studies, with the same diet, these results could not be confirmed and only reported a reduction in the incidence of nosocomial pneumonia and organ dysfunction.

As regards their use in PN, the results are somewhat more conclusive and are related to the dose of ω-3 provided. In a prospective study on a survey involving 661 ICU patients with PN ≥ 3 days, with a 10% emulsion of fish oil added to LCT versus a control of LCT, the dose-dependent effects of ω-3 on survival, days of stay, use of antimicrobials and organ dysfunction were evaluated[25]. The most favorable effects were obtained at doses of 0.1-0.2 g/kg/day for survival, infection rates and length of stay. In addition, antimicrobial requirements decreased 26% when comparing doses of 0.15-0.2 g/kg/day to doses < 0.05 g/kg/day[25] (III).

A subsequent randomized, double-blind, controlled study including 166 critically-ill medical patients receiving PN with MCT/LCT, or MCT/LCT supplemented with fish oil, in the subgroup of patients with sepsis[26] no differences were found on both IL-6 or other inflammatory markers, but also on mortality, days of stay at an ICU, days on mechanical ventilation, infectious or bleeding complications[26] (Ib).

A recent randomized, single-blind study[27] including 25 patients with sepsis receiving PN with MCT/LCT versus MCT/LCT/fish oil did not show significant differences in terms of mortality, days on mechanical ventilation or length of stay in ICUs[27] (IIa).

Do antioxidants play a relevant role in patients with sepsis?

The plasma concentration of micronutrients with antioxidant capacity decreases in critically-ill patients, particularly in septic patients[28] (IV). Therefore, special attention should be paid to the supply of trace elements (particularly selenium, zinc and copper) and vitamins in these patients.

It has been suggested that high-dose selenium supplements in patients with severe sepsis or septic shock can improve outcome. However, the studies available to date have found no significant differences versus the control group when analyses by intention to treat are performed[29,30] (Ib). Further clinical studies are required to evaluate the efficacy and safety of selenium in septic patients. The neutral outcomes of these studies may be related to inadequate doses, an inadequate method of administration or an incipient toxicity of sodium selenite, that could have masked a positive effect. The REDOX study, in the recruitment phase, may shed some light on the potential beneficial effect of selenium for these patients[31].

Recommendations

– In patients with septic shock and hemodynamic instability it is recommended to delay the start of specialized nutritional support until the patient has been adequately resuscitated and is in a stable condition (C).

– Parenteral nutrition is a safe route in sepsis when there is no other option for feeding patients (C). Complementary parenteral nutrition could be used when calorie supply requirements may not be reached by the enteral route (C).

– Enteral diets with mixtures of substrates with different pharmaconutrient capacity can provide outcome benefits in septic patients (C).

– Administration of diets enriched with arginine in severe sepsis and septic shock is not cleary associated with deleterious effects in patient outcomes (C).

– When parenteral nutrition is indicated, it is recommended to use glutamine supplements (B).

– In parenteral nutrition it is recommended to use lipid emulsions with low contents in ω-6 (B). Emulsions containing ω-3 may be used in these patients (C).

– High-dose selenium supplements alone may not be recommended routinely in septic patients (C).

Conflict of interests

The authors declare that they have participated in activities funded by the pharmaceutical industry for marketing of nutritional products (clinical studies, educational programmes and attendance to scientific events). No pharmaceutical industry has participated in the preparation, discussion, writing, and establishing of evidences in any phase of this article.

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