Total enteral nutrition vs. total parenteral nutrition in patients with severe acute pancreatitis

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RESUMEN

Objetivo: comparar la eficacia de la instauración precoz de nutrición enteral total (NET) frente a nutrición parenteral total (NPT) en pacientes con pancreatitis aguda grave (PAG).

Métodos: estudio prospectivo aleatorio. Se incluyeron consecutivamente 22 pacientes con PAG aplicando los criterios APACHE II, valores de PCR y graduación de Balthazar en la TC. El grupo I (n = 11) recibió NPT y el grupo II (n = 12) NET. Se valoró la respuesta inamatoria (PCR, TNF-α, IL-6), las proteínas viscerales (pre-albúmina, albúmina), la tasa de complicaciones (síndrome de respuesta inflamatoria sistémica, fallo multiorgánico, infecciones), las intervenciones quirúrgicas, la estancia hospitalaria y la mortalidad.

Resultados: no hubo diferencias significativas en los primeros 10 días entre los dos grupos en la evolución de los criterios APACHE II, en las concentraciones de PCR, TNF-α e IL-6 ni tampoco en los valores de pre-albúmina y albúmina. Siete pacientes del grupo I presentaron complicaciones graves frente a 4 del grupo II. Requirieron intervención quirúrgica 3 pacientes del grupo I. La estancia hospitalaria fue similar en los dos grupos. Dos pacientes del grupo I fallecieron.

Conclusiones: se ha observado una tendencia a una mejor evolución de los pacientes con PAG que utilizaron NET frente a los que utilizaron NPT.

Palabras clave: Pancreatitis aguda grave. Nutrición. PCR. TNF-α. IL-6.

ABSTRACT

Objective: to compare the efficacy of early total enteral nutrition (TEN) vs. total parenteral nutrition (TPN) in patients with severe acute pancreatitis (SAP).

Methods: a total of 22 consecutive patients with SAP were randomized to receive TPN (group I) or TEN (group II). SAP was defined applying APACHE II score, C-reactive protein (CRP) measurements and/or Balthazar CT scan score. Acute inflammatory response (CRP, TNF-α, IL-6), visceral proteins (pre-albumin, albumin), complications (systemic inflammatory response syndrome, multiorgan failure, infections), surgical interventions, length of hospital stay and mortality were evaluated.

Results: no significant differences were found between the two groups in the APACHE II score, in CRP, TNF-α and IL-6 concentrations or in pre-albumin and albumin levels over the first 10 days. Seven patients in group I and 4 in group II suffered severe complications. Three patients in group I required surgical intervention. Length of hospital stay was alike in the two groups. Two patients from group I died in the course of the hospitalization.

Conclusions: SAP patients with TEN feeding showed a tendency towards a better outcome than patients receiving TPN.

Key words: Severe acute pancreatitis. Nutrition. C-reactive protein. TNF-α. IL-6.


INTRODUCTION

Severe acute pancreatitis (SAP) is a hypermetabolic, hyperdynamic process that creates a state of catabolic stress with an acute inflammatory response and consequent nutritive damage (1). According to the 1992 Atlanta classification (2), SAP can progress in two stages (3). In the first stage (7-10 days), which is initially sterile, a systemic inflammatory response syndrome (SIRS) (4) with septic complications (5) and
multiple organ failure (MOF) (6) may occur, leading to death. In the second stage, usually after the second week in the course of disease, local complications such as pancreatic necrosis may develop. In cases of infected pancreatic necrosis the patient’s life is threatened (2). Most complications and deaths that occur in SAP are due to an inflammatory immune response to pancreatic necrosis and/or infection.

An increasing body of evidence suggests that the gut plays an important role in the immune and inflammatory response to SAP. Experimental data suggest that the endogenous cytokines involved in this response are stimulated by endotoxin and other bacterial products absorbed by a metabolically altered intestine (7). Several studies in patients with severe trauma and burns have shown that total enteral nutrition (TEN) significantly diminishes the acute inflammatory response phase and the incidence of septic complications when compared to total parenteral nutrition (TPN) (8,9). The suggested mechanism of this response is that feeding through the gut would maintain the intestinal barrier function, thus precluding bacterial and toxin translocation from the intestinal lumen.

TPN has been the standard practice for providing exogenous nutrients in patients with SAP in order to improve patient nutritional status, and to avoid the stimulus of pancreatic secretion. However, TPN has several disadvantages such as an increased risk of infection through the central venous catheter, severe hyperglycemia, and electrolyte disturbances. Furthermore, removal of oral feeding could favor a disruption of the intestinal barrier function, thus increasing its permeability (10,11).

In the last few years several prospective randomized studies (12-19) have proposed early TEN for patients with acute pancreatitis as a therapeutic tool to attenuate SIRS and septic complications. The potential advantages of this strategy would include a support of the intestinal barrier to prevent bacterial translocation, and also the elimination of TPN-associated infections. However, among the above-mentioned studies those including only SAP patients were scarce (13,18,19). The aim of this study was to compare the efficacy of early TEN vs. TPN in the course of SAP in our population.

**PATIENTS AND METHODS**

This prospective randomized trial included 22 consecutive patients who were distributed into two groups according to a computerized random number generation. The option corresponding to each patient was placed in sealed envelopes that were opened immediately prior to inclusion: patients in group I (n = 11) received TPN and patients in group II (n = 11) received TEN.

Patients of either sex who were 18 years or older with a SAP diagnosis of any etiology were included at admission to hospital. Clinical criteria of acute pancreatitis included: abdominal pain and increased serum amylase and/or lipase levels at least 3 times the upper limit of the reference range. The diagnosis of SAP was made within 48 hours when two or more of the following criteria were evidenced: an Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 8 (20), a C-reactive protein (CRP) level in excess of 150 mg/L, and/or a Balthazar D or E grade in the abdominal CT scan (21). Patients under 18 years of age, pregnant women, and relapsing chronic pancreatitis cases were excluded.

All patients were submitted to intensive control for at least the first 72 hours after admission. Their water and electrolytic balance was maintained during the acute phase, and patients were then subjected to strict hemodynamic control. They were transferred to an intensive care unit (ICU) if respiratory and/or renal function deteriorated (7 patients in group I and 4 patients in group II). At this point, with a maximum of 72 hours, all patients were randomized and distributed to one of the two groups, and the assigned nutrition was immediately started.

Group I patients received a 24-hour continuous infusion of TPN through a central venous catheter (subclavian/jugular). Venous infusion was started at a rate of 40 ml/h and increased 20 ml/h every 4 hours until the required needs were met. The goal of feeding rates was to administer a rate of 1.5-2 g proteins/kg/day and 30-35 kcal/kg/day. A ratio of 100-125/1 of non-protein calories/nitrogen was aimed for.

Group II patients received TEN (PEPTISORB®, Nutricia S.R.L., Madrid) through a single-lumen, 114-cm long naso-jejunal 10 F feeding tube whose tip was placed, under fluoroscopic screening, close to Treitz’s ligament. The initial infusion rate was 25 ml/h with increases of 25 ml/4 h until requirements were reached. The goal of feeding rates was the same as that proposed for group I (1.5-2 g of proteins/kg/day and 30-35 kcal/kg/day).

During the first 10 days after admission, besides regular clinical and biochemical monitoring, serum CRP, levels of pro-inflammatory interleukines TNF-α and IL-6, and visceral proteins (prealbumin, albumin) were monitored. The total number of analyzed samples corresponding to both groups was 396. Patients included in the study were followed up during their hospitalization for clinical control of pain, bowel movements, metabolic disorders, fluid cultures (if needed), and computerized tomography (CT) scans when considered necessary in order to detect pancreatic necrosis or abscess formation. Serum TNF-α and IL-6 concentrations were measured using two enzyme-chemoluminometric assays on the automated Immulite, analyzer (Diagnostic Products Corporation, Los Angeles, CA, U.S.A.). Reference ranges were ≤ 8 ng/L for TNF-α and ≤ 4 ng/L for IL-6, in accordance with manufacturer’s data based on healthy controls.

The goals of the study were to evaluate inflammatory response (CRP, TNF-α, IL-6), visceral proteins (pre-albumin, albumin), rate of complications (SIRS, MOF, and infections), number of surgical interventions, length of hospital stay, and mortality rate.
Statistical analyses included a Mann-Whitney test, Fisher’s exact test, and $\chi^2$ test with a confidence interval of 95%.

This study was authorized by the Hospital Ethics Committee, and a written informed consent was obtained for all patients.

RESULTS

Demographic data and etiology are shown in table I. At the initial evaluation APACHE II criteria and CRP determinations showed no significant differences between the two groups regarding the severity of acute pancreatitis. With regard to severity as measured by CT and applying the Balthazar score, 5 patients in group I and 3 patients in group II were classified as grade D-E.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Group I (TPN)</th>
<th>Group II (TEN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 11 p.</td>
<td>n = 11 p.</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.6 ± 15.6</td>
<td>61.2 ± 16.6</td>
</tr>
<tr>
<td>Sex</td>
<td>8 males</td>
<td>8 males</td>
</tr>
<tr>
<td></td>
<td>3 females</td>
<td>3 females</td>
</tr>
<tr>
<td>Etiology</td>
<td>7 biliary</td>
<td>4 biliary</td>
</tr>
<tr>
<td></td>
<td>4 alcoholic</td>
<td>1 alcoholic</td>
</tr>
<tr>
<td></td>
<td>3 other etiologies</td>
<td>3 other etiologies</td>
</tr>
<tr>
<td></td>
<td>3 idiopathic</td>
<td></td>
</tr>
</tbody>
</table>

In group II, other etiologies were: 2 of pharmacological origin and 1 hypertriglyceridemia.

There were no complications related to the placement of the feeding tube. NET administration was well tolerated by all patients, although infusion rate had to be reduced in most cases due to nausea, abdominal fullness, or diarrhea, etc. After 5 days all patients on NET received the predicted amount of calories (Table II). The feeding tube remained in place in most patients for a minimum of 15 days. In the course of the disease, 2 patients from group I developed an infection of the central venous catheter that was confirmed by tip culturing. Three other patients in this group had positive blood cultures for: 1 *Staphylococcus epidermidis* and *Pseudomonas*, 1 *Staphylococcus aureus*, and 1 *Streptococcus agalactiae*.

During the first 10 days of disease no significant differences were observed between the two groups in APACHE II criteria, CRP, TNF-α or IL-6 serum levels (Figs. 1 and 2), or prealbumin and albumin levels (Fig. 3).

Seven patients in group I had severe complications: 3 patients had infection (2 pancreatic infected necrosis), 2 patients MOF (1 with infection) and 2 patients had SIRS (both with infection). In group II 4 patients presented with severe complications: 2 SIRS, 1 infection of the lower urinary tract, and 1 portal venous thrombosis (Table III). Eleven patients, 6 from group I and 5 from group II, were treated with antibiotics. Two patients from...
group I and all patients in group II were treated with imipenem, whereas the remaining 4 patients in group I were treated with piperacillin-tazobactam.

Three group I patients required surgery during their hospital stay. One patient had pancreatic necrosis and MOF, and was submitted to debridement. The second patient underwent surgical drainage for fluid collections, one of which was infected, in a first procedure, and debridement of pancreatic necrosis and drainage of fluid collections in a second intervention. Lastly, the third patient underwent pancreatic abscess drainage (Table IV).

Mean length of hospital stay was similar in both groups (Table IV). Two patients in group I and 1 patient in group II required ICU admission.

Finally, 2 patients in group I died: one as a consequence of pancreatic necrosis and MOF, and the other following bronchoaspiration in the postoperative period after a surgical drainage of peripancreatic collections (Table IV).

**DISCUSSION**

The treatment of SAP is initially based on supportive measures including, as an essential goal, the maintenance of an adequate nutritional status. Human and animal studies have shown that the use of TPN may deteriorate systemic and intestinal immunity, and contribute to the atrophy of intestinal mucosa, with the resulting damage of the intestinal barrier function (22-25).

Studies with a rigorous, randomized, prospective design comparing TEN vs. TPN are scarce in acute pancreatitis (15). Likewise, studies in which only SAP patients are included—as in the present work (13,19)—are lacking. Although our study has a limited number of patients, the results obtained are consistent with those reached in other works with SAP patients (13,14,26).

In the present study no difficulties were encountered in the placement of feeding tubes or in their maintenance in the correct position. As in other series (27), TEN was usually well tolerated in patients with paralytic ileus. However, providing the predicted amount of calories or keeping a feeding tube properly in place may be necessary before TPN initiation (28). Neither of these events occurred in any patient in the present series. It has recently been reported that no clinical differences were found between patients who received TEN through a naso-gastric tube and patients who were fed through a naso-jejunal tube. Such findings need to be confirmed in order to open new possibilities in the nutritional support of acute pancreatitis (29).
In our study no significant differences were found between TEN and TPN in acute inflammatory markers (CRP, TNF-α and IL-6) or in APACHE II scores during the first 10 days of disease. These results are similar to those obtained by Powell et al. (26) in a randomized group of 28 SAP patients. However, other reports have shown improvements in systemic inflammatory response. Wilson et al. (14) emphasized a significant reduction of CPR levels in patients subjected to TEN, with the condition in this case that initial CPR levels were lower than those observed in our series. Furthermore, McClave et al. (12), including mild and moderate acute pancreatitis cases, observed a reduction of baseline severity scores (Ranson, APACHE III) in the group of patients fed by TEN. An increased systemic inflammatory response evidenced by elevated levels of pro-inflammatory cytokines (IL-6, etc.) has been reported in other hypermetabolic stress states (30,31).

Regarding the number of complications observed in this series of SAP we found that they predominated in the group of patients receiving TPN with the development of pancreatic necrosis, fluid collections, MOF, and SIRS, to which infections with several germs were frequently added. This observation is in accordance with most studies in which, in contrast to patients fed by TPN, those receiving TEN had a significant reduction of infections (15). In this sense, Windsor et al. (14) reported 3 episodes of sepsis in 18 patients fed by TPN as compared to none in the group of patients receiving TEN. Kalfarentzos et al. (13) described 4 patients with infected pancreatic or peripancreatic necrosis in a group of 20 patients with TPN as opposed to only 1 patient in the group of 18 patients with TEN. It is noteworthy that in other nondigestive disorders fewer septic complications have been observed with TEN as compared to TPN (32,33). On the other hand, although it has not been proven irrefutably, the fact that most microorganisms causing SAP infection are enteropathogens suggests that bacterial translocation could be the mechanism responsible for sepsis in pancreatitis (34-36).

### Table IV. Data corresponding to surgical interventions, mean length of hospital stay, and mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (TPN)</th>
<th>Group II (TEN)</th>
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<tbody>
<tr>
<td>n = 11 p.</td>
<td>n = 11 p.</td>
<td></td>
</tr>
<tr>
<td>Surgical interv.</td>
<td>3 (1 necrosis and MOF, 1 necrosis and fluid collections, 1 abscess)</td>
<td>–</td>
</tr>
<tr>
<td>Mean length hospital stay (days)</td>
<td>30.7</td>
<td>30.2</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1 necrosis and MOF, 1 post-op. bronchial aspiration)</td>
<td>–</td>
</tr>
</tbody>
</table>

Finally, although the two patients who died in the present study belonged to the TPN group, most published works have not detected significant differences in mortality related to the nutrition type used (15).

As with results from most published series, our present findings support a better outcome in SAP patients receiving enteral rather than parenteral nutrition.

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**REFERENCES**


