ORIGINAL ARTICLE

EARLY NASOGASTRIC FEEDING IN PREDICTED SEVERE ACUTE PANCREATITIS - A CLINICAL RANDOMIZED STUDY

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MINIABSTRACT

Early, nasogastric enteral nutrition (EN) in patients with predicted severe acute pancreatitis was feasible and resulted in better blood-glucose control as compared to isocaloric total parental nutrition. No benefits on intestinal permeability or the acute inflammatory response were seen by EN.

STRUCTURED ABSTRACT

Objective: To compare the efficacy and safety of early, nasogastric enteral nutrition (EN) with total parenteral nutrition (TPN) in patients with predicted severe acute pancreatitis (SAP).

Summary Background Data: In SAP, the magnitude of the inflammatory response as well as increased intestinal permeability correlates with outcome. Enteral feeding has been suggested superior to parenteral feeding due to a proposed beneficial effect on the gut barrier.

Methods: Fifty patients who met the inclusion criteria were randomized to TPN or EN groups. The nutritional regime was started within 24 hours from admission and EN was provided through a nasogastric tube. The observation period was ten days. Intestinal permeability was measured by excretion of polyethylene glycol (PEG) and concentrations of anti-endotoxin core antibodies (Endocab). Interleukines (IL) -6, -8 and CRP (C-reactive protein) were used as markers of the systemic inflammatory response. Morbidity and feasibility of the nutritional route were evaluated by the frequency of complications, gastrointestinal symptoms and abdominal pain.

Results: PEG, Endocab, CRP, IL-6, APACHE II score, severity according to the Atlanta classification (22 patients), gastrointestinal symptoms or abdominal pain did not significantly differ between the groups. The incidence of hyperglycemia was significantly higher in TPN patients (21/26 vs. 7/23; $p < 0.001$). Total complications (25 vs. 52; $p = 0.04$) and pulmonary complications (10 vs. 21; $p = 0.04$) were significantly more frequent in EN patients, although complications were diagnosed dominantly within the first three days.

Conclusion: In predicted SAP, nasogastric early EN was feasible and resulted in better control of blood glucose levels, though the overall early complication rate was higher in the EN group. No beneficial effects on intestinal permeability or the inflammatory response were seen by EN treatment.

INTRODUCTION

The mortality rate in patients with severe acute pancreatitis (SAP) is reported in the range 9 – 27% [1, 2]. Mortality has two peaks, i.e. "early" during the first week, when the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) develop and "late" after 1-3 weeks, when mortality often is caused by MODS together with infections and sepsis [3, 4]. The production of cytokines, like interleukines (IL) -6 and -8, increase early on during the course of SAP and play a dominant role in the development of SIRS [5]. The magnitude of the inflammatory response correlates with the development of MODS and death [6].

The second peak in mortality usually involves MODS together with infections, that frequently are caused by gram-negative bacteria [7]. The predominance of gram-negative bacteria found in pancreatic infections supports the theory on the gut fuelling the disease process [8]. Gut barrier injury results in potential translocation of endotoxin and bacteria through the epithelial layer to the lamina propria, mesenteric lymph nodes and the systemic circulation and thereby cause sepsis and infections also at distant sites. Bacterial translocation has been demonstrated in experimental acute pancreatitis, but is still not proven in humans. Indirectly, there are evidence on translocation by the findings of bacteria of enteric origin in patients with infected necrotic pancreatic tissue [9]. Possibilities to measure translocation are not directly available and this has resulted in the frequent use of intestinal permeability as a mode of evaluating gut barrier function. Intestinal permeability may play an important role in the pathophysiology of SAP and clinical prospective studies have shown that increased gut permeability correlates with increased levels of endotoxin and also the grade of severity of pancreatitis [10, 11].

Therapies that aim to preserve and restore intestinal barrier function and thereby improve outcome have included enteral nutrition (EN). In experimental studies enteral feeding preserves the gastrointestinal mucosa and microbial ecology, reduces bacterial translocation and maintain immunocompetence of the host [12]. Comparisons of enteral versus parenteral nutrition in patients with SAP have pointed at a reduction of infectious complications, length of hospital stay and costs [13-17].

In SAP, enteral feeding is usually delivered via the nasojejunal route, which is more inconvenient as compared to a nasogastric position of the tube. The insertion of jejunal tubes involves radiographic screening and endoscopic placement, which delays the start of EN, and moreover, proximal dislocation of the tube is frequent [18]. The rational for using the jejunal route or alternativly fasting the patients is that nutrients passing the duodenum induce a cholecystokinin release that stimulates pancreatic enzyme secretion and therefore is thought to cause exacerbation of the pancreatitis and potential tissue injury [19]. However, the relevance of the concept of "put the pancreas at rest" is not truly proven in clinical studies. The exocrine pancreatic secretion is suppressed during the course of experimental acute pancreatitis [22], and in a recent clinical randomized study 49 patients with SAP, nasogastric feeding was not found to exacerbate the pancreatitis process [20, 21].

Proper timing is probably crucial for achieving success with therapeutic interventions, including modulation of inflammatory mediator production and release. In SAP, plasma concentrations of IL-6 peaks about 36 hours after onset of pain and organ dysfunction develop most commonly on the second or third day [22]. Potentially, a therapeutic window exist up to about 48 and 72 hours

from pain onset, i.e. in the time phase usually required for the development of remote organ dysfunction [23].

The present study aimed to evaluate the efficacy and safety of early, nasogastric, enteral nutrition as compared to total parenteral nutrition in patients with predicted SAP.

METHODS

Protocol

This prospective randomized study was conducted between June 2002 and December 2004. Adults (≥ 18 years) admitted to Lund University Hospital with the clinical diagnosis of acute pancreatitis were considered for inclusion. Inclusion and exclusion criteria are summarized in Table 1 [24-26]. Fifty patients were recruited, 26 in TPN (total parental nutrition) group and 24 in EN group. One patient from each group was considered as protocol violators (not fulfilling set criteria for study nutrition) due to surgery performed after study inclusion on day two in one case and a dislocated tube that the patient did not accepted to be replaced in the other. Written informed consent was obtained from all participating patients. The local ethic committee of the University of Lund approved the study protocol.

Patients were assigned to receive either TPN or EN and the nutritional support to start within 24 hours from admission. The nutritional regime per protocol aimed to be isocaloric between groups with the energy target of 25 cal/kg/day based on admission weight. In both groups, standard formulas without specific immunomodulating nutrients were used. TPN (Kabiven® PI, Fresenius-Kabi, Uppsala, Sweden) was infused via a peripheral or central venous catheter. EN

(Fresubin® original, Fresenius-Kabi, Uppsala, Sweden) was administered via a nasogastric tube (Flocare, Nutricia Healthcare SA, Châtel-St-Denis, Switzerland). The initial rate of EN was 25 ml/h and gradually increased daily up to 100 ml/h if tolerated and needed. The aim was to reach full nutrition within 72 hours. If a patient was unable to tolerate the prescribed rate of enteral feeding, the rate was reduced by 50 % and gradually increased again when tolerated. In order to maintain isocaloric groups, the TPN group did not receive Kabiven® on day one since the amounts of delivered in EN patients initially were small. Fluids, such as crystalloids or colloids, were added in both groups in order to fulfill the individual's needs of fluid and energy (in case of reduced rate). Oral feeding was reintroduced when amylase and CRP levels had decreased and abdominal pain had resolved. Regular hospital diet was introduced gradually, in general initially starting with liquid and then solid food. Patients were monitored daily for nutritional supply, gastrointestinal symptoms (nausea, vomiting, and diarrhea) and pain by visual analog scale (VAS) performed at rest. Patients were treated according to clinical routine including pain control, symptomatic and organ supportive treatment and when indicated, restrictive indications for surgery. Broad-spectrum antibiotic therapy was used according to current recommendations [27]. The observation period was ten days and follow-up was conducted after three months.

The primary endpoint was intestinal permeability measured by excretion of polyethylene glycol (PEG) in urine. Concentrations of antiendotoxin core antibodies (Endocab) for immunglobulin M (IgM) were also used as an indirect marker for intestinal permeability. IL -6, -8 and C-reactive protein (CRP) were used as markers of the systemic inflammatory response. Morbidity and feasibility of the nutritional route were evaluated by the frequency of complications, gastrointestinal symptoms and abdominal pain. Power calculations were based on published data [10, 28] and a sample size calculation showed that 42 patients would be required to demonstrate a

difference of 10% between groups in PEG excretion at the 5% level of significance with a power of 80%.

Data are presented as median and interquartile range. Comparisons between groups were performed using the χ^2 tests for binary data or Fisher's exact test for small samples. Continuous variables were compared with the Mann-Whitney *U* test. P-values of less than 0.05 were considered significant. Statistical analyses were performed with SPSS version 12.0.2. (SPSS, Chicago, Illinois, USA). Patients had to receive the study diet for at least 48 hours to be counted in the calculations of outcome data and the two groups were compared on an intention-to-treat basis.

Assignment

The patients were randomly divided into two groups and allocation concealment was by the use of sealed, numbered envelopes. The assignment was balanced with the use of blocks of four.

Blinding Procedures

It was not possible to blind the present study because of the nature of the treatment arms. Physicians and nurses from the staff collected patient data and fulfilled the study documentation in an attempt to minimize observer bias. A data analyst from the Competence Centre for Clinical Research at the Lund University Hospital performed the statistical analyses on the primary and secondary endpoints.

Analysis

Intestinal permeability was assessed noninvasive by measuring urinary excretion of an orally

administered marker. The substance PEG is non-toxic, not normally absorbed, not naturally present in urine, non-degradable by bacteria and permeates the epithelial layer paracellularly [29]. The patients were given 40 g of PEG (Macrogolum® 3000, M=3000 Da, Apoteksbolaget, Stockholm, Sweden) day one, three and seven. PEG was dissolved in 150 ml of water and administered either orally or through a nasogastric tube. Urine was collected over 24 hours, the volume was measured, and the sample was stored in –20°C and subsequently PEG was quantified using liquid chromatography and mass spectrometry as detector (Hewlett Packard 1100 series LC system, Esquire-LC trap mass spectrometer, Bruker Daltonics Inc, Billerica, Massachusetts, US) [30]. Urinary PEG excretion was expressed as the percentage of the administered dose. Samples from ten healthy volunteers were used as controls.

Blood samples were collected after the inclusion in the study (baseline) and after 12 hours, 1, 3, 5, and 7 days. The samples were centrifuged at 2200 x g (3200 rpm, rotor diameter 19.1 cm) at 10 minutes, plasma collected and stored at – 70°C for subsequent analysis. Determination of EndoCab for immunglobulin M (IgM) levels by enzyme linked immunosorbent assay (ELISA) was used as an indirect measure of lipopolysacharide (LPS) exposure. An increase in systemic LPS levels results in decreased levels of unbound antibodies [31]. Values were expressed as median units / ml (MU/ml) (HyCult Biotechnology, Uden, Netherlands). Samples from ten healthy volunteers were used as controls. Levels of IL-6 and -8 were measured by ELISA (Quantikine®, R&D Systems Europe, Abingdon, UK).

Clinical data

Clinical data that was collected included age, gender, etiology, time from onset of pain to baseline, weight at admission, APACHE II on day 1 and 3, total parental nutrition, enteral

nutrition, fluid administration, energy delivery, route of nutrition, hyperglycemia (defined as blood glucose ≥ 10 mmol/L), insulin treatment, gastrointestinal symptoms (nausea, vomiting, diarrhea), abdominal pain, days until intake of oral food, pain recurrence after refeeding, antibiotic prophylaxis, surgery, complications, mortality, length of hospital stay, days at the intensive care unit and compliance to protocol.

RESULTS

At inclusion, the groups were comparable with respect to clinical characteristics such as age, sex, etiology, weight, BMI, APACHE II and time from onset of pain to baseline (Table 2). According to the Atlanta classification system [32], 22 (46%) patients were defined as severe and 26 (54%) as mild of the finally evaluated 48 patients. There was a tendency to more severe patients in the EN group (14/23 [61%] severe) as compared to the TPN group (8/25 [32]% severe), although the differences did not reach clinical significance ($p = 0.08$).

Intestinal permeability

PEG excretion was assessed in 40 of the 48 (83%) patients. Missing samples were equally distributed between the groups. The median PEG excretion in the TPN group was 1.2% (0.3-2.3) as compared to 1.6% (0.7-3.2) in the EN group; $p > 0.30$ at baseline, 0.6% (0.4-1.0) in the TPN group versus 2.0% (1.1-3.9) in the EN group; $p = 0.003$ on day 3 and 1.1% (1.0-1.9) in the TPN group versus 2.0% (1.0-3.8) in the EN group; $p > 0.30$ on day 7. No significant differences were found in Endocab IgM levels at any time point between the TPN and EN group. For all patients EndoCab concentrations decreased between day 2 and 5.

Systemic inflammatory response

The concentrations of IL -6, -8 and CRP at baseline are shown in Table 2. No significant differences were found in IL-6 or CRP levels between the treatment groups. The baseline concentrations of IL-8 were significantly higher in the EN group as compared to the TPN group (22.3 [13.3-27.8] versus 79.8 [46.3-127.3] pg/ml; $p = 0.03$). For all patients the IL-6 peak early, maybe even before admission and CRP peaked as expected, later with maximal concentrations on day 3. At every time point, when comparing mild and severe pancreatitis patients, both IL-6 and CRP median concentrations were significantly higher in severe disease e.g on the day for their peak values were 100 [55-210] vs. 275 [158-315] pg/ml; $p = 0.001$ for IL-6 at baseline and 143 [79-199] vs. 278 [230-332] mg/L; $p < 0.001$ for CRP on day 3.

Nutritional outcome

The nutrition per protocol was initiated in median 17 (10-24) hours after admission in the TPN group and 19 (14-24) hours in the EN group. The energy delivery per protocol was 1300 (1230-1530) calories / day in the TPN group versus 1250 (1100-1530) calories / day in the EN group ($p > 0.30$). The nutritional goal of 25 kcal/kg/day was achieved in 66% (based on median weight for each group) in both groups. Intake of liquid or solid food without TPN/EN supplement was achieved in median on day 6 (5-9) in both groups. By the time when oral food was reintroduced, 13 of 25 (52%) patients in the TPN group and 12 of 22 (55%) patients in the EN group still had limited abdominal pain, but no patient interrupted their oral feeding because of pain relapse.

Route

The enteral nutrition was delivered through a clinifeeding tube in 18 of 24 (75%) patients, while 6 (25%) patients received their enteral feeding in an already placed nasogastric tube. TPN was

administered via the peripheral route in all patients except for two patients who received a central venous catheter. Five of 24 (21%) patients in the EN group received central venous catheters for the administration of fluids and drugs.

Feasibility

There were no complications associated with insertion of the nasogastric tubes. In no patient, EN had to be withdrawn. In 3 of 23 (13%) patients, the feeding had to be interrupted for a maximum of 12 hours due to gastric retention. No patients demonstrated any signs of aspiration. The number of gastrointestinal symptoms was 23 in the TPN group and 17 in the EN group and did not statistically differ between the groups ($p > 0.30$). Abdominal pain, evaluated by VAS, was in median 6 (4-8) in the TPN group and 7 (6-8) in the EN group on day one. No significant differences were shown on any day when comparing TPN and EN patients.

Clinical outcome

The length of hospital stay was in median 7 (6-14) days in the TPN group and 9 (7-14) days in the EN group ($p = 0.19$). A total of 6 out of 50 (12%) patients were admitted to the intensive care unit (2 patients in the TPN group and 4 patients in the EN group), five due to organ failure and one patient due to severe pain. No significant difference was seen between the groups in the frequency of antibiotic prophylaxis (17/25 vs. 18/23; $p > 0.30$). One patient in each group underwent surgery during hospital stay; cholecystectomy (on day 2) and necrosectomy (after 10 weeks), respectively, was performed. The incidence of hyperglycemia at any time point during nutritional support and during the first 7 days was significantly higher in TPN patients (21/26 versus 7/23; $p < 0.001$). The concentrations of plasma glucose are shown in Figure 1. One patient in the EN group had diabetes mellitus prior to admission and was therefore excluded in the

calculations of hyperglycemia. No significant differences were shown between the groups concerning the number of patients treated with insulin (9 patients in the TPN group versus 3 patients in the EN group; p = 0.10). Insulin was administered at a blood glucose level of in median 16 (14-19) mmol/L in both groups.

Complications

Twenty-six patients developed complications, 10/26 (40%) in the TPN group and 16/23 (70%) in the EN group (p = 0.05). Pulmonary complications and the total number of complications were significantly more frequent in EN patients (Table 3). Three septic complications were found in the EN group and none in the TPN group (p = 0.10). In both groups, most of the complications were diagnosed early, i.e. within the first three days. Thus in the TPN group 18/25 (72%; p = 0.01) and in the EN group 41/51 (80%; p < 0.001) of the total complications were early. Late complications did not differ between groups, being 7/25 (28%) in the TPN group and 10/51 (20%) in the EN group (p >0.30 in both groups). Multiple organ failure, defined as two or more failing organ systems [32], was found in 2 (4%) patients, one in each group. One death in the EN group occurred on day 3 in a 91 years old female, caused by circulatory failure. The overall mortality rate was thus 2% (1/48).

Follow-up

By the time of follow-up after three months, 23 of 25 (92%) patients in the TPN group and 18 of 22 (82%) in the EN group (p > 0.30) had no symptoms left related to their SAP. Symptoms in the six patients with some complaints were pain, fever or pathologic liver function tests. Three of these patients had underlying pseudocysts, all in the EN group.

DISCUSSION

Knowledge from clinical studies on the efficacy of EN on intestinal gut barrier function in SAP is limited[33]. In the present study, it does not seem that early EN without supplements renders any benefits on gut barrier function, as evaluated by urinary excretion of orally administered PEG and systemic levels of EndoCab, in patients with SAP. On day three, the intestinal permeability (measured by PEG) was increased in the group that received EN. The permeability parameters in our study do not fully support the otherwise frequently suggested benefits provided by EN on the gut, including restoration of permeability changes. Instead, the present findings support the results presented by Powell et al., demonstrating that intestinal permeability was not favoured by EN and permeability instead significantly increased by day four after initiated EN [34]. EN per se may increase the demands on mucosal blood supply and this might contribute to the leakage over the endothelial barrier and interstitial oedema formation, thereby facilitating gut barrier permeability. Powell et al. administered a minimal dose of nutrition and it may not have been sufficient to influence on the gut mucosal barrier. In the present study, the amounts of EN administered were 66% of the estimated energy target, which is in the upper range of what has been achieved in other studies comparing EN with TPN [15-19]. There are other factors than administered volumes that could influence on the efficacy of enteral feeding on gut barrier function; such as time of insertion, composition, and duration of feeding but so far, no precise clinical recommendations exist. The present study evaluated the effects of a standard composition inserted early by the nasogastric route, thus the formula did not contain fibers and glutamine, substances suggested to be beneficial for the epithelial cells and the structure of the mucosa [34].

Previous studies have reported that gut permeability increases mainly early in the course of acute pancreatitis [10, 11]. In the present study, the hypothesis that early intervention by EN would influence on early gut permeability was tested. However, no beneficial effects were found. The concentrations of EndoCab were lower than normal between day 2 and 5 in both groups. It may be that the consumption of antibodies increased i.e gut permeability of endotoxin was increased and higher concentrations of endotoxin reached into the systemic circulation. Experimentally, gut permeability increased by fasting as compared with EN, though without increasing bacterial translocation [35]. In humans, pathways for endotoxins and bacteria through the intestinal barrier are not fully understood.

In a trial by Windsor et al., it was suggested that acute inflammatory markers were modulated by EN in acute pancreatitis [14]. In previous studies on EN in SAP, the time interval prior to initiation of nutritional support has been poorly defined, usually varying from 48 to 72 hours from admission and furthermore, the time of pain onset has not been stated [13-17]. In the present study, the curves for IL-6 and CRP for all patients peaked in accordance with what has been reported in the literature and the time for the insertion of nutrition (in median 17 hrs in the TPN and 19 hrs in the EN group after admission) was within the suggested potential therapeutic window for modulating the peaks of IL-6 and CRP. However, no significant differences were seen between the treatment groups. This absence of an influence on the inflammatory response (studied up to seven days), despite early inserted EN may e.g. be due to that potential modulation of gut-associated immune-competent cells is not enough to influence on the systemic inflammatory response. Furthermore, specific, known immunomodulating supplements (e.g. glutamine, arginine and omega-3 fish oils) to EN may be required [36]. These aspects have to be investigated in future studies.

In the present study, the nasogastric route was feasible in the aspect of frequency of gastrointestinal complications and abdominal pain. A larger number of overall complications were shown in the EN group than in the TPN group. In both groups, most of the complications were diagnosed during the first three days and most frequent were pleural effusions, atelectasis and peripancreatic fluid collections. It is unlikely that the route of nutrition could have an impact on the development of these early complications. In the study by Eatock et al., the nasogastric route for administration of enteral feeding in SAP was suggested to be safe, although the number of local or systemic complications were not reported [21]. No other infectious complications were found except for two cases of sepsis and one infected pancreatic necrosis in the EN group. Side effects of central venous catheters, such as line-infections, are reported also in SAP [16]. Some previous studies comparing EN with TPN in SAP have reported a reduction in infectious complications in the EN group, though the numbers of patients with central venous lines within the groups were not reported [15, 17, 18]. In the present study, only a total of seven patients had central venous catheters, since TPN mostly was delivered through a peripheral catheter and this might have influenced on the rate of infectious complications.

Hyperglycemia is common in SAP, and in the present study the incidence of hyperglycemia was significantly lower in the EN group. A recent trial in critical illness, practicing strict glucose control with glucose levels maintained below 6 mmol/L, has pointed at an improved outcome with decreased morbidity and mortality [36]. In the present study, the median blood glucose levels were 16 mmol/L when insulin therapy was initiated and not all patients with hyperglycemia received insulin. The effects of normoglycemia in SAP have not yet been studied, but potentially this concept might further improve outcome also in patients with SAP.

The varying definitions of SAP, as well as the fact that no reliable, simple method of severity prediction at admission exists, complicates study design and makes comparisons between studies difficult [37]. In the present study, only 22 of 50 patients were finally severe as classified by the Atlanta classification system, which indicates that the used inclusion criteria overestimated severity. In the study performed by Ammori et al. comparing intestinal permeability between mild and severe acute pancreatitis [10], the subgroup of patients who developed MODS had a significantly higher excretion of PEG as compared to patients with severe disease who developed single organ failure or local pancreatic complications. The lower number of deaths and incidence of MODS in the present study might be a reason for the absence of significance in intestinal permeability when comparing the mild and severe pancreatitis groups.

In conclusion, in predicted SAP, nasogastric early EN was feasible and resulted in better control of blood glucose levels, though the early complication rate was higher in the EN group. Intestinal permeability was overall not influenced by EN and PEG-measured permeability actually increased on day three in the EN group. Furthermore, no effects on the inflammatory response were seen by the EN treatment. In current literature and guidelines, enteral feeding is recommended as the preferred route in SAP, although mechanisms and details in the management, such as initiation time, route, composition and volumes of the nutrition, are not fully addressed [38]. In the present study, early insertion of EN does not seem to be crucial, at least not when considering our results. If so, this would allow sufficient time for the clinician to define true severity of the disease (within 2-3 day) prior to defining demands and route of administration of nutritional support. EN has its role in the management of patients with SAP and may very well be provided nasogastrically, thereby facilitating the handling of the patients. Factors that need

further clarification are, however, potential benefits of various supplements to EN and whether late or prolonged EN might contribute to an improved outcome. It may very well be that future EN management could be “tailored” as comes to specific composition of the nutritional formula to patients identified as being at high risk for complications.

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Abdominal pain	AP due to surgery
Amylase ≥ three times upper limit of normal	trauma
Onset of abdominal pain within 48 hours	cancer
APACHE ll score ≥ 8	Inflammatory bowel disease
and/or	Stoma
CRP ≥ 150 mg/L	Short bowel
and/or	Chronic pancreatitis with exacerbation
Peripancreatic liquid shown on CT	

APACHE ll; acute physiological and chronic health evaluation, CRP; C-reactive protein, CT; computed tomography, AP; acute pancreatitis

Table 2. Patient characteristics at baseline

	TPN (n = 26)	EN (n = 24)	*P*
Age	68 (60 - 80)	71 (58 - 80)	0.99
Sex	14:12	10:14	0.41
Etiology bilary	17	14	0.77
alcohol	4	3	1.00
ERCP	1	3	0.34
unknown	4	4	1.00
Weight (kg)	79 (69 - 86)	76 (70 - 86)	0.67
BMI	28 (27 - 30)	27 (25 - 30)	0.24
APACHE II	9 (8 - 10)	10 (8 -13)	0.36
Pain onset to inclusion (hrs)	30 (20 - 35)	25 (22 - 35)	0.50
IL-6 (pg/ml)	121 (69-299)	213 (110-296)	0.21
IL-8 (pg/ml)	22 (13-28)	80 (46-127)	0.03
CRP (mg/L)	113 (62-101)	128 (101-201)	0.37

ERCP; endoscopic retrograde choleangio-pancreatography, BMI; body mass index, APACHE II; acute physiological and chronic health evaluation, IL; interleukine, CRP; C-reactive protein. Values are median (IQR).

Table 3. Complications

	TPN (n = 25)	%	EN (n = 23)	%	*P*
Shock	0		1	4	0.48
Pulmonary insufficiency	2	8	2	9	1.00
Renal failure	1	4	1	4	1.00
Hypocalcaemia	1	4	1	4	1.00
Pleural effusion	6	24	12	52	0.07
Atelectasis	3	12	9	39	0.05
Pulmonary oedema	1		0		1.00
Acute fluid collection	7	28	13	57	0.08
Necrosis	4	16	6	30	0.31
Pseudocyst	0		3	13	0.10
Sepsis	0		2	9	0.22
Infected pancreatic necrosis	0		1	4	0.48
Total	25		51		0.04
MODS	1	4	1	4	
Death	0		1	4	

MODS; multiple organ dysfunction syndrom. Statistical significance at $p < 0.05$

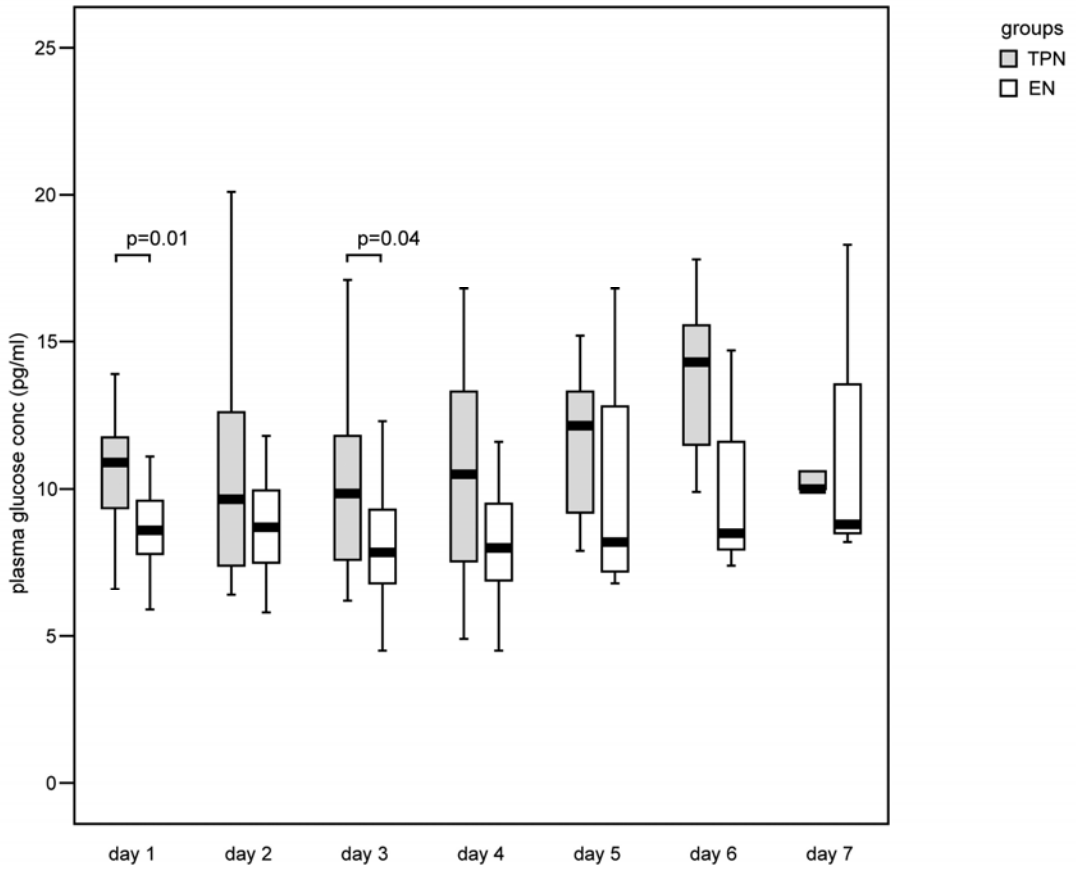

Figure 1. Plasma concentrations of glucose during nutritional support were significantly increased on day 1 and 3 in patients in the TPN group compared to those in the EN group. Boxes represent medians and interquartile ranges. Statistical significance at $p < 0.05$.