

ORIGINAL ARTICLE

Enteral Nutrition in Severe Acute Pancreatitis

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ABSTRACT

Context There is controversy concerning the merits of enteral and parenteral nutrition in the management of patients with severe acute pancreatitis. **Objective** This study was undertaken to evaluate the effect of enteral nutrition *versus* parenteral nutrition on serum markers of inflammation and outcome in patients with severe acute pancreatitis. **Setting** Tertiary care centre in North India. **Design** A prospective clinical trial. **Methods** Fifty consecutive patients with severe acute pancreatitis were randomized in a prospective trial to receive total enteral nutrition (n=25) or total parenteral nutrition (n=25). Enteral nutrition was delivered distal to the ligament of Treitz. Serum C-reactive protein, transferrin levels, albumin, surgical intervention, infections, duration of hospital stay and mortality were compared in the two groups. **Results** The mean age in the enteral nutrition group was 38.4±13.8 years and in the total parenteral nutrition group 41.1±11.3 years. The etiological factors were alcohol (n=19), gallstones (n=23), idiopathic (n=7) and drug-induced (n=1). There was a significant decrease in serum C-reactive protein values in both the enteral nutrition group and the total parenteral nutrition group at one week and two weeks (P<0.001 for both). Serum albumin rose from a prenutritional value of 2.82±0.51 g/dL to 3.34±0.45 g/dL on day 14 of nutritional support in the enteral nutrition group (P=0.003); in the total parenteral nutrition group, the level rose from 3.10±0.59 g/dL to 3.21±0.30 g/dL (P=0.638). A significant rise in transferrin value was observed from day 0 to day 14 in enteral nutrition group (169±30 to 196±36 mg/dL; P<0.001) whereas, in the total parenteral nutrition group, a less significant difference (191±41 to 201±29 mg/dL; P=0.044) was observed. There was no significant difference in surgical intervention (56.0% *versus* 60.0%; P=1.000), infective complications (64.0% *versus* 60.0%; P=1.000), hospital stay (42 days, 15-108 days, *versus* 36 days, 20-77 days; median, range; P=0.755), or mortality (20.0% *versus* 16.0%; P=1.000) in enteral nutrition *versus* total parenteral nutrition, respectively. **Conclusion** Enteral nutrition and total parenteral nutrition are comparable in the management of severe acute pancreatitis in terms of hospital stay, need for surgical intervention, infections and mortality.

INTRODUCTION

Patients with severe acute pancreatitis suffer from nutritional impairment during the course of the disease and nutritional support is mandatory [1, 2, 3, 4]. Total parenteral nutrition (TPN) and enteral nutrition (EN), generally delivered beyond the duodenum are the two options available. While a meta-analysis demonstrated decreased pancreatic infection rates, need for surgical intervention, hospital stay and costs in EN patients [5] and a prospective randomized control study showed a significantly decreased mortality rate in EN patients

[6], another randomized study showed that total TPN was more effective in providing increased calories and proteins in comparison to EN [7]. Yet another recent meta-analysis of high quality studies has demonstrated that EN results in clinically relevant and statistically significant risk reduction of infectious complications, pancreatic infections and mortality in patients with predicted severe acute pancreatitis [8]. EN has also been shown to be beneficial as an adjunct to the management of severe acute pancreatitis by obviating the systemic inflammatory response syndrome and in modifying the course of the disease [9].

Various approaches adopted for nutritional support in recent clinical trials include TPN, nasojejunal feeding, nasogastric feeding, and dual enteral and parenteral nutritional support [1, 10, 11, 12]. Spanier *et al.* [13] evaluated nutritional management in a Dutch cohort (EARL study) and concluded that nutritional interventions were rapidly undertaken with enteral feeding via the jejunum as the preferred route. A critical analysis of trials comparing EN with TPN has concluded that, although there is evidence to support EN as the preferred option, both EN and TPN have a

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Key words C-Reactive Protein; Debridement; Enteral Nutrition; Pancreatitis, Acute Necrotizing; Parenteral Nutrition

Abbreviations CTSI: computed tomography severity index; EN: enteral nutrition; TPN: total parenteral nutrition

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role [10]. Nutritional supplementation with the addition of specific agents - immunomodulation and probiotics is still an unresolved issue [13, 14, 15, 16, 17, 18, 19]. The present study was undertaken to compare the two forms of nutrition in severe acute pancreatitis as regards inflammatory markers, serum albumin and outcome.

METHODS

All patients with severe acute pancreatitis admitted to Nehru Hospital affiliated with the Postgraduate Institute of Medical Education and Research, Chandigarh, India between July 2006 and December 2007 were included in the study. Severe acute pancreatitis was defined using the Atlanta criteria [20]: clinical features, hyperamylasemia (three times the normal upper limit), and radiological evidence of severe acute pancreatitis (contrast enhanced CT (CECT) scan evidence of pancreatic necrosis and a computed tomography severity index (CTSI) equal to, or greater than, 7). The exclusion criteria were acute or chronic pancreatitis, patients who had undergone intervention prior to admission, patients requiring inotropic support at inclusion, or complications requiring surgical intervention at the time of inclusion. Fifty consecutive patients with severe acute pancreatitis with a CTSI equal to or greater than 7 were randomized to receive either EN (n=25) or TPN (n=25). All patients were managed routinely by gastrointestinal decompression, prophylactic antibiotics (ciprofloxacin/metronidazole or imipenem/cilastatin), intravenous fluids and organ system support. Nutritional support was initiated within 72 hours of admission and was continued for a minimum of 14 days. The need for further continuation of nutritional support was decided on the basis of the patients' clinical status. Image-guided fine needle aspiration or percutaneous drainage of pancreatic or peripancreatic collection as a temporizing measure was resorted to in patients who continued to be toxic.

The characteristics of the study patients are shown in Table 1. No significant differences were found between the two groups of patients. Their age ranged from 17-70 years in EN group and 18-65 years in TPN group. The etiological factors were alcohol (n=19, 38.0%) gallstones (n=23, 46.0%), idiopathic (n=7; 14.0%) and drug-induced (n=1, 2.0%). The mean duration of

presentation was 3.52±0.9 days in the EN group and 3.40±1.29 days in the TPN group.

Data Collection

The following data were collected prospectively from all patients: i) demographic data including gender, age and etiology of pancreatitis; ii) clinical data including number of days of abdominal pain, and paralytic ileus defined by abdominal distension and absence of bowel sounds; iii) biochemical data including serum levels of amylase at hospital admission and thereafter periodically, serum C-reactive protein (CRP) using the latex slide agglutination test (Telco Diagnostics, Anaheim, CA ,U.S.A.) before the initiation of nutrition and on the 3rd, 5th, 7th and 14th day of nutrition support, serum albumin and transferrin before the initiation of nutritional support and repeated on the 7th and 14th day of nutritional support; iv) radiological data including pancreatic necrosis and peripancreatic fluid collections determined by CECT performed before the initiation of nutritional support and repeated on day 14 to look for any changes in the CTSI [21]; v) radiological or surgical intervention; vi) hospital stay and vii) mortality.

Nutritional Support

Patients were randomized using odd/even numbers to either enteral nutrition or total parenteral nutrition. The targeted caloric and protein requirements were 2,500-2,700 kcal/day, and 120-130 g/day of protein. Feeding for study purposes was given for 14 days, and the last evaluation was done on day 14. Jejunal feeding was started at low flow rates - an initial rate of 20-30 mL/h until achievement of the full regime of EN.

Delivery of Enteral Nutrition

For placement of an enteral tube, the patients were shifted to an endoscopic suite and a 16F single lumen 125 cm long red rubber feeding tube was placed over a 400 cm long stainless steel guidewire (Wilson Cook, Winston, Salem, U.S.A.) beyond the ligament of Treitz using fluoroscopic control. Seven of 25 patients required a second attempt at placement of the tube in the desired position. A test feed with 500 mL of normal saline was administered over a period of 4-5 hours and jejunostomy feed was started subsequently. Minor complications such as diarrhea and distension were

Table 1. Characteristics of study patients.

	Enteral nutrition (No. 25)	Total parenteral nutrition (No. 25)	P value
Age (years; mean±SD and range)	38.4±13.8 (17-70)	41.1±11.3 (18-65)	0.312 ^a
Etiology			0.571 ^b
- Alcohol	11 (44.0%)	8 (32.0 %)	
- Gallstones	10 (40.0 %)	13 (52.0 %)	
- Idiopathic	4 (16.0 %)	3 (12.0 %)	
- Drug induced	0	1 (4.0%)	
Duration of pancreatitis at admission (days; mean±SD and range)	3.52±0.92 (1-5)	3.40±1.29 (1-5)	0.373 ^a

^a Mann-Whitney U-test

^b Pearson chi-square test

managed by altering the infusion rate and adding an antimotility agent.

Parenteral Nutrition

A 16G central venous catheter was inserted through the subclavian or internal jugular vein. A chest X-ray was taken after insertion to check the catheter tip position and also to check for complications of central venous line placement. Commercially available parenteral nutrition formula (PNA: parenteral nutrition admixture; Claris Lifesciences Ltd., Ahmedabad, India) was administered. The target caloric and protein requirements were similar to the enteral group. Glycemic control and metabolic parameters were monitored. All patients in the parenteral group could be weaned to oral diet (those managed conservatively) and feeding through a jejunostomy catheter placed intraoperatively (those operated on).

STATISTICS

Statistical data analysis was performed by using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, U.S.A.) for Windows version 13.0. A non-parametric Mann-Whitney U-test was used to compare the continuous values between groups. Comparison between pre-nutritional and post-nutritional variables was carried out using the non-parametric Wilcoxon signed-rank test. Categorical data were described as absolute and relative frequencies, and were compared by the Pearson chi-square or the Fisher's exact (2x2 tables) tests. Two-tailed P values of less than 0.05 were considered statistically significant.

ETHICS

The protocol for the study was approved by Ethical Committee of our institution and written informed consent was obtained from all patients. The study protocol conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving

Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004.

RESULTS

C-Reactive Protein (CRP)

At admission, the CRP level was found to be high in both groups (Table 2). In the EN group, a decreasing trend was observed during the course of the nutritional support. A similar trend was observed in the TPN group. The decrease in CRP level was statistically significant in both groups.

Serum Albumin

In the EN group, a significant sequential rise in serum albumin was observed after admission up to day 14. In the TPN group, no significant differences were observed during the course of the nutritional support (Table 2). However, the two groups did not differ statistically (Table 2).

Serum Transferrin

In the EN group, a significant rise in transferrin value was observed during the course of nutritional support (Table 2). In TPN, the transferrin value also increased during the course of nutritional support, but the differences between the two groups were not statistically different at days 7 and 14 (Table 2).

CTSI

The mean CTSI on admission in the EN group was 8.84±1.07, and it was 9.08±2.08 on the 14th day of nutritional support. The CTSI increased during the study period in 8 patients (32.0%) while no change was observed in 16 patients (64.0%); one patient (4.0%) showed a reduction in the CTSI. In the TPN group, the mean index on admission was 8.72±1.14 and was 9.26±1.09 on day 14 of nutritional support. The disease severity index increased in 7 patients (28.0%) and, in

Table 2. Markers of disease activity at admission and during hospital stay.

	Enteral nutrition (No. 25)		Total parenteral nutrition (No. 25)		P value EN vs. TPN ^b
	Mean±SD (range)	P vs. day 0 ^a	Mean±SD (range)	P vs. day 0 ^a	
C-reactive protein					
- Day 0	162.3±195.4 (1-822)	-	117.5±118.7 (1-410)	-	0.709
- Day 7	31.6±27.9 (2-102)	<0.001	28.6± 44.1 (0-205)	<0.001	0.179
- Day 14	10.0±11.8 (0-51) ^c	<0.001	14.0± 24.1 (0-102) ^d	<0.001	0.692
Serum albumin (g/dL)					
- Day 0	2.82±0.51 (2.0-4.0)	-	3.10±0.59 (2.0-4.0)	-	0.058
- Day 7	3.04±0.49 (2.0-4.0)	0.016	3.01±0.43 (2.0-4.0)	0.628	0.866
- Day 14	3.34±0.45 (2.0-4.0) ^e	0.003	3.21±0.30 (3.0-4.0) ^f	0.638	0.170
Serum transferrin					
- Day 0	169±30 (110-210)	-	191±41 (100-286)	-	0.019
- Day 7	181±40 (100-230)	0.007	194±28 (138-239)	<0.001	0.466
- Day 14	196±36 (112-240) ^g	<0.001	201±29 (140-243) ^h	0.044	0.820
CTSI					
- Day 0	8.84±1.07 (7-10)	-	8.72±1.14 (7-10)	-	0.684
- Day 14	9.08±2.08 (7-10)	0.102	9.26±1.09 (7-10)	0.016	0.843

CTSI: computed tomography severity index

^a Wilcoxon signed-rank test

^b Mann-Whitney U-test

^cP<0.001; ^dP<0.001; ^eP=0.047; ^fP=0.018; ^gP=0.058; ^hP=0.165 (comparison between day 7 and day 14^a)

Table 3. Comparison of surgical procedures in the two groups.

Surgical procedure	Enteral nutrition (No. 25)	Total parenteral nutrition (No. 25)	P value ^a
Debridement and closed lesser sac lavage and feeding jejunostomy	14 (56.0%)	15 (60.0%)	1.000
- After percutaneous catheter drainage	8	7	
Additional procedures	7 (28.0%)	6 (24.0%)	1.000
- Cholecystectomy	3	5 ^b	
- Splenectomy	2	1 ^b	
- Ileostomy	1	0	
- Sleeve resection of stomach and gastrostomy	1	0	
- Abscess drainage	0	1	
Re-exploration	1 (4.0%)	1 (4.0%)	1.000

^a Fisher's exact test

^b One patient had two procedures: cholecystectomy and splenectomy

the other 18 (72.0%), the CTSI was unchanged. There was no significant difference in the CTSI on admission and on day 14 of nutritional support between the two groups (Table 2).

Management

Supportive treatment was instituted in all patients. Six patients (24.0%) in each of the two groups, EN and TPN, were managed successfully without any radiological or surgical intervention. Thirteen patients (52.0%) in the EN group underwent percutaneous catheter drainage; five of these patients were managed successfully with percutaneous catheter drainage alone. In the TPN group, 11 patients (44.0%) underwent percutaneous catheter drainage and four of them were managed successfully without surgical intervention. Therefore, surgical intervention was undertaken in 14 patients (56.0%) in the EN group and 15 patients (60.0%) in the TPN group. The median time interval to surgical intervention was 18 days (range: 0-42 days) in the EN group and 18 days (0-43 days) in the TPN group (P=0.369). The surgical procedures employed were pancreatic debridement, closed lesser sac drainage and placement of a feeding jejunostomy tube (Table 3).

Morbidity

There was no significant difference in locoregional complications between the two groups: 13 patients (52.0%) in the EN group and 10 (40.0%) in the TPN group had locoregional complications (P=0.571).

Infective Complications

Documented infection was not significantly different between the two groups (Table 4; P=1.000): 16 (64.0%) patients in the EN group had documented infection (positive culture of FNA: 5, blood: 5, culture

of operative specimen: 11 and culture of drain fluid: 8) while, in the TPN group, 15 (60.0%) patients had positive cultures (FNA: 11, blood: 8, operative specimen: 6, and drain fluid: 5). There was a significant difference in the organisms found in the two groups (Table 5). While *Escherichia coli* was the predominant organism in the EN group, *Staphylococcus aureus*, *Enterococci* and *Candida albicans* were more often found in the TPN group. Statistical significance was reached only for gram positive organisms (P<0.001).

Mortality

The mortality rate was similar (P=1.000) between the EN (20.0%) and the TPN (16.0%) groups (Table 4). In the EN group, all 5 deaths occurred due to sepsis and multiorgan failure; 4 out of 5 deaths occurred in the post-operative period. In the TPN group, all 4 deaths occurred in the post-operative phase: 3 due to sepsis and multiorgan failure and one due to operative hemorrhage.

Hospital Stay

There was no significant difference in hospital stay between the two groups (P=0.755; Table 4). The duration of hospital stay in the EN group ranged from 15 to 108 days (median 42 days) and, in the TPN group, it ranged from 20 to 77 days (median 36 days). Similar behavior was observed for the intensive care unit (ICU) stay (Table 4).

DISCUSSION

Nutritional support is emerging as a vital component of the management of severe acute pancreatitis, and enteral nutrition is reported to be the best nutritional support in severe acute pancreatitis [2]. EN avoids TPN complications, maintains intestinal health and may prevent the progression of multiple organ failure [2].

Table 4. Outcome in the two groups.

	Enteral nutrition (No. 25)	Total parenteral nutrition (No. 25)	P value
Infection	16 (64.0%)	15 (60.0%)	1.000 ^a
ICU stay (days; median and range)	10 (0-44)	15 (0-60)	0.625 ^b
Hospital stay (days; median and range)	42 (15-108)	36 (20-77)	0.755 ^b
Mortality	5 (20.0%)	4 (16.0%)	1.000 ^a

ICU: intensive care unit

^a Fisher's exact test

^b Mann-Whitney U-test

Table 5. Organisms found in the two groups.

Organism	Enteral nutrition (No. 25)	Total parenteral nutrition (No. 25)	P value ^a
Gram negative:	18 (72.0%)	14 (56.0%)	0.377
- <i>Escherichia coli</i>	12	5	
- <i>Acinetobacter</i>	5	4	
- <i>Proteus</i>	0	2	
- <i>Klebsiella</i>	1	2	
- <i>Pseudomonas</i>	0	1	
Gram positive:	2 (8.0%)	15 (60.0%)	<0.001
- <i>Staphylococcus aureus</i>	2	11	
- <i>Enterococci</i>	0	4	
Fungi:	2 (8.0%)	7 (28.0%)	0.138
- <i>Candida albicans</i>	2	7	

^a Fisher's exact test

This prospective randomized study focused on the effects of EN delivered beyond the ligament of Treitz via an endoscopically-placed nasojejunal feeding tube and compared it with TPN. It has been suggested that EN ameliorates the inflammatory response better than TPN in severe acute pancreatitis [22, 23]. Both forms of nutritional support helped in significantly reducing serum CRP levels during the period of nutritional support in our study. In patients with infective complications, the serum CRP level was significantly high until day 5 in the EN group and until day 7 in the TPN group as compared to patients without infective complications (data not shown). Other studies have also not shown any significant reduction in CRP levels after 7 days in the enteral feeding group; Loule *et al.* [22] reported that CRP levels were reduced to 50% of the enrolment levels a average of 5 days faster for EN than TPN, and Zhao *et al.* [23] found a reduction of CRP on day 4 in the EN group and on day 7 in the TPN group.

Powell *et al.* [24] reported that early EN did not ameliorate the inflammatory response in patients with severe acute pancreatitis. In their study, the introduction of EN did not affect the serum concentrations of interleukin-6 (IL-6), soluble tumor necrosis factor receptor I (STNFR1) and CRP over the first 4 days of the study. Pearce *et al.* [16] have shown that, after 3 days of feeding, 13% of patients had reduced their CRP by 40 mg/L or more in the study group. In the control group, 3.8% of patients had reduced their CRP by this amount. Serum transferrin levels rose significantly in both the EN and the TPN groups in our study, corresponding to the changes in serum CRP. The improvement was more marked, however, in EN group (Table 2).

In our study, the serum albumin level increased gradually during the nutritional support in both groups. The increase in albumin levels was found from the beginning of nutritional support in the enteral group. In the TPN group, a significant increase was observed only between day 7 and day 14 days of nutritional support. Loule *et al.* [22] observed that both EN and TPN were equally effective in improving serum albumin level. Zhao *et al.* [23] showed a significant increase of body weight and pre-albumin levels in the EN group while serum albumin levels were not increased. In another study regarding EN, serum

albumin concentration increased from 3.0 to 3.8 g/dL (P<0.001) [25].

There are limited studies on the effect of nutritional support on the CTSI. No significant difference has been reported on CECT findings in the studies reported [22, 26, 27]. We looked at the change in the CTSI at 14 days after admission, and a significant increase of the CTSI score was seen in the TPN group. However, there was no significant difference in the CTSI score between the two groups both at admission and after nutritional support. Makola *et al.* [25] have reported a decrease in the CTSI from 4 to 2 in their patients following enteral nutrition. Our patients had a much higher CTSI at admission than those reported by Makola *et al.* [25] denoting a more severe disease state which still evolved in the following 14 days.

The type of nutrition has also been shown to influence infectious complications. Petrov *et al.* [6] reported significantly lower infections in the EN group as compared to the TPN group. We found similar rates of infection in the two groups (Table 4). However, there was a striking difference in the type of organisms found in the two groups (Table 5). Patients given TPN were more often infected by gram-positive organisms and fungi as compared to those given EN who were more often infected by a gram-negative organism. This observation has an important bearing on the outcome of severe acute pancreatitis as fungal infection carries a higher risk of mortality. Though proper aseptic precautions were maintained, the occurrence of infections with gram positive organisms such as *Staphylococci* in the TPN group suggests that it could be due to the invasion of central line catchers with cutaneous commensals.

In our study, no significant difference was found in the rate of surgical intervention in either group. Modena *et al.* [26] reported a significantly lower rate of surgical intervention in the EN group. In their series, 38 out of 43 patients (88.4%) in the TPN group required surgical intervention *versus* 11 patients out of 44 (25.0%) in the EN group (P<0.01). Petrov *et al.* [6] also reported a lower surgical intervention rate in the EN group as compared to the TPN group. Our observations are different, perhaps due to a more severe disease state in our patients. There was no significant difference in hospital stay in the two groups; the median duration of the hospital stay was 42 days for the EN group, and 36

days for the TPN group. Some studies have shown a reduced hospital stay in the EN group [28, 29] and several studies have reported a reduced mortality rate in the EN group. Modena *et al.* [26] and Petrov *et al.* [6] have reported significantly lower mortality rates in the EN group as compared to the TPN group. In our study, no significant difference was observed between the EN (20.0%) and the TPN (16.0%) groups. In conclusion, our prospective study has shown that TPN and EN were equally effective in ameliorating the inflammatory response and improving the nutritional status of the patients. Mortality, hospital stay and ICU stay were also similar in the two groups. The two forms of nutrition differed, however, in terms of infective organisms. The use of TPN was more often associated with infection with gram positive and fungal organisms whereas the use of EN was associated with gram negative organisms.

Conflict of interest The authors have no potential conflicts of interest

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