European Journal of Clinical Nutrition (2007) 61, 1429–1434

0954-3007/07 $30.00
www.nature.com/ejcn

ORIGINAL ARTICLE

Effects of glutamine-enriched total parenteral nutrition on acute pancreatitis

H Şahin[1], SM Mercanlıgil[2], N Inanç[1] and E Ok[3]

[1]*Department of Nutrition and Dietetics, Ataturk School of Health, University of Erciyes, Kayseri, Turkey;* [2]*Department of Nutrition and Dietetics, School of Health Technology, University of Hacettepe, Ankara, Turkey and* [3]*Department of General Surgery, Faculty of Medicine, University of Erciyes, Kayseri, Turkey*

Aim: This study was performed to determine the effects of glutamine enriched total parenteral nutrition (TPN) on the patients with acute pancreatitis (AP).
Method: Forty patients with AP, who had Ranson's score between 2 and 4 received either standard TPN (control group) or TPN with glutamine (treatment group). The patients in the treatment group received TPN containing 0.3 g/kg/days glutamine. At the end of the study, patients were evaluated for nutritional and inflammatory parameters, length of TPN and length of hospital stay.
Results: The length of TPN applications were 10.5 ± 3.6 days and 11.6 ± 2.5 days, and the length of hospital stays were 14.2 ± 4.4 and 16.4 ± 3.9 days for the treatment and control groups (NS), and the complication rates in the treatment and control groups were 10 and 40%, respectively ($P < 0.05$). The transferrin level increased by 11.7% in the group that received glutamine-enriched TPN ($P < 0.05$), whereas the transferrin level decreased by 12.1% in the control group (NS). At the end of the study, slight but not significant changes were determined in both groups in fasting blood sugar, albumin, blood urea nitrogen (BUN), creatinine, total cholesterol concentrations, aspartate aminotransferase (AST), alanine transaminase (ALT) and lactate dehydrogenase (LDH) activities, leukocytes, CD_4, CD_8, serum Zn, Ca and P levels compare to the baseline levels (NS). Significant decreases were determined in serum lipase, amylase activities and C-reactive protein (CRP) levels in both groups ($P < 0.05$).
Conclusions: The results of this study have shown that glutamine supplementation to TPN have beneficial effects on the prevention of complications in patients with AP.
European Journal of Clinical Nutrition (2007) **61,** 1429–1434; doi:10.1038/sj.ejcn.1602664; published online 21 February 2007

Keywords: Acute pancreatitis; glutamine; total parenteral nutrition

Introduction

Glutamine, which is synthesized in various cells such as skeletal, muscle, lungs and brain, is the most abundant amino acid in the plasma and intracellular amino-acid pool. Although glutamine is a nonessential amino acid, it is recognized as 'conditionally essential amino acid' because of the increased body's demand in catabolic state (Hall *et al.*, 1996; Fürst *et al.*, 1997; Oğuz, 1998).

It has been suggested that the support of the patients with acute pancreatitis (AP) with total parenteral nutrition (TPN) provides relaxation for gastrointestinal system and pancreas. Furthermore, the long-term ileus, respiratory and renal failure as well as severe metabolic disorders and surgical operations preclude the oral and enteral nutrition (EN) of patients with severe AP. TPN has been suggested in the management of the patients with AP for preventing the exocrine secretions so that autodigestion of pancreas. It has also been used as a support for optimal recovery as well as a life support (Havala *et al.*, 1989; Latifi *et al.*, 1991; Scolapio *et al.*, 1999).

In recent years, EN has been considered as a method, which has the priority in the nutrition of the patients with

Correspondence: Dr H Şahin, Department of Nutrition and Dietetics, Ataturk School of Health, University of Erciyes, Kayseri 38039, Turkey.
E-mail: habibe@erciyes.edu.tr
Guarantor: H Şahin.
Contributor: HS was responsible for conception, design, analysis and interpretation of data, and the final approval of the version to be published. SMM helped to coordinate the study, do statistical analysis and write the report. NI helped to coordinate the study, do statistical analysis and write the report. EO helped in drafting the article and revising it critically for important intellectual content.
Received 28 April 2006; revised 8 December 2006; accepted 2 January 2007; published online 21 February 2007

mild AP. However, TPN is still a choice for the patients suffering from the mild AP with nausea and vomit (Meier *et al*., 2002, 2006).

Although TPN contribute to optimal recovery and proper function of the pancreas, longer period of TPN (over 10 days) administration increases the risk factors for acute inflammatory response and septicemia (McClave and Ritchie, 2000; Maroulis and Kalfarentzos, 2000). To prevent these adverse effects, TPN is supplemented with glutamine in the form of dipeptide (alanyl-glutamine, glycyl-L glutamine) as a fuel for rapidly growing cells such as intestinal enterocytes, lymphocytes, macrophages and neutrophils (Hardy *et al*., 1993; Ziegler *et al*., 1996; Meier *et al*., 2002). The results of previous studies have shown that glutamine-enriched TPN formulas improve the prognosis of the disease (Karner *et al*., 1989; O'Riordain *et al*., 1996; Griffiths *et al*., 1997; Ziegler *et al*., 1997; Morlion *et al*., 1998; Ockenga *et al*., 2002).

This study was performed to determine the effects of early administration (at the first 48 h) of glutamine dipeptide-supplemented TPN on the nutritional status, occurrence of the complications and length of hospital stay of the patients with AP.

Materials and methods

This study was approved by a local ethical committee (Ethical Committee of Faculty of Medicine, University of Erciyes) and the procedures followed were in accordance with Helsinki Declaration. All patients were informed about the content of the study.

This is a cross-sectional study that was conducted on patients with AP. The study was conducted at the Clinics of General Surgery, on 40 patients consisting of 17 male (42.5%) and 23 female (57.5%), aged between 20 and 81 years (mean age 58.9 ± 14 years) whose Ranson's score was lower than 4.

The patients who had been unable to eat for a week or longer period, and expected to require parenteral nutrition (PN) support and had not have any chronic diseases except pancreatitis were selected for the study.

AP was diagnosed by clinical examination, Ranson's diagnostic criteria and the radiologic criteria of pancreatitis (ultrasonography and Balthazar classification was based on computerized tomography). Serum amylase concentration was used to support the diagnosis of AP (the presence of threefold increase in serum concentrations).

Patients were randomly assigned to two groups as control and treatment group. The patients, who had nasogastric intolerance and were suffering from the mild AP with nausea and vomiting, were parenteral fed. The patients in control group received standard TPN, whereas the patients in treatment group received TPN supplemented with 0.3 g/kg/days glutamine (Dipeptiven, Fresenius, Germany). There was no difference between the TPN solutions except glutamine supplementation. The basal energy requirements of patients were calculated by the equation of Schofield and Scrimshaw stress factors. Nonprotein energy/nitrogen rate was used for the determination of protein requirements (NPE/N = 125/1 × 6 = 25). About 60 and 40% of the nonamino acid energy were provided with glucose (Dextrose 50%, Eczacıbaşı-Baxter, Turkey) and lipid (Intralipid 20%, Fresenius Kabi, Germany) solutions, respectively. The patients in treatment and control groups received standard amino-acid solution (FreAmine 10%, Eczacıbaşı-Baxter, Turkey) at a level of 1.1 ± 0.3 and 1.4 ± 0.3 g/kg/days, respectively (Table 1). The TPN formula given to the patients in both group supplemented with the same levels of calcium (Calcium-Picken% 10, Adeka, Turkey), vitamin C (Redoxon, Roche, Switzerland), B group vitamins (Bepanthene, Roche, Switzerland) and trace elements (Tracutil-Braun, Germany). The TPN solution was prepared by the nutrition team of the hospital.

Table 1 Composition of the solutions with and without glutamine fed via parenteral route to the patients

	Gln+	*Gln−*
Energy (kcal/kg/day)	25 ± 4	24 ± 3
Glucose (g/kg/day)	4 ± 0.5	3.6 ± 0.6
Lipids (g/kg/day)	1.0 ± 0.2	0.95 ± 0.2
Amino acids (g/kg/day)	1.1 ± 0.3	1.4 ± 0.3
Glutamine (g/kg/day)	0.3	0

The values are means ± SD.

At the beginning and at the end of the study, height and weight of the patients were measured, and body mass index (BMI) was calculated. Blood samples were collected and sera were analyzed for glucose, blood urea nitrogen (BUN), creatinine, bilirubin, total protein, albumin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) concentrations and aspartate aminotransferase (AST), alanine aminotransferase activities by commercial kits using an auto analyzer (MEGA, Merck). Electrolytes were determined by AVL 988-3 and hematological measurements were performed by Cell-Dyn 1700.

Low-density lipoprotein cholesterol (LDL-C) levels and very low-density lipoprotein (VLDL) levels were calculated by the Friedewald's formula (Friedewald *et al*., 1972) (LDL-C (mg/dl) = Total cholesterol (mg/dl) − HDL-C (mg/dl) − Triglycerides (mg/dl)/5, VLDL = Triglycerides/5).

Serum zinc (Zn) and copper (Cu) concentrations were determined by flame atomic absorption spectrophotometer (Hitachi Z-8000, Tokyo, Japan). C-reactive protein (CRP) (Dade Behring 2) and transferrin were measured by nephelometric method (IMAGE), CD_4 and CD_8 measurements were carried out by commercial kit (Immunotech PN IM 0448-FITC) using flow cytometry.

Urine urea nitrogen was measured by photometric method from 24-h urine samples. Four points were added to obtained values to compensate the losses via different routes such as feces, hair, menstruation, skin and nail. Nitrogen balance

was calculated by the standard formula (Konstantinides *et al*., 1988):

$$\text{Nitrogen intake} = \frac{\text{Protein intake (g/24h)}}{6.25\text{g Protein/g nitrogen}}$$

$$\text{Urine nitrogen losses (g/24h)} = \frac{\text{Urine urea} + 4}{2.14\,(\text{nitrogen in urea})}$$

$$\text{Nitrogen balance} = \text{Nitrogen intake} - \text{Nitrogen excretion}$$

Data were analysed with SPSS for Windows version 9.0. The differences between the groups were determined with independent Student's *t*-test, χ^2-test and the differences within the groups were determined with paired samples test. *P*-values <0.05 were considered significant. Data were expressed as means $\pm$ s.d.

Results

Ranson's scores were found as 2.7 ± 0.9 in the group receiving TPN with glutamine and 2.8 ± 0.8 in the group receiving TPN without glutamine (NS). It was accepted that there was no necrosis in mild AP according to the Balthazar's radiological classification. Thus, no sign of necrosis was found in both groups.

The patients in both groups lost weight, but the weight loss of the patients in the treatment group was less than control group (2.5 vs 2.7%). Serum total protein levels of the patients in treatment group unchanged whereas total protein concentrations of the patients in control group decreased by 3.2% (NS). Albumin levels decreased by 3.0 and 8.8% in treatment and control groups (NS), respectively. Serum transferrin levels of the patients increased by 11.7% in the treatment group ($P<0.05$) and decreased by 12.1% in the control group (NS).

The nitrogen balance of the patients in both groups was improved at the end of the study compare with the values obtained at the beginning of the study ($P<0.05$) (Table 2).

Complication was observed in eight of the patients (40%) in control group and in two of the patients (10%) in treatment group. The most common complication seen in both group was respiratory failure (53.4%). Any cardiac failure, sepsis due to catheter and resistant sepsis were not observed in the patient in treatment group but in control group, 23.0% of the patients showed cardiac failure and sepsis due to catheter and resistant sepsis were present in 15.4% of the patients. During the study, two (10%) patients in the treatment group and six (30%) patients in the control group died (Table 3).

The mean length of the TPN administration was 10.5 ± 3.6 (7–15) days for the patients in treatment group; this period was 11.6 ± 2.5 (7–21) days for the patients in control group. Oral feeding was started at similar times in both groups (8.4 ± 3.1 days for the treatment group and 8.5 ± 2.7 days for the control group). The length of the hospital stay of the patients in the treatment group was shorter than the control

Table 3 Complications in patients with AP

Complications	*Gln+* n *(%)*	*Gln–* n *(%)*	*Total* n *(%)*
Respiratory failure	2 (100.0)	6 (43.2)	8 (53.4)
Catheter sepsis	—	2 (15.4)	2 (13.3)
Resistant sepsis	—	2 (15.4)	2 (13.3)
Cardiac failure	—	3 (23.0)	3 (20.0)
Total	2 (100.0)	13 (100.0)	15 (100.0)
Complications/patients	2/2	13/8	15/10
Mortality	2/20	6/20	8/40

Abbreviation: AP, acute pancreatitis.

Table 2 Baseline characteristics and changes of inflamatory and nutritional parameters during treatment period with (gln+) and (gln–) glutamine supplementation

Characteristics	*Gln+*				*Gln-*			
	Baseline	*Final*	*Difference %*	P	*Baseline*	*Final*	*Difference %*	P
Weight (kg)	68.4±15.5	66.7±14.4	−2.5	0.01	74.2±15.9	72.2±16.3	−2.7	0.00
BMI (kg/m^2)	25.8±5.1	25.0±4.9	−3.1	0.03	27.8±5.3	27.0±5.4	−2.9	0.00
Protein (mg/dl)	6.1±0.8	6.1±0.9	0.0	0.97	6.1±1.04	5.9±1.03	−3.2	0.37
Albumin (g/dl)	3.3±0.5	3.2±0.4	−3.0	0.60	3.4±0.6	3.1±0.6	−8.8	0.06
Transferin (mg/dl)	171.7±46.9	191.9±54.8	11.7	0.02	202.5±77.3	177.9±53.2	−12.1	0.07
Hematocrit (%)	36.7±6.07	34.0±4.0	−7.3	0.03	36.7±6.9	33.0±4.7	−10.0	0.01
Urine urea nitrogen (g/l)	8.0±4.2	4.3±3.0	−46.2	0.00	6.3±2.4	5.1±2.7	−19.0	0.01
Nitrogen balance	1.3±4.3	4.8±5.2	269.2	0.00	1.6±4.2	6.1±3.3	281.2	0.03
Amylase (U/l)	604.5±630.4	350.2±602.9	−42.0	0.01	807.4±642.5	317.4±312.8	−60.7	0.02
Lipase (U/l)	187.4±194.2	122.0±81.6	−34.8	0.05	92.6±82.4	74.8±70.3	−19.2	0.04
CRP (mg/dl)	151.8±79.8	94.1±62.4	−38.0	0.00	150.6±63.4	122.5±65.1	−18.6	0.01
Leucocytes (10^9 l)	20.4±29.9	14.6±14.9	−27.9	0.43	15.7±6.4	20.4±3.2	29.9	0.53

Abbreviations: BMI, body mass index; CRP, C-reactive protein.
The values are means ± SD.

Table 4 The mean length of the TPN administration, start of oral feeding and hospitalization duration

Characteristics (day)	*Gln+*		*Gln–*		
Duration of TPN	10.5±3.6	(7–15)	11.6±2.5	(7–21)	0.36
Start of oral feeding	8.4±3.1	(5–15)	8.5±2.7	(4–18)	0.91
Hospitalization duration	14.2±4.4	(8–26)	16.4±3.9	(10–25)	0.11

Abbreviation: TPN, total parenteral nutrition.
The values are means±SD and minimum-maximum values are indicated in parenthesis.

group (14.2±4.4 days vs 16.4±3.9 days). However, the differences between the groups were not statistically significant with regard to length of TPN, start of oral feeding and length of hospital stay (Table 4).

At the end of the study, slight but not significant changes were determined in both groups in fasting blood sugar, BUN, creatinine, serum Na, K, Cl, triglycerides, total cholesterol concentrations, AST, ALT and LDH activities, leukocytes, CD_4, CD_8, serum Zn, Ca and P levels compare to the values obtained at the beginning of the study. Significant decreases were determined in serum lipase, amylase activities and CRP levels in both groups ($P< 0.05$) (Table 2).

Discussion

If the patients with mild AP (Ranson's score <3) can begin oral feeding after 5–7 days, EN/PN is considered unnecessary. However, in several studies and guidelines, the superiority of EN/PN has been emphasized (McClave *et al.*, 1997; Marik and Zaloga, 2004; Meier *et al.*, 2006). PN is still a choice in patient who could not be fed orally or intolerant. In patients included in this study, retching, nausea and vomiting was accompanying to abdominal pain therefore TPN was applied.

In this study, patients in the treatment groups and control groups were lost weight. Malnutrition owing to abdominal pain and malabsorption has been seen in about 30% of the patients with AP. In addition, these patients resemble to septic patients with regard to metabolic status. The increase in metabolic rate occurs owing to energy expenditure, proteolysis, and gluconeogenesis and insulin resistance. Delay in the starting of oral feeding (over 10 days) results in the increases in the risk of malnutrition of the patients. The patients with AP lose weight, and body functions decrease depending on the severity and length of the disease (Scolapio *et al.*, 1999; Maroulis and Kalfarentzos, 2000; McClave and Ritchie, 2000; Meier *et al.*, 2002).

In this study, there was no change in total protein level of the patients who received glutamine-enriched TPN. Transferrin levels of these patients increased in contrast to the decreases in control group consistent with the results of the previous studies (Yoshida *et al.*, 2001; Ockenga *et al.*, 2002).

In this study, urea nitrogen excretion with urine decreased in both groups thus nitrogen balance could be established. Nutritional support provides a rapid improvement in nitrogen balance of the patients with AP. In the body, glutamine is used for the nitrogen requirements of immune system cells, enterocytes, and also for nitrogen resources of metabolic activities, and for filling the glutamine pool (Ziegler *et al.*, 1996; Fürst *et al.*, 1997). In some studies, it has been shown that TPN without glutamine had beneficial effects on the nitrogen balance like the glutamine-enriched TPN (Sitzman *et al.*, 1989; Scolapio *et al.*, 1999).

The level of CRP, that is the most important biological function in the body is to recognize and to stimulate the clearance of the cell remnants, was decreased in both groups. The decrease in the treatment group was pronounced, but the values were still higher than the normal. The high CRP levels may be due to the presence of the factors that affecting the CRP levels such as fever, leukocytosis and surgical operation as well as the presence of the inflammation. In a previous study investigating the effects of standard and glutamine-enriched PN on AP, CRP levels were determined for the evaluation of systemic inflammatory response, and CRP concentrations of the patients had decreased in the treatment group, whereas CRP level in the control group had decreased at the first week and increased thereafter. Similarly a total leukocyte count was determined in both groups (Ockenga *et al.*, 2002).

Glutamine is, generally, accepted as an immunomodulatory agent. In many studies performed on human and animals, glutamine has been beneficial effects on the immune system cells and their functions, thus reduction in infection rates was observed (O'Riordain *et al.*, 1996; Ziegler *et al.*, 1998; Karwowska *et al.*, 2001; Ockenga *et al.*, 2002). However, in some other studies, these effects have not been observed (Van der Hulst *et al.*, 1993, 1997). Similarly, in this study, CD_4 and CD_8 counts were increased, but the increases did not reach statistical significance. The mean leukocyte counts of the patients in the treatment group reduced by 27.9% almost returning the normal levels, in contrast, leukocyte counts increased by 29.3% in the control group. The relationship between the increased peripheral blood leukocyte count and infections, trauma and acute response to inflammation is well known, and this increase is considered as a part of acute phase response. It was considered that the leucocytosis that was observed in this study might be related to the inflammation due to infection.

Several previous studies reported that glutamine supplementation to TPN shortens the length of hospital stay, reduces infection depended-complications, increases the survival rate and finally reduces overall treatment cost per patient (McBurney *et al.*, 1994; Griffiths *et al.*, 1997; Morlion *et al.*, 1998; Ziegler *et al.*, 1998; Neri *et al.*, 2001; Ockenga *et al.*, 2002). In this study, although the difference between the groups was not statistically significant, the duration of the PN of the patients who received glutamine-enriched TPN was shorter than controls (10.5±3.6 days vs 11.6±2.5 days)

and oral feeding start earlier in the treatment group (8.4 ± 3.1 days for the treatment group vs 8.5 ± 2.7 days for the control group).

Local and systemic complications occur frequently in AP patients. The systemic inflammatory response syndrome (SIRS) or insufficient functions of multiple organs, thus the development of necrosis in pancreas is considered to be responsible for the complications and deaths at the early stage. Pancreatic inflammation, which makes the treatment difficult, is the primary reason for the development of complications at the late stage of the infection. Pancreatic infections occur at the first 4 weeks of the disease and reach to peak levels at 2 or 3 weeks. It has been reported that pancreatic infections are responsible for 80% of the deaths in AP (Neoptolemos *et al.*, 1998; Quamruddin and Chadwick, 2000).

The nutritional support is considered to be effective in the prevention of the inflammation in AP (McClave *et al.*, 1997; Guillou 1999; McClave and Ritchie, 2000). Recent studies have shown that early enteral nutrition (EEN) provides better clinical course than TPN. Furthermore, some special nutritional substance like glutamine has potential benefits (Fish *et al.*, 1997; Abou-Assi and O'Keefe, 2002)

In many studies investigating the effects of glutamine, it was reported that complications were reduced by nutritional support (Ziegler *et al.*, 1996, 1997; Morlion *et al.*, 1998; Ockenga *et al.*, 2002). In this study, complications developed in 10% of the patients in treatment group, whereas in 40% of the patients in control group. Of 86.7% of the complications were seen in control group, whereas 13.3% of the complications were seen in treatment group. The most frequently seen complication was respiratory insufficiency (53.4%). A study was conducted by Kalfarentzos *et al.* (1991) that included on 67 patients with severe AP whose Ranson's score was 3.8 ± 0.2. The authors applied the TPN at early stage (first 72 h) and found the complication and mortality rates as 23.6 and 13%, respectively in the patients who received TPN at early stage, and they found the complication rate as 9.5% and mortality rate as 38% in the patients who received TPN at the late stage of the disease.

In conclusion, the results of this study has shown that a beneficial effect of glutamine supplementation in patients with AP.

References

Abou-Assi S, O'Keefe SJ (2002). Nutrition support during acute pancreatitis. *Nutrition* **18**, 938–943.

Fish J, Sporay G, Beyer K, Jones J, Kihara T, Kennedy A *et al.* (1997). A prospective randomized study of glutamine-enriched parenteral compared with enteral feeding in postoperative patients. *Am J Clin Nutr* **65**, 977–983.

Friedewald WT, Levy RI, Fredrickson DS (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* **18**, 499–552.

Fürst P, Pogan K, Stehle P (1997). Glutamine dipeptides in clinical nutrition. *Nutrition* **13**, 731–737.

Griffiths RD, Jones C, Palmer TE (1997). Sixth month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* **13**, 295–302.

Guillou PJ (1999). Enteral versus parenteral nutrition in acute pancreatitis. *Gastroenterology* **13**, 345–355.

Hall JC, Heel K, McMauley R (1996). Glutamine. *Br J Surg* **83**, 305–312.

Hardy G, Bovan SJ, Mc Elroy B (1993). Stability of glutamine in parenteral feeding solution. *Lancet* **342**, 186.

Havala T, Shronts E, Cerra F (1989). Nutritional support in pancreatitis. *Gastroenterol Clin North Am* **18**, 525–542.

Kalfarentzos FE, Karavias DD, Karatzas TM, Alevizatos BA, Androulakis JA (1991). TPN in severe acute pancreatitis. *J Am Coll Nutr* **10**, 156–162.

Karner J, Roth E, Fürst P (1989). Glutamine containing dipeptides as infusion substrates in the septic state. *Surgery* **106**, 893–900.

Karwowska KA, Dworacki G, Szulc R, Trybus M, Zeromski J (2001). Influence of glutamine enriched parenteral nutrition on nitrogen balance and immunological status in patients undergoing elective aortic anevrysms repair. *Nutrition* **17**, 475–478.

Konstantinides FN, Boehm KA, Cerra FB, Rdamer WJ, Strom MC, Adderly JT *et al.* (1988). Real time cost-effective method for determining total urinary nitrogen in clinical nitrogen-balance studies. *Clin Chem* **34**, 2518–2520.

Latifi R, McIntoch JK, Dudrick SJ (1991). Nutritional management of acute and chronic pancreatitis. *Surg Clin North Am* **71**, 579–595.

Maroulis J, Kalfarentzos F (2000). Complications of parenteral nutrition at the end of the century. *Clin Nutr* **19**, 295–304.

Marik PE, Zaloga GP (2004). Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ* **328**, 1407–1413.

McBurney M, Young LS, TR Ziegler, Wilmore DW (1994). A cost-evaluation of glutamine supplemented parenteral nutrition in adult bone marrow transplant patients. *J Am Diet Assoc* **94**, 1263–1266.

McClave SA, Ritchie CS (2000). Artificial nutrition in pancreatic disease: What lessons have we learned from the literature? *Clin Nutr* **19**, 1–6.

McClave SA, Greene LM, Snider HL, Makk LJ, Cheadle WG, Owens NA *et al.* (1997). Comparison of the safety of early enteral and parenteral nutrition in mild acute pancreatitis. *JPEN* **21**, 14–20.

Meier R, Beglinger C, Layer P, Gullo L, Keim V, Laugier R *et al.* (2002). ESPEN guidelines on nutrition in acute pancreatitis. *Clin Nutr* **21**, 173–183.

Meier R, Ockenga J, Pertkiewicz M, Pap A, Milinic N, MacFie J (2006). ESPEN guidelines on enteral nutrition: pancreas. *Clin Nutr* **25**, 275–284.

Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Köller M, König W *et al.* (1998). TPN with glutamine dipeptide after major abdominal surgery. *Ann Surg* **227**, 303–308.

Neoptolemos JP, Raraty M, Sutton R (1998). Acute pancreatitis: the substantial human and financial costs. *Gut* **42**, 886–891.

Neri A, Mariani F, Cosmo LD, Piccolomini JW, Testa G, Vuolo G (2001). Glutamine supplemented total parenteral nutrition in major abdominal surgery. *Nutrition* **17**, 968–969.

O'Riordain MG, Fearon KC, De Beaux A (1996). Effects of glutamine on immune function in the surgical patient. *Nutrition* **12**, 84–86.

Ockenga J, Borchert K, Rifai K, Manns MP, Bischoff SC (2002). Effect of glutamine enriched total parenteral nutrition in patients with acute pancreatitis. *Clin Nutr* **21**, 409–416.

Oğuz M (1998). Glutamin ve beslenmedeki önemi. *T Klin Cerrahi* **3**, 120–125. (Turkish).

Quamruddin AO, Chadwick RR (2000). Preventing pancreatic infection in acute pancreatitis. *J Hospital Infect* **44**, 245–253.

Scolapio JS, Malhi-Chowla N, Ukleja A (1999). Nutrition supplementation in patients with acute and chronic pancreatitis. *Gastroenterol Clin North Am* **28**, 695–707.

Sitzman JV, Steinborn PA, Zinner MJ (1989). Total parenteral nutrition and alternate energy substartes in treatment of severe acute pancreatitis. *Surg Gynecol Obstet* **168**, 311–317.

Van der Hulst RR, Van Kreel BK, Von Meyenfelt MF, Brummer RJ, Arends JW, Deutz NE (1993). Glutamine and the preservation of gut integrity. *Lancet* **44**, 1363–1365.

Van der Hulst RR, Von Meyenfelt MF, Burman WA (1997). Glutamine and intestinal immune cells in humans. *JPEN* **21**, 310–315.

Yoshida S, Kaibara A, Ishibashi N, Shirouzu K (2001). Glutamine supplementation in cancer patients. *Nutrition* **17**, 766–768.

Ziegler TR, Bye R, Persinger RL (1998). Effects of glutamine supplementation on circulating lymphocytes after bone marrow transplantation: a pilot study. *Am J Med Sci* **315**, 4–10.

Ziegler TR, Leader LM, Jonas CR, Griffiths DP (1997). Adjunctive therapies in nutritional support. *Nutrition* **13**, 64–74.

Ziegler TR, Szeszycki EE, Estivariz CF, Puckett AB, Leader LM (1996). Glutamine: from basic science to clinical application. *Nutrition* **12**, 68–70.