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Original Article

Cyclic Total Parenteral Nutrition Decreases Conjugated Bilirubin in Adult Patients with Parenteral Nutrition-Associated Liver Disease

Shu-yin Liao[1], Li-Chun Hsieh[2], Frank Cheau-Feng Lin[1,3,*]

[1] *Department of Parenteral Nutrition, Chung Shan Medical University Hospital, Taichung, Taiwan*
[2] *Department of Nutrition, Chung Shan Medical University Hospital, Taichung, Taiwan*
[3] *School of Medicine, Chung Shan Medical University, Taichung, Taiwan*

Purpose: Parenteral nutrition-associated liver disease (PNALD) is one of the most common complications of total parenteral nutrition (TPN). The adjustment from continuous TPN (24TPN) to cyclic TPN (*c*TPN) provides the liver with a time of metabolic rest, which may facilitate recovery from PNALD. The purpose of this study was to evaluate the effects of *c*TPN on liver function of patients with PNALD.
Materials and methods: A retrospective study was carried out at a medical center in Taiwan between January 2014 and March 2016. Inpatients who were ≥18 years old, prescribed TPN for >7 days, and demonstrated impaired liver function were enrolled. Serum hepatic biochemical parameters were measured at baseline, the start of TPN, the end of TPN, and before discharge, and compared.
Results: Among the 56 patients enrolled, 28 (50%) were on *c*TPN following elevation of total (median 1.9 to 6.2, p=0.010), direct (median 1.2to 3.4, p=0.036), and indirect bilirubin (median 0.8 to 2.2, p=0.013). Total (median 4.4, p=0.014) and direct bilirubin (median 2.9, p=0.022) recovered after *c*TPN intervention. Such recovery was not observed in *24*TPN group.
Conclusions: Administration of *c*TPN is effective for treating PNALD, especially in terms of direct bilirubin recovery.

Keywords: Cyclic total parenteral nutrition, bilirubin, direct, indirect, parenteral nutrition-associated liver disease, cholestasis.

Introduction

Nutrition is essential to human survival. Total parenteral nutrition (TPN) is necessary when the alimentary system fails and no nutrition can be absorbed or used by the intestine. TPN is provided continuously, 24 hours a day, in high amounts and with high osmolality. It is administered via a central venous route such as Port-A-Cath, central venous pressure catheter, or peripherally inserted central catheter. Complications of TPN include bloodstream infection, electrolyte imbalance, hyperglycemia, hyperlipidemia, refeeding syndrome, renal function impairment, bone demineralization, and parenteral nutrition-associated liver disease (PNALD) [1-3]. PNALD is defined as abnormal liver function, as determined by elevated bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphate (ALk-P) levels, after a period of TPN [4]. Although difficult, PNALD must be well

* Correspondence Author: Frank Cheau-Feng Lin MD, PhD
Address: No.110, Sec.1, Jianguo N. Rd., Taichung City 40201, Taiwan
Tel: +886-4-24739595 ext. 34601
E-mail: frnklin@gmail.com

managed as it can lead to liver cirrhosis and death [4, 5]. Active enteral feeding is the best treatment option [6, 7] to avoid development of cholestastic jaundice [5]. However, if enteral feeding is not possible, high quality fat emulsion and cyclic total parenteral nutrition (*c*TPN) is the preferred treatment [6-9].

*c*TPN enables patients to carry out daily activities, as it can be administered at home, and is recommended for those with poor hepatic function. It has been reported to improve bilirubin, AST, and ALT levels. However, results have been inconsistent [10]. Most of the literature has focused on pediatric patients [11]. In this study, we examined *c*TPN data in adult patients to determine the effects of *c*TPN on liver function.

MATERIALS AND METHODS

Consecutive patients admitted to a medical center in Taiwan, who were aged over 18 with liver function impairment at the starting point of TPN, were enrolled from January 2014 to March 2016. Those on TPN for less than 7 days were excluded. Patients were divided into two groups in accordance with their use of continuous TPN (*24*TPN) or *c*TPN. The decision to start *c*TPN was based on clinical judgement and patient willingness. The most frequent indications were high bilirubin level and the desire for time away from TPN to carry out daily activities. TPN was prescribed with Harris-Benedict equitation for energy and 1g/kg/day of protein. Data on age, gender, diseases, total energy expenditure (TEE), infusion energy, and protein was collected retrospectively. Serum data associated with nutrition such as glucose, triglycerides, albumin, transferrin, and prealbumin was also collected. Data on hepatic functions included total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT and ALk-P. Serum levels were monitored before the start of TPN and then weekly until the end of TPN. We chose 4 time points for testing: before TPN (pre-TPN), one week after TPN (intra-TPN), end of TPN (post-TPN), and before discharge (final).

The two groups were compared. Chi-square tests were used for categorical data. Student t-test and Mann-Whitney U tests were used for continuous data depending on the normality of data distribution. Comparisons of the data at different time points were conducted with Wilcoxon signed rank test.

Results

Between January 2014 and March 2016, 122 consecutive adult patients with abnormal hepatic function at the start of TPN were considered for enrollment. Sixty-six patients were excluded due to TPN duration of less than 7 days (Figure 1) and 56 patients withdrew. Finally, 28 patients each were enrolled in the *24*TPN and *c*TPN groups.

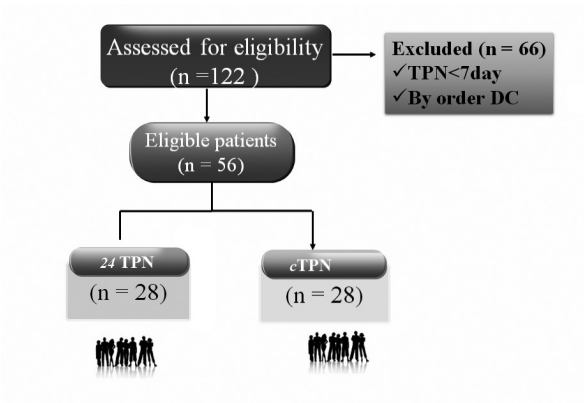


Figure 1. Inclusion protocol.

There were no differences in age or gender distributions between these two groups. In both groups, mean age was 65 with 68% males (Table 1). There were also no differences in height, weight, or body mass index (BMI). Average height was 162cm, average weight was 65kg, and average BMI was 21.5 for both groups. TEEs were calculated for TPN supplementation. TEE was about 80kcal/day higher on average in the *c*TPN group. This difference was not statistically significant.

As energy and protein were provided by TPN, there were no problems related to absorption rate or appetite. Provided energy was 92kcal/day higher on average for *c*TPN group, which was consistent with TEE, and provided protein was 5.7g/day higher on average for *c*TPN group. These differences were not statistically significant. The median durations of TPN were 30.0 and 24.5 days for *c*TPN and *24*TPN groups, respectively. Although TPN duration was

longer in *c*TPN group, this difference was not statistically significant. The median duration of *c*TPN was 20.5 days. The most common disease was colon cancer in both groups. Patients with gastric cancer, ileus, or pancreatic disease tended to stay on *24*TPN. Patients with perforated peptic

Table 1A. Demographics

	24TPN n (%)	**cTPN n (%)**	p
Total	28 (100)	28 (100)	1.000
Gender male	19(68)	19(68)	1.000
Disease			
colon cancer	7(25)	10(36)	0.078
colon cancer	6(21)	1(4)	0.101
ileus	6(21)	4(14)	0.729
pancreatitis	5(18)	1(4)	0.193
perforated peptic ulcer	3(11)	8(29)	0.117
esophageal cancer	0	1(4)	1.000
gastric bleeding	1(4)	1(4)	1.000
bile duct cancer	0	1(4)	1.000
gall bladder cancer	0	1(4)	1.000

Fisher's Exact test

Table 1B. Demographics (Continued)

	***24*TPN mean± SD**	***c*TPN mean± SD**	**P**
Age (years)	65.6±12.5	63.0 ±16.4	0.500
Height (cm)	161.5±8.1	63.0 ±16.4	0.419
Body weight (kg)	56.1±10.4	56.6±8.0	0.848
BMI	21.7±4.0	21.6±3.3	0.945
Total Energy	1697.3±238.5	1777.3±290.2	0.269
Energy (kcal/day)	1531±303	1629±300	0.226
Protein (g/day)	55.0±10.7	60.7±15.1	0.109
	median (quartiles)	**median (quartiles)**	
TPN (days)*	24.5 (15, 30)	30.0 (16.5, 56.5)	0.091
cTPN (days)		20.5 (10.3, 38.8)	

Two-tailed Student t-test.
*TPN durations were analyzed by Mann-Whitney U test.

ulcer or biliary system cancer tended to change to *c*TPN.

Nutritional status and liver function test results were compared before TPN. Median blood sugar was 27mg/dL higher in the *24*TPN group and reached the level of hyperglycemia (Table 2). The differences in median blood sugar between the groups were statistically significant. There were no statistically significant differences in other nutrition-related parameters including lipids and proteins between the groups. Triglyceride levels were lower and cholesterol levels were higher in *c*TPN group but were all within normal range, except for final triglyceride level in *24*TPN. All 3 protein levels, albumin, prealbumin, and transferrin, were below normal but were slightly higher in the *c*TPN group. This baseline data provided us with a good foundation for observing the subsequent effects of parenteral nutrition.

Serum liver function tests were also compared before TPN (Table 3). There were mild abnormalities in *c*TPN group. There were also abnormalities in the *24*TPN group except for ALT and AST. Results were worse in the *c*TPN group but the differences did not reach statistical significance.

There was little change in nutritional parameters after TPN. Hyperglycemia was more severe in *24*TPN group before and at the beginning of TPN.

Table 2. Changes in the nutritional parameters of continuous TPN and cyclic TPN patients.

		pre-PN		intra-PN		post-PN		Final
		Median (Quarters)	*p*	Median (Quarters)	*p*	Median (Quarters)	*p*	Median (Quarters)
Glucose [70~100] mg/dL	*c*TPN	134 (114,148)	***0.757***	131 (108, 143)	***0.781***	127 (114,152)	***1.000***	133 (112, 149)
	P	***0.004****		***0.000****		***0.159***		***0.090***
	*24*TPN	161 (132, 199)	***0.072***	151 (133, 237)	***0.008****	142 (121,186)	***0.396***	126 (108,187)
Triglyceride [<150] mg/dL	*c*TPN	103 (72,198)	***0.927***	124 (71,183)	***0.483***	119(78,183)	***0.917***	130 (81,187)
	P	***0.418***		***0.646***		***0.460***		***0.599***
	*24*TPN	131 (92,176)	***0.695***	117 (67,192)	***0.987***	107 (62,170)	***0.180***	196 (82, 307)
Cholesterol [<200] mg/dL	*c*TPN	113 (75, 160)	***0.023****	86 (64, 130)	***0.302***	108 (89,130)	***0.411***	109 (86,126)
	P	***0.621***		***0.979***		***0.231***		***0.364***
	*24*TPN	102 (84, 132)	***0.065***	86 (68, 104)	***0.676***	94 (72, 120)	***1.000***	92 (82, 122)
Albumin [3.5~5.7] g/dL	*c*TPN	2.5 (2.3, 3.3)	***0.183***	2.4 (2.0, 3.0)	***0.448***	2.4 (2.1, 2.9)	***0.121***	2.4 (1.9, 2.9)
	P	***0.485***		***0.901***		***0.891***		***0.111***
	*24*TPN	2.4 (2.0, 3.2)	***0.315***	2.4 (2.2, 2.7)	***0.847***	2.6 (1.8, 3.1)	***0.348***	3.0 (1.8, 3.3)
Prealbumin [18~39] mg/dL	*c*TPN	10.7 (7.1, 16.8)	***0.469***	14.0 (10.7, 27.3)	***0.293***	14.1 (5.7, 23.4)	***0.109***	27 (9.1, 30.1)
	P	***0.208***		***0.621***		***0.145***		***0.770***
	*24*TPN	10.1 (5.6, 13.3)	***0.866***	11.9 (8.7, 17.6)	***0.465***	10.1 (5.8, 14.3)	***0.263***	19.4(19.4,19.4)
Transferrin [180~329] mg/dL	*c*TPN	113 (93, 163)	***0.397***	124 (104, 145)	***0.091***	119 (89, 134)	***0.782***	119 (92, 159)
	P	***0.158***		***0.480***		***0.675***		***0.380***
	*24*TPN	99 (70, 140)	***0.463***	120 (90,139)	***0.600***	90 (75, 144)	***0.725***	81.6(81.6,81.6)

P, Independent nonparametric Mann-Whitney U test

p*, paired nonparametric Wilcoxon Signed Ranks Test*

Normal ranges are in []. Abnormal data is underlined with shading.

However, due to the efforts of the TPN team, there were no significant differences in blood sugar level at the end of TPN or before discharge between the groups. Blood sugar decreased during TPN in both groups especially in *24*TPN group (p=0.008). Serum cholesterol dropped at the beginning of TPN and returned to the original level after TPN. Protein levels including those of albumin, transferrin, and prealbumin remained low and did not change much after TPN.

Once TPN began, the median value of total bilirubin increased from 1.9 to 6.2 and this group of patients shifted from *24*TPN to *c*TPN (Figure 2). Direct and indirect bilirubin increased significantly in the *c*TPN group (Figures 3, 4). After *c*TPN, total bilirubin decreased significantly from 6.2 to 4.4 (p=0.014). Once TPN ceased, the level dropped further to 3.4. Direct bilirubin also decreased from 3.4 to 3.0 (P=0.022) and ended at 2.2. However, indirect bilirubin remained at 2.2 during *c*TPN and ended at 1.3 (p=0.484). *c*TPN demonstrated a greater effect on direct bilirubin. Indirect bilirubin increased (p=0.032) with total bilirubin in *24*TPN group after intervention with TPN (p=0.031 and 0.040).

These figures present the medians and quartiles of serum total bilirubin levels at different time points. As demonstrated in Figure 2A, total bilirubin was elevated after *24*TPN. Figure 2B shows that

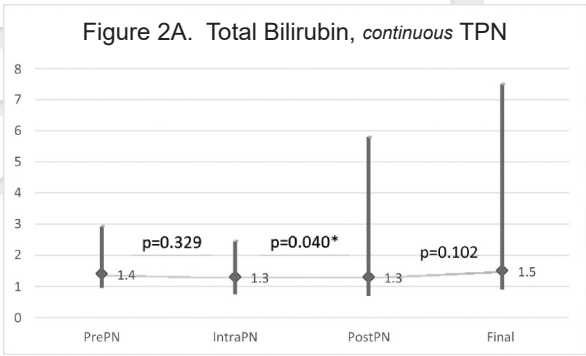
Table 3. Changes in liver function tests.

		pre-PN		intra-PN		post-PN		Final
		Median (Quarters)	*p*	Median (Quarters)	*p*	Median (Quarters)	*p*	Median (Quarters)
Total Bilirubin [0.3~1.2] mg/dL	*c*TPN	1.9 (0.8, 5.1)	***0.010****	6.2 (3.3, 10.9)	***0.014****	4.4 (1.6, 9.0)	***0.086***	3.4 (1.1, 8.6)
	P	***0.168***		***<0.001****		***0.021****		***0.386***
	*24*TPN	1.4 (1.0, 2.9)	***0.329***	1.3 (0.8, 2.5)	***0.040****	1.3 (0.7, 5.8)	***0.102***	1.5 (0.9, 7.5)
Direct Bilirubin [0~0.5] mg/dL	*c*TPN	1.2 (0.3, 4.9)	***0.036****	3.4 (1.9, 5.3)	***0.022****	2.9 (1.0, 6.1)	***0.338***	2.2 (0.7, 5.8)
	P	***0.090***		***<0.001****		***0.028****		***0.511***
	*24*TPN	0.6 (0.3, 1.4)	***0.613***	0.6 (0.2, 1.4)	***0.121***	0.6 (0.2, 3.2)	***0.225***	1.0 (0.4, 8.0)
Indirect Bilirubin [0.3~0.7] mg/dL	*c*TPN	0.8 (0.5, 1.7)	***0.013****	2.2 (1.3, 4.0)	***0.098***	2.2 (0.8, 4.2)	***0.484***	1.3 (0.5, 3.8)
	P	***0.806***		***0.002****		***0.509***		***0.902***
	*24*TPN	0.9 (0.6, 1.4)	***0.100***	0.7 (0.5, 1.2)	***0.031****	0.8 (0.6, 2.1)	***0.068***	0.7 (0.5, 2.5)
AST N [15~41] IU/L	*c*TPN	43 (31, 84)	***0.730***	52 (33,73)	***0.348***	59 (33, 86)	***0.597***	56 (37, 86)
	P	***0.392***		***0.890***		***0.777***		***0.214***
	*24*TPN	35 (22, 83)	***0.265***	49 (31,88)	***0.830***	54 (27, 90)	***0.917***	39 (28, 79)
ALT N [7~35] IU/L	*c*TPN	47 (15, 92)	***0.345***	44 (14, 101)	***0.990***	35 (21, 86)	***0.841***	40 (27,86)
	P	***0.829***		***0.424***		***0.986***		***0.603***
	*24*TPN	33 (17, 69)	***0.959***	30 (17, 61)	***0.469***	39 (21, 71)	***0.263***	51 (13, 76)
Alkaline-Phosphatase N [32~91] IU/L	*c*TPN	98 (57, 241)	***0.812***	105 (75, 166)	***0.433***	143 (96, 214)	***0.465***	129 (99,252)
	P	***0.260***		***0.403***		***0.409***		***0.288***
	*24*TPN	94 (63, 212)	***0.304***	90 (71,138)	***0.062***	108 (90, 201)	***0.465***	159 (128, 229)

P, Independent nonparametric Mann-Whitney U test

p*, paired nonparametric Wilcoxon Signed Ranks Test*

Normal ranges are in []. Abnormal data is underlined with shading.



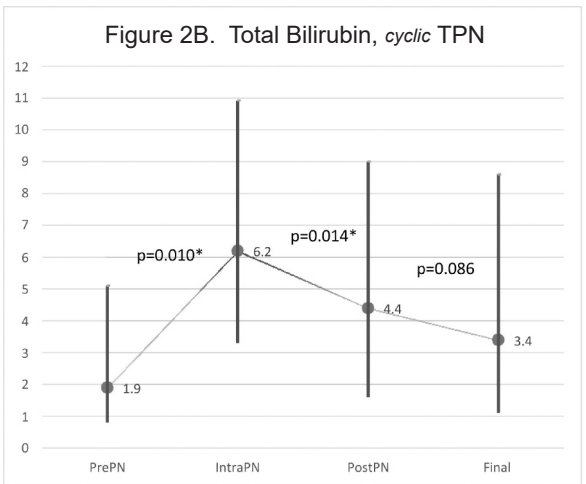
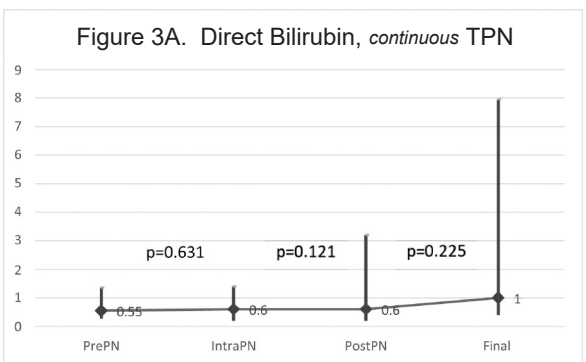


Figure 2. *Total* bilirubin trends in TPN patients.



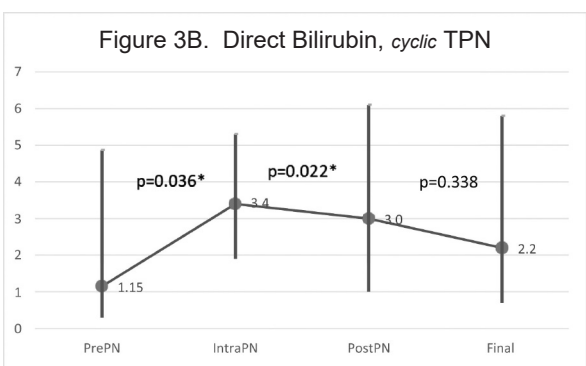
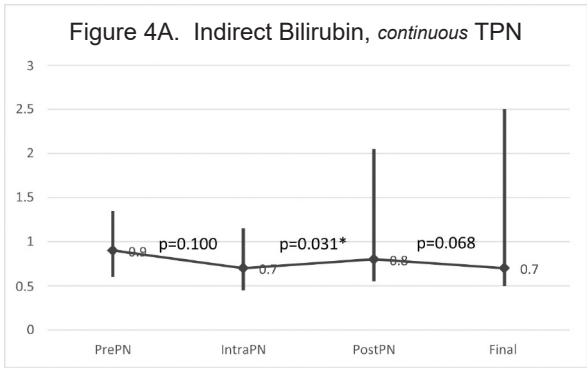


Figure 3. *Direct* bilirubin trends in TPN patients.



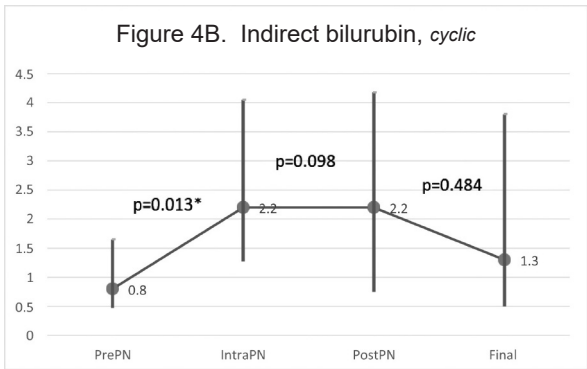


Figure 4. *Indirect* bilirubin trends in TPN patients.

after *24*TPN, total bilirubin was elevated from 1.9 to 6.2 (p=0.010). After *c*TPN, total bilirubin decreased to 4.4 (p=0.014).

These figures present the medians and quartiles of serum direct bilirubin level at different time points. As demonstrated in Figure 3A, there were no changes in indirect bilirubin for the duration of *24*TPN. Figure 2B shows that after *24*TPN, direct bilirubin was elevated from 1.15 to 3.4 (p=0.036). After intervention with *c*TPN, direct bilirubin decreased to 3.0 (p=0.022).

These figures present the medians and quartiles of serum indirect bilirubin level at different time points. As demonstrated in Figure 4A, indirect bilirubin was elevated from 0.7 to 0.8 (p=0.031) after *24*TPN. Figure 4B shows that after *24*TPN, indirect bilirubin was elevated from 0.8 to 2.2 (p=0.013). There was no significant impact on indirect bilirubin following *c*TPN.

TPN had no effect on serum levels of AST, ALT, or ALk-P (Table 3), which were at the high end of the normal range. AST remained slightly abnormal in *c*TPN patients and abnormal in *24*TPN patients. ALT was in the normal range for the *c*TPN

group and slightly higher than normal at discharge in the *24*TPN group. ALk-P was abnormal initially and worsened at the end of TPN in *c*TPN group. It was highest at the time of discharge in the *24*TPN group. However, the differences were not statistically significant.

Discussion

In this retrospective study, patients with abnormal liver function at the start of TPN were enrolled. Those with TPN duration of less than 7 days were excluded, as serum data was obtained every 7 days [10]. Half of the patients (28 of 56) showed elevated serum bilirubin after TPN and accepted change to *c*TPN. Case numbers were matched for these 2 groups in addition to age and gender distributions. However, we did not carry out propensity matching. All patients had alimentary system disease with colon cancer the most common. Patients receiving *c*TPN showed slightly worse liver function initially. Those with hepatobiliary system disease were all in this group.

There were no statistically significant differences in terms of disease. The results of this study suggested that in patients with abnormal serum liver data receiving TPN, bilirubin levels rise aggressively, requiring change to *c*TPN, especially for patients with hepatobiliary system disease. Further studies are needed to confirm if preventive *c*TPN or other preventive protocol is beneficial for patients with hepatobiliary disease with abnormal liver function on TPN [12].

*c*TPN has the benefit of "resting" the liver, enabling it to recover. There is higher glucose utilization with CO_2 production and lipogenesis during infusion and decreased CO_2 production and lipolysis during rest [13, 14]. Moreover, the energy expenditure shows diurnal changes [15]. In this study, there were more physiologically normal parameters with *c*TPN than with *24*TPN. In addition to the liver, vessels rest during *c*TPN, resulting in decreased incidence of parenteral nutrition-associated phlebitis[16].

After TPN, serum bilirubin levels, total, direct, and indirect, increased in half of our patients with *c*TPN. (Fig 2-4). Median total bilirubin decreased from 6.2 to 4.4 after shift from continuous TPN to *c*TPN. Further analysis revealed that direct bilirubin is significantly reduced, from 3.4 to 3.0. Indirect bilirubin remained at 2.2. The *24*TPN group showed continuous mild elevation of total bilirubin. On further analyses, there was greater elevation of indirect bilirubin. In patients without bilirubin rise after TPN, indirect bilirubin levels were further elevated.

Some studies have shown improvements in AST and total bilirubin after *c*TPN in adult patients [10]. The normalization of conjugated bilirubin via *c*TPN only has been reported in infants [17]. The results of this study implied that *24*TPN induces increases in both serum conjugated and unconjugated bilirubin levels. *c*TPN intervention recovers serum total bilirubin level, especially that of conjugated bilirubin, and prevents unconjugated bilirubin level increase. It has been shown that *c*TPN can reduce the risk of development of PNALD to about 30% [2].

In most studies, duration of TPN is longer in *c*TPN group probably due to disease severity [18]. In our study, this duration was around one month, which was about one week longer than for *c*TPN patients.

Before TPN, no subjects were considered underweight based on average body weight and BMI. Protein levels including transferrin, pre-albumin, and albumin levels were all below normal. *c*TPN was carried out for 12-16 hours, with a shorter time and higher infusion speed than *24*TPN. Blood sugar level was significantly higher in the *24*TPN group. Even with more rapid nutrient infusion, control of blood sugar in the *c*TPN group was not inferior to that in the *24*TPN group and *c*TPN did not impair sugar control [19-21]. After TPN, blood sugar did not increase in either group, as the TPN team focused on intensive blood sugar control. Median blood lipid levels were all within the normal range. In addition to nutrition, proteins represent inflammatory status [22, 23]. For patients with poor liver function, amino acids should be used meticulously, especially in the presence of high serum ammonia levels. TPN intervention with 1g/kg/day of amino acids did not reverse the lowered levels of serum proteins. In patients with poor liver function, aggressive amino acid supplement is not

encouraged. However, 1.2~2.0g/kg/day has been suggested [23]. Serum levels of proteins did not improve, perhaps due to unresolved inflammation or insufficient amino acid supplementation. Our results indicated that under meticulous supervision of the nutritional support team, *c*TPN does not negatively impact blood sugar or triglyceride control. However, limited amino acid supplement may not be enough for protein synthesis.

CONCLUSION

In this retrospective study, the 2 study groups were well matched. Patients with abnormal liver function had a higher rate of elevation of bilirubin after TPN for more than 7 days. Moreover, *c*TPN was effective in normalizing bilirubin level, especially that of direct bilirubin.

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