Original Article

Glutamine supplementation in preterm infants receiving parenteral nutrition leads to an early improvement in liver function

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Objective: The aim of study was to confirm the protective effects of parenteral glutamine supplementation on liver injury in premature infants and determine how quickly effects became evident. Methods: We performed a double-blind, randomized, controlled clinical study to assess the effect of parenteral nutrition (PN) supplemented with glutamine in premature infants. Thirty infants from two children's centers, were randomly assigned to either a control group (Standard PN; n=15) or a glutamine-supplemented group (GlnPN; n=15). The primary endpoint was hepatic function. The secondary endpoints were total duration of PN, weight and head circumference gain, length of hospitalization, and days on a ventilator. Results: The serum level of alkaline phosphatase (AKP) after parenteral nutrition for 14 days was significantly higher (p<0.05) in the control group. But in the glutamine-supplemented group, the serum concentration of aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT) significantly decreased after PN for 7 days and 14 days (p<0.05), and the level of alkaline phosphatase (AKP) showed no increase. The levels of AKP and GGT were significantly different with time by group interaction. Levels of AKP was higher in control group than glutamine-supplemented group, and GGT level was lower in glutamine-supplemented group compared with controls. There were no significant differences between the groups in terms of total duration of PN, weight gain (g/d), increase in head circumference (cm/w), length of hospitalization, and duration of mechanical ventilation. Conclusion: The longer the duration of parenteral nutrition, the more severe hepatic dysfunction became. Parenteral glutamine supplementation suggested a hepatoprotective effect.

Key Words: parenteral nutrition, glutamine, premature infant, liver function, neonate

INTRODUCTION

Liver dysfunction is common in individuals receiving parenteral nutrition (PN) and particularly in neonates and infants.[1] It remains a life threatening complication, which poses particular concern in infants dependent on long-term support.[2] Although the incidence and severity of this complication has decreased, it remains a major cause of morbidity and mortality in patients on long-term PN.[3,4]

Glutamine is one of the most abundant amino acids in both plasma and human milk, yet it is not included in standard intravenous amino acid solutions. In critically ill adults, placebo-controlled randomized studies have shown that glutamine supplementation normalizes intestinal permeability, attenuates nitrogen losses, and enhances immunological defenses against infection.[5] Although a Cochrane review in very low birth weight (VLBW) infants suggested that glutamine supplementation did not confer benefits for preterm infants,[6] it did not consider the effect of glutamine supplementation on liver function and some animal studies have demonstrated that glutamine supplementation significantly decreases liver complications.[7-9] Our previously published studies show that in rabbits, glutamine was an effective agent against PN-induced liver damage and glutamine supplementation attenuated PN-associated liver injury,[9] and that in VLBW infants parenteral glutamine supplementation improved hepatic tolerance.[10] This study was designed to confirm the protective effect of glutamine supplementation in premature infants receiving parenteral nutrition and de-

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termine how quickly the effects became evident.

PATIENTS AND METHODS

Patients

The patients were 30 premature infants being treated in the neonatal intensive care units (NICUs) of Xin Hua Hospital and Shanghai Children's Medical Center School of Medicine, Shanghai Jiao Tong University. The inclusion criteria were gestational age <37 weeks and recieving parenteral nutrition for 14 days or more. The exclusion criteria were pre-existing renal or hepatic dysfunction, congenital errors of metabolism, major chromosomal disease, CMV infection, viral hepatitis, and congenital or acquired immune deficiency. Ethical approval was obtained from the Research Ethical Committee of Xin Hua Hospital, School of Medicine, Shanghai Jiao Tong University. Written informed consent was obtained from the parents of all infants before enrollment.

Randomization

The study was a double-blind, randomized, and controlled clinical trial. Patients were randomly assigned to either a control group or a glutamine-supplemented group in the following manner. Treatment-assignment cards were created with a unique randomization code and placed in sequentially numbered, opaque envelops. At each site, the cards were pulled in sequential order and the randomization number was used to assign the patient to a treatment group. All investigators, parents, physicians, and nurses involved in patient care were blinded to the nutrition assignment; the randomization schedule was made available only to the pharmacist who supervised the processing of PN. Infants were followed until they were discharged from the hospital or died. They were withdrawn from the trial if severe adverse effects developed, or if parents withdrew their consent.

Nutrition support

Parenteral nutritional support was provided according to published guidelines for the use of nutritional support in critically ill neonates.[11] PN decreased when enteral intake increased and withheld once patients were receiving more than 70% of their recommended intake via the enteral route. The "All-in-One" solution contained lipids (20% Lipofundin; B. Braun), amino acids(6% pediatric amino acid or 6% pediatric amino acid and glutamine), glucose solution, minerals, trace elements, and water-soluble and fat-soluble vitamins. Infants in the control group received 6% pediatric amino acid compound injection (18AA-11; Treeful Pharmaceutical Co., Shanghai, China), the composition of which is shown in Table 1. The amino acid dosage was determined according to the guidelines; amino acids (in g/kg/d) were started at 1.0 to 1.5 and advanced or weaned, depending on enteral nutrition. The average amino acid dosage was 2.0 and infants in the glutamine-supplemented group received 6% pediatric amino acid solution 1.7 with glutamine (20% Ala-Gln; Fresenius Kabi,) at a dose of 0.3. The two solutions looked identical to the clinical staff. The "All-in-One" nutritional solution was infused continuously for 24 hours via peripherally inserted central catheters (PICCs; 1.9F; BD Medical) by infusion pumps (WZ-50C2; Tianjing). All babies were fed with the same formula (Pre-LACTOGEN; Nestle) via nasogastric tube and the amount of enteral nutrition was recorded daily by nursing staff.

Table 1. Composition of 6% pediatric amino acid compound injection (18AA-11)

Amino acid	g/ L
Isoleucine	4.9
Leucine	8.4
Lysine ethanoic	6.9
Methionine	2.0
Phenylalanine	2.9
Threonine	2.5
Tryptophane	1.2
Valine	4.7
Cysteine hydrochloride	<0.2
Histidine	2.9
Tyrosine	1.4
Alanine	3.2
Arginine	7.3
Proline	4.1
Serine	2.3
Aspartic acid	1.9
Glutamate	3.0
Glycine	2.2
Taurine	0.15

Measurement parameters

The following data were recorded on all infants: 1) liver function tests, which were recorded just before commencement of PN then once weekly; 2) body weight, which was measured three times per week; 3) head circumference, which was measured twice weekly.

The primary endpoints were the tests of hepatic function. Bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), gamma glutamyltransferase (GGT), total bilirubin (Tbi) and direct bilirubin (Dbi) were assessed by automated clolrimetric method (Beckman SYNCHRON LX20 system). Reference range were: TBA 0-10 μmol/L, ALT 0-75 U/L, AST 8-38 U/L, AKP 42-121 U/L, GGT 16-73 U/L, Tbi 3.42-20.5 μmol/L, Dbi 0-6.8 μmol/L. The secondary endpoints were total duration of PN, weight and head circumference gain, length of hospitalization, and number of days on a ventilator.

Statistical analysis

Data, which are expressed as mean±SD or median and interquartile range, were analyzed using SPSS 21.0 for Windows software. Continuous variables were compared between the two groups using a two-sample *t*-test or a Mann–Whitney nonparametric test. Repeated measure ANOVA was used to make the within group comparisons. A linear mixed model regression analysis was used for repeated measures fixed and random effects within and between groups. A p value of <0.05 was considered statistically significant. Bonferroni correction was used to conserve the overall type I error at $\alpha=0.05$.

Results

Of the 30 premature infants enrolled in our study, 26 completed the study (13 infants in the control group and

Table 2. Clinical data of control and glutamine-supplemented groups

	GlnPN	Standard PN	*p*-value
N	13	13	
M:F	9:4	8:5	
Age (d)	2.5±1.0	1.9±0.6	0.084
Gestation (w)	31.3±1.3	31.2±2.7	0.969
Birthweight (g)	1450±351	1444±450	0.868

GlnPN, glutamine-supplemented group; Standard PN, control group; M, male; F, female.

Table 3. Characteristics of control and glutamine-supplemented groups

	GlnPN (n=13)	Standard PN (n=15)	*p*-value
Lipid (g/kg/d)	1.35±0.32	1.59±0.41	0.104
Amino acid (g/kg/d)	1.96±0.25	2.12±0.55	0.340
PN calori (g/kg/d)	52.0±10.3	57.2±6.96	0.151
EN calori (g/kg/d)	35.8±17.0	36.5±19.8	0.931

PN, parenteral nutrition; EN, enteral nutrition

13 in the glutamine group). Four infants did not complete the study as they received PN for less than 14 days. The clinical data and nutritional characteristics were not significantly different between the two groups (see Tables 2 and 3).

The results of the liver function tests before commencement of PN (PN-0) and after 7 and 14 days (PN-7 and PN-14 respectively) are shown in Tables 4. In the control group, the serum level of AKP was significantly higher after PN for 14 days ($p<0.05$); the level of total bilirubin (Tbi) was significantly higher after PN for 7 days, but decreased after 14 days. In the glutamine-supplemented group, the serum concentrations of AST and GGT decreased significantly after PN for both 7 and 14 days ($p<0.05$); there were no further significant changes between PN-7 and PN-14; and the level of AKP did not increase(see Table 4). The level of AKP and GGT were significant differences with the time by group interaction. Levels of AKP was higher in control group than glutamine-supplemented group ($p=0.017$), and GGT level was lower in glutamine-supplemented group compared with controls ($p=0.001$), (see Figure 1 and 2). And the level of GGT was significantly different between the groups by linear mixed model statistics ($p=0.004$).

There were no significant changes in the total duration of PN given, weight gain (g/d), head circumference (cm/w), length of hospitalization, and the duration of mechanical ventilation ($p>0.05$; see Table 5).

Discussion

Parenteral nutrition has been widely and successfully used in the pediatric population for more than 40 years. However, one of the major complications of parenteral nutrition is still hepatic dysfunction, which may even be fatal to those dependent on long-term PN. Neonates are more susceptible to liver complications because of their physiological immaturity. The incidence of total parenteral nutrition associated cholestasis (TPNAC) has been reported to be as high as 40%-60%.[12] Its etiology is considered to be multifactorial: in neonates, it is associated with prematurity, low birth weight, duration of PN, and recurrent sepsis.[13-15] In addition, excessive amino acids, hepatotoxic bile acids, bacterial overgrowth, and micronutrient deficiency all contribute to liver injury.

Glutamine, a nonessential amino acid, becomes essential when the body is subjected to metabolically stressful situations. Premature infants are susceptible to glutamine depletion as placental supply ceases at birth, tolerance of enteral nutrition is limited, and parenteral nutrition does not contain glutamine because of solubility and stability issues. Furthermore, these infants are highly stressed and have an increased utilization of glutamine during their first few weeks of life. Although glutamine is considered a nonessential amino acid, its synthesis may not keep up with requirements during times of stress, which therefore makes it a "conditionally essential" amino acid.

During the past decade, many studies have considered the role of glutamine supplementation. A recent Cochrane publication found that available data from good quality, randomized controlled trials indicated that glutamine supplementation does not confer benefits for preterm infants. The narrow confidence intervals for the effect size estimates suggest that a further trial of this intervention is not a research priority. However, in the review, the primary outcomes were death prior to hospital discharge and neurodevelopment; the secondary outcomes were invasive infection, necrotizing enterocolitis, growth during the trial period, days from birth to establishment of full enteral feeding, and days from birth to discharge from hospital. Liver function was not used as an endpoint.[6]

A number of clinical studies have revealed that the incidence of PNAC increases with longer duration of parenteral nutrition; we found the same result in this study. As the duration of PN increased, so did the serum AKP levels in the control group, being significantly higher after 14 days. In contrast, in the glutamine-supplemented group, the serum concentrations of AST and GGT significantly decreased after PN for 7 days and the serum AKP did not increase. The protective effect of parenteral glutamine supplementation appeared after only 7 days of PN. The level of AKP and GGT were significantly different with time by group interaction, the level of AKP was higher in control group than glutamine-supplemented group, and the level of GGT was lower in glutamine-supplemented group than control group.

PN-associated liver injury in infants often include intrahepatic cholestasis, steatosis, and even fibrosis or cirrhosis. But in the current clinical study, we do not have access to liver tissue, and can only judge PN-associated liver injury through the biochemical index, including TBA, ALT, AST, AKP, GGT, Tbi and Dbi. There is still debate as to which is the most sensitive biochemical index of PN-associated liver injury. Some investigators prefer ALT and GGT, whereas others incline toward conjugated bilirubin, AST or AKP. Hata *et al*[16] experimented on newborn Japanese rabbits, and found that Tbi was elevated in one group after 7 days of PN. The study of Hong *et al* [17] on New Zealand rabbits found that the serum levels of Tbi and bile acid in the PN group were significantly higher than those in the control group. In our previously published study in animals, the serum levels of Dbi and

Table 4. Results of the liver function tests between of control and glutamine-supplemented group

	GlnPN			*p-value**	Standard PN			*p-value**	*p-value*
	PN-0	PN-7	PN-14		PN-0	PN-7	PN-14		
TBA (μmol/L)	10.6±4.52	12.2±10.5	15.0±5.92	NS	14.1±6.78	21.4±5.79	19.8±12.1	NS	NS
ALT (IU/L)	15.0±11.1	10.0±6.34	10.6±9.94	NS	13.4±9.66	13.2±12.7	9.33±6.42	NS	NS
AST (IU/L)	77.6±40.0 †	45.3±22.3	40.5±38.4	0.028	69.2±47.4	53.1±49.4	55.3±25.0	NS	NS
AKP (IU/L)	223±81.3	251±70.9	291±151	NS	199±86.9	207±80.4	356±118§	0.001	0.017
GGT (IU/L)	215±123 †	100±55.9	74.3±36.0	0.002	133±106	85.6±90.0	100±79.9	NS	0.001
Tbi (μmol/L)	95.3±75.4	155±74.9	107±80.1	NS	76.8±43.3	145±79.7 ‡	88.3±55.9	0.012	NS
Dbi (μmol/L)	4.44±5.27	8.76±5.76	9.79±6.66	NS	5.78±4.77	8.32±4.17	8.02±4.15	NS	NS

NS, $p>0.05$ for all parameters.
*for intra-group comparisons over time
PN-0, before commencement of PN; PN-7,PN after 7 days; PN-14, PN after 14 days;
TBA, bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase, GGT, gamma glutamyltransferase; Tbi, total bilirubin; Dbi, direct billirubin,
† $p<0.05$ compared with PN-7 group and PN-14 group
‡ $p<0.05$ compared with PN-0 group and PN-14group
§ $p<0.05$ compared with PN-0 group and PN-7group

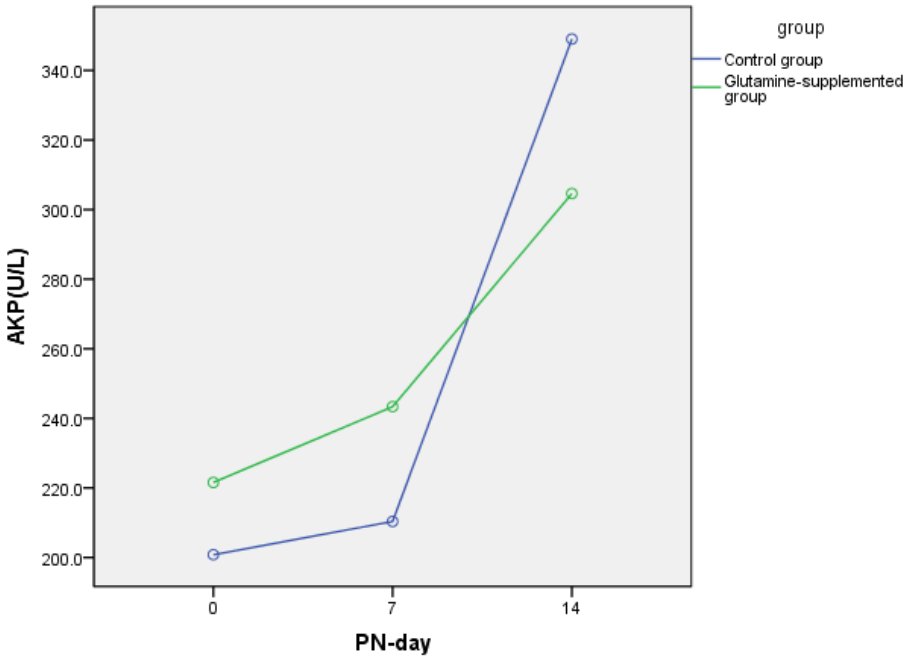

Figure 1. The level of AKP between control and glutamine-supplemented group

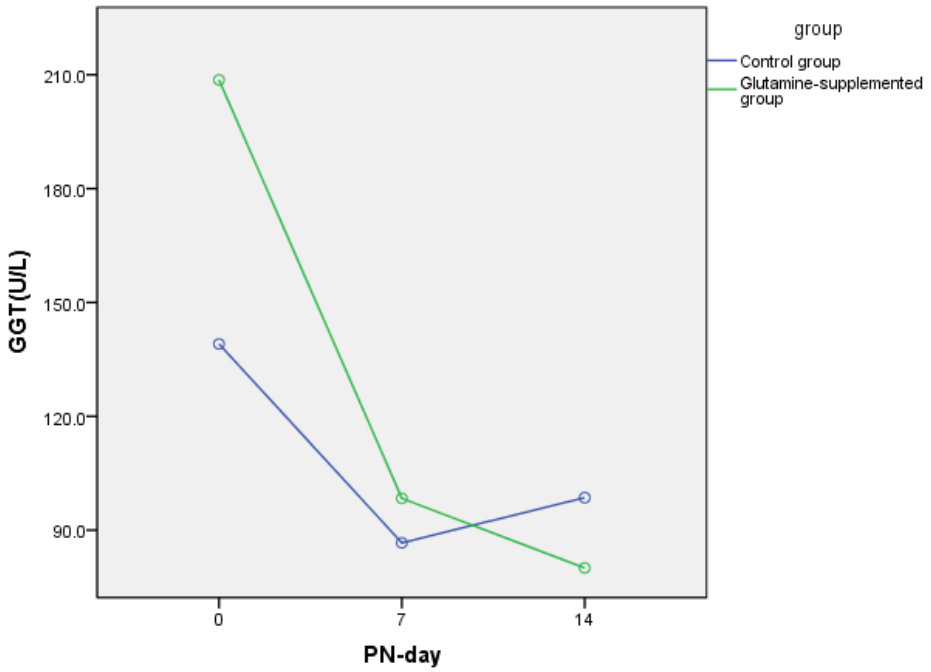

Figure 2. The level of GGT between control and glutamine-supplemented group

Table 5. Secondary endpoints in control and glutamine-supplemented groups

	GlnPN (n=13)	Standard PN (n=13)	*p*-value
Total duration of PN (d)	21.2±4.20	20.0±6.73	0.609
Weight gain (g/d)	16.4±4.06	18.5±6.99	0.356
Head circumference (cm/w)	0.58±0.23	0.74±0.45	0.292
Length of hospitalization (d)	42.5±15.5	41.2±16.0	0.834
Days on ventilator (d)	2.75±2.26	2.08±3.75	0.596

bile acid significantly increased in the PN group, and AST concentration was lower in the glutamine group.[9] In addition, our previous study in VLBW infants showed that the concentrations of AST and Tbi were lower in the glutamine-supplemented group after parenteral nutrition.[10]

Jaundice is the most common condition that requires medical attention in newborn babies. About 50%of term and 80% of preterm babies develop jaundice in the first week of life, usually appearing 2-4 days after birth and disappearing 1-2 weeks later.[18] In our study, the serum level of Tbi in the control group was significantly higher after PN for 7 days, but decreased after 14 days, which may be due to neonatal jaundice.

Glutamine may be an effective agent against PN-induced liver damage. Shaw *et al* [19] found, using rat models of PN, that PN bypassed the gut leading to decreased hepatic cytochrome P450 activity, but that addition of glutamine to parenteral nutrition prevented PN-induced depression in hepatic P450 activity. Another study[20] found that glutamine could effectively diminish hepatocyte apoptosis after common bile duct ligation for 3 days. Wu *et al* [9] found that glutamine could decrease liver malondialdehyde (MDA) production and hepatocyte apoptosis during PN. Hong *et al* [16] found the hepatocyte superoxide dismutase (SOD) activity was inhibited along with a concomitant increase in MDA levels following a 10-day infusion of PN, Cytochrome C was released and caspase 3 activity was significantly stimulated after infusion of PN. DNA fragmentation results revealed more obvious apoptosis in the PN group than in the control group, which suggested that PN-associated liver dysfunction was related to hepatocyte oxidative injury and apoptosis in the rabbit PN model, and oxidative damage is an inducer of mitochondrial permeability transition (MPT). Triggering of MPT leads to the release of several different factors relevant to apoptosis, such as cytochrome C, and to significant activation of caspase 3, with subsequent activation of the caspase cascade causing hepatocyte apoptosis. Therefore, oxidative damage may be one of the essential mechanisms of PN-associated liver dysfunction and mitochondria-initiated apoptosis triggered by oxidative damage may play an important role in this process. Glutamine supplementation can therefore decrease hepatocellular apoptosis and reduce hepatic oxidative injury. The mechanism may relate to improved anti-oxidative and anti-apoptotic capacity. We speculate that this may be related to the increase in glutathione concentration in liver tissue because glutamine is the effective precursor of glutathione.

In summary, preterm infants who received parenteral glutamine have improved hepatic tolerance after PN for 7 days, which may be related to a reduction in apoptosis and oxidative injury. Glutamine may be an effective agent against PN-induced liver damage; however, further studies are required to explore the molecular mechanisms.

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AUTHOR DISCLOSURES

All authors have no conflicts of interest or financial or other contractual agreements that might cause conflicts of interest.

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Original Article

Glutamine supplementation in preterm infants receiving parenteral nutrition leads to an early improvement in liver function

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静脉补充谷氨酰胺可以早期改善早产儿肝脏功能

目的: 本研究目的是证实补充谷氨酰胺肠外营养(PN)对早产儿肝脏功能的保护作用。方法:采用双盲、随机、对照试验，评价补充谷氨酰胺肠外营养对早产儿的作用。来自两家儿童医疗中心的30例早产儿随机分为对照组(标准PN；n=15)和谷氨酰胺组(GlnPN；n=15)。首要终点指标为肝功能。次要终点指标为PN持续时间，体重和头围增长情况，住院天数和呼吸机应用天数。结果：肠外营养应用14天后，血清碱性磷酸酶(alkaline phosphatase, AKP)水平在对照组明显升高(p<0.05)。在谷氨酰胺组，谷草转氨酶(aspartate aminotransferase, AST)水平和γ-谷氨酰转肽酶(gamma glutamyltransferase, GGT)水平在肠外营养应用7天和14天后明显下降(p<0.05)，AKP水平无明显升高。AKP水平和GGT水平在两组比较具有统计学差异。AKP水平在对照组较谷氨酰胺组明显升高，GGT水平在谷氨酰胺组下降较对照组明显。肠外营养应用时间、体重和头围增长情况、住院天数和呼吸机应用天数， 两组比较无差异。结论: 肠外营养持续时间越长，肝功能损害越严重，而肠外补充谷氨酰胺具有保护肝脏功能的作用。

关键词：肠外营养、谷氨酰胺、早产儿、肝功能、新生儿