

## ORIGINAL ARTICLE

# A double-blind, randomized, controlled crossover trial of glutamine supplementation in home parenteral nutrition

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**Objective:** Studies suggest clinical benefit of glutamine-supplemented parenteral nutrition. The aim was to determine if the inclusion of 10 g of glutamine as part of the nitrogen source of home parenteral nutrition (HPN) reduces infectious complications.

**Subjects/Methods:** Thirty-five patients on HPN were recruited and 22 completed the study. Patients were randomized to receive either standard HPN or glutamine-supplemented HPN. Patients were assessed at randomization, 3 and 6 months later then they were crossed over to the alternative HPN and reassessed at 3 and 6 months. Assessments included plasma amino acid concentrations, intestinal permeability and absorption, nutritional status, oral and parenteral intake, quality of life, routine biochemistry and haematology.

**Results:** No difference was seen between the groups at randomization. No difference was detected between the treatment phases for infective complications (55% in the standard treatment phase and 36% in the glutamine-supplemented phase  $P=0.67$ ). There were no differences in nutritional status, intestinal permeability, plasma glutamine concentrations or quality of life.

**Conclusion:** Although limited by the sample size, the study has shown that glutamine as part of the nitrogen source of parenteral nutrition can be given to patients on HPN for 6 months without any adverse effects.

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**Keywords:** glutamine, home parenteral nutrition, infective complications, intestinal permeability, TPN

## Introduction

Glutamine is the most abundant-free amino acid in extra- and intracellular compartments, contributing more than

50% of the body-free amino acid pool (Krebs, 1935). It is a major fuel for rapidly replicating cells such as immune cells (Calder, 1994) and enterocytes (Windmueller, 1982). Conventional parenteral nutrition solutions do not contain glutamine, as adults are considered able to synthesize glutamine from glutamate and glutamic acid (Rose, 1938). In addition, until recently, problems with stability and solubility have hindered its addition to parenteral nutrition. However, an increasing number of studies in humans suggest clinical benefits of glutamine supplementation in acutely unwell patients on exclusive parenteral nutrition. Glutamine supplementation appears to be beneficial following burns (Ogle *et al.*, 1994), major surgery (Hammarqvist *et al.*, 1989), bone marrow transplantation (Ziegler *et al.*, 1992), sepsis and critical illness (Griffiths *et al.*, 1997) due to its effect on nitrogen balance (Morlion *et al.*, 1998), immune function

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**Contributors:** AC was the study lead and involved in recruitment, data collection, blood and urine sample collection and preparation, data interpretation and writing the article. SMG was involved in the protocol development, supervision of the data collection and interpretation and writing the article. IB and GG were involved in the protocol development. AF was involved in the protocol development and writing the article. AMM was involved in writing the article.

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(O'Riordan *et al.*, 1994) and intestinal permeability (van der Hulst *et al.*, 1993). During catabolic states, glutamine concentration in the intracellular pool falls rapidly because glutamine serves as a fuel for stimulated lymphocytes, macrophages (Calder, 1994) and intestinal mucosal cells (Windmueller, 1982). Patients on home parenteral nutrition (HPN) are susceptible to recurrent central venous catheter (CVC) infections, and animal studies have demonstrated that parenteral glutamine reduces CVC infections (McAndrew *et al.*, 1999). It is therefore hypothesized that HPN patients may benefit from glutamine supplementation. To date, no studies have been undertaken to investigate the effect of glutamine supplementation on infective complications in patients on long-term HPN. Safety data exist both for normal volunteers at a dose of 0.57 g/kg/day over 5 days, and for bone marrow transplant patients receiving glutamine-supplemented parenteral nutrition to approximately the same level over 28 days. Safety was considered good in these contexts (Ziegler *et al.*, 1990). However, a study of patients on HPN receiving 0.285 g/kg/day of parenteral glutamine over 4 weeks resulted in abnormal liver function tests (LFTs), which necessitated the discontinuation of glutamine supplementation in two patients (Hornsby-Lewis *et al.*, 1994).

## Patients and methods

The study was a randomized, double-blind, controlled crossover trial carried out from June 2001 to December 2002. All adults on HPN under the care of the Nutrition and Intestinal Failure Clinic at St Mark's Hospital were considered for the study. Patients were excluded if they did not consent, were due to undergo planned surgery, were pregnant or had severe liver or renal failure or an inborn error of amino acid metabolism (e.g. phenylketonuria).

Our primary end point was infective complications. Our secondary end points were intestinal permeability, quality of life and plasma amino acid concentrations during the two phases of the study. The crossover design was chosen due to the heterogeneous population being studied so that patients could act as their own control.

## Protocol

After written consent had been obtained, patients were randomized to receive either standard HPN (for which the amino acid solution was Intrafusin 22, Fresenius Kabi, Stockholm) or glutamine-supplemented HPN (for which the amino acid solution was Glamin, Fresenius Kabi, Stockholm). A pharmacist performed the randomization by opening sealed envelopes and allocated patients to receive either glutamine-supplemented HPN or standard HPN first. The homecare companies who deliver HPN did not display the amino acid source on the bag label. All other investigators, including the statistician who analysed the data, were

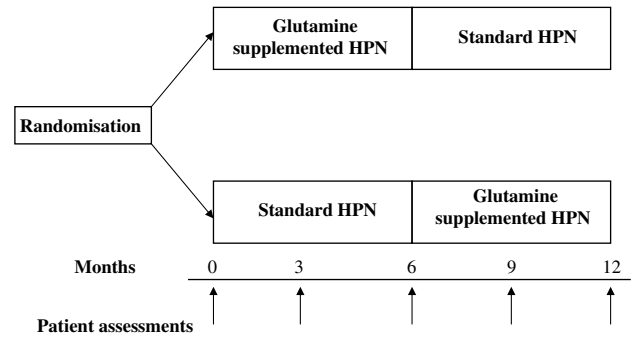


Figure 1 Trial protocol.

blind to the randomization process. Patients were assessed as outpatients at randomization, and 3 and 6 months later. After the 6-month assessment, the patients were crossed over onto the alternative amino acid solution and reassessed 3 and 6 months later (Figure 1). Assessments included an examination of plasma amino acid concentrations, intestinal permeability and absorption, nutritional status, oral and parenteral nutrient intake, quality of life and routine biochemistry and haematology.

## Parenteral nutrition

This was a comparison of two commercially available amino acid solutions with similar nitrogen content. An exact isonitrogenous comparison was not possible in this study and so we compared our standard amino acid solution with a glutamine-supplemented solution. Table 1 shows the composition of the two parenteral amino acid solutions. The glutamine was present as a dipeptide with glycine. The energy and nitrogen content of the HPN for each patient were not altered during the study so that individual patients remained isonitrogenous and isocaloric during the study period. All patients received at least 11 g of nitrogen intravenously on the days they received HPN. For patients not receiving HPN every day an average intake of nutrients per day were calculated. From these figures, patients received a mean intake of  $0.14 \pm 0.04$  g/kg/day of glutamine (range 0.08–0.24 g/kg/day) during glutamine supplementation. Parenteral fluid, electrolytes, trace elements and vitamins were prescribed according to the patient's individual requirements.

Patients on HPN are trained to report any signs or symptoms of a possible infection, which is then investigated. During the trial if patients developed signs or symptoms of catheter-related sepsis (chills, flu-like symptoms or fever of  $>38^{\circ}\text{C}$ , rigors), central and peripheral blood cultures were obtained, sent to microbiology for culture and the patient was screened for other causes of infection. Any positive central blood culture was recorded as an infective complication and the organism noted. Parenteral nutrition is stopped and peripheral fluids are commenced while awaiting the results of the cultures. Patients are administered appropriate

**Table 1** Composition of glutamine-supplemented HPN and standard HPN per 500 ml

Amino acid	Glutamine-supplemented HPN (g)	Standard HPN (g)
<i>Indispensable</i>		
L-Leucine	3.95	2.85
L-Isoleucine	2.80	2.10
L-Lysine	4.5	6.75
L-Valine	3.65	2.35
L-Phenylalanine	2.93	2.05
L-Histidine	3.40	1.75
L-Threonine	2.80	2.70
L-Methionine	2.80	2.70
L-Tryptophan	0.95	1.05
<i>Dispensable</i>		
L-Alanine	8.00	13.0
L-Arginine	5.65	7.00
Glutamic acid	2.80	3.75
L-Glutamine	10.0	—
Glycine	5.60	7.80
L-Proline	3.40	7.05
L-Serine	2.25	7.05
L-Tyrosine	1.14	1.13
L-Cysteine	—	0.35
Aspartic acid	1.70	—
Total L-amino acids (g)	77.0	76.2
Total nitrogen (g)	11.2	11.4
Energy content (kcal)	270	300
pH	5.80	5.20
Osmolality (mosmol/kg water)	1140	1400

Abbreviation: HPN, home parenteral nutrition.

antibiotics (according to sensitivities) via the CVC for 1 week. Parenteral nutrition is then restarted and patients are monitored for signs and symptoms of catheter-related sepsis as detailed above.

#### Quality of life

Quality of life measurements were assessed using the SF-36 and EuroQol questionnaires, which have previously been used to assess patients on HPN (Richards *et al.*, 1997). The SF-36 is designed to examine eight aspects of life, and scores each domain on a scale of 0–100%. It was scored according to the published scoring manual (Ware, 1993). The EuroQol is a simple generic measure designed to assess health using descriptive statements. These statements generate a single numeric index to estimate quality of life status used for clinical evaluations of health. It also includes a visual analogue scale from 0 to 100 with 0 being worst imaginable health state to 100 being best imaginable (Dolan *et al.*, 1995). Both questionnaires are designed for self-completion.

#### Nutritional status and oral intake

The assessment of nutritional status was performed using anthropometry including measurement of height, weight and calculation of body mass index (BMI), mid-arm

circumference, tricep skinfold thickness and calculation of mid-arm muscle circumference. This was undertaken by a trained research dietitian using standardized procedures (Gurney and Jelliffe, 1973). In the week before each assessment, patients were asked to record their food and fluid intake over a 3-day period using a diary. The diaries were verified by the dietitian at an outpatient visit and then the description of food was converted to weight in grams using a photographic atlas of food portion sizes (Nelson *et al.*, 1997). A computerized nutrient analysis programme was used to calculate the energy, protein, fat and carbohydrate content of the 3 days and the average was calculated (COMP-EAT, Carlson Bengston Consultants Limited, London).

#### Intestinal permeability and absorptive capacity

The differential urinary excretion of lactulose and L-rhamnose (L/R ratio) was used as a specific index of intestinal permeability, and the differential urinary excretion of rhamnose and 3-O-methyl-D-glucose (R/3OMG ratio) was used as an index of intestinal carbohydrate absorptive capacity. After an overnight fast, the patient was instructed to empty the bladder and to drink a test solution containing 0.2 g 3-O-methyl-D-glucose, 1 g L-rhamnose and 5 g of lactulose made up to 100 ml with tap water. Food and fluids were withheld until 2 h after ingestion of the solution. Over the next 5 h, patients collected their urine into containers containing 5 ml 10% thymol. The volume of the urine collected was recorded and a 20 ml aliquot removed from the final collection and stored at  $-70^{\circ}\text{C}$  before analysis of urinary sugars by thin layer chromatography (Menzies and Crane, 1998).

#### Additional variables/measurements

Routine haematology and biochemistry tests were performed at each visit. Patients infuse HPN overnight and then travel to St Mark's for their outpatient appointments, hence we were unable to standardize the timing of the samples for glutamine analysis but this would have been within 6–8 h post infusion. An extra blood sample was taken in a heparinised tube and spun at 2000 g for 10 min. The plasma was then stored at  $-70^{\circ}\text{C}$  before analysis of amino acids by high-performance liquid chromatography (Sherwood, 1990).

#### Statistics

Statistical analyses were performed at randomization to ensure that the randomization process was effective. The statistics reported are mean  $\pm$  standard deviations (s.d.) in each group, together with the *P*-value resulting from the *t*-test for those variables found to be normally distributed. For variables found not to be normally distributed, the median and inter-quartile range (IQR) are reported, together with the *P*-value from the Mann–Whitney test.

A paired *t*-test was used for parametric data and a Mann–Whitney test for non-parametric variables to compare patients in the two phases of the study. All values are given as mean  $\pm$  s.d. together with the *P*-value for those variables found to be normally distributed. For variables not normally distributed, the median and IQR are reported, together with the *P*-value from the Mann–Whitney test. We were unable to incorporate a washout period as part of the trial as patients are dependent on parenteral nutrition. Any carry over effect, due to the lack of a washout period, was assessed using the difference in results between the periods for each subject and comparing between treatment orders using a paired *t*-test. All analysis was restricted to patients who had completed both periods of the study. Fischer's exact test was used to assess if the number of CVC infections varied between the two treatments.

Informed consent was obtained from the patient and the study protocol was approved by the Harrow Local Research Ethics Committee (2654).

## Results

Thirty-five patients were entered into the study. Twenty-two completed both periods of the study. Five patients no longer required HPN of which four remained on intravenous fluids and electrolytes, four withdrew consent and three died. One patient was withdrawn due to protocol deviation, as she had not received any parenteral nutrition for over 2 months during an inpatient stay for recurrent infections. The allocation of the patients who did not complete the study is shown in Figure 2. There were no statistically significant differences at baseline between patients allocated to receive glutamine-supplemented HPN first and those who were allocated to receive standard HPN first (Tables 2 and 3) with the exception of more patients with an ileostomy being randomized to the standard HPN first ( $P=0.04$ ) showing that the randomization process was successful.

### Complications

Complications were classified into infective, non-infective, vascular and disease related (Table 4). There was no significant difference in the total rate of any complications during the two phases of the study ( $P=0.67$ ). Patients receiving standard HPN had 0.1 infections/patient/month compared to 0.06 infections/patient/month on glutamine-supplemented HPN. One patient had their CVC removed and replaced. Of the other infective episodes three patients had a subsequent re-infection of the same CVC with the same organism that may in one case have been due to concurrent dental treatment. The other two patients had a repeat infection but this occurred 7 months later. There were three deaths during the study of which one occurred during glutamine-supplemented HPN and two during the standard HPN phase but this difference was not statistically significant.

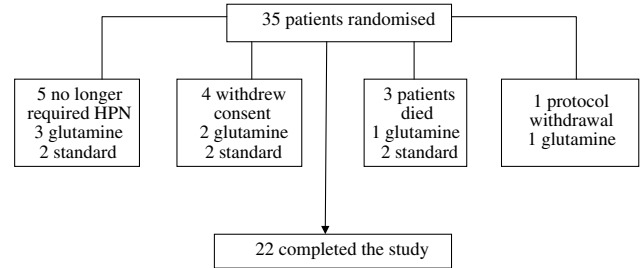


Figure 2 Trial profile.

cant. Causes of death included cancer ( $n=2$ ) and respiratory failure not thought to be related to the study ( $n=1$ ). No non-catheter-related infective complications occurred during the study period.

### Quality of life

Twenty-one patients completed the SF-36 and EuroQol questionnaires at each visit during the study period. Glutamine-supplemented HPN had no obvious effect on quality of life in these patients at any point during the study (Table 5).

### Nutritional status and oral intake

There was no significant change in nutritional status during the study (Table 5). Patients in both groups had similar intakes of oral protein and parenteral nitrogen throughout the study period. The addition of glutamine to HPN had no effect on oral intake at any point during the trial period (data not presented).

### Intestinal permeability and absorption

Results were available for 20 patients who completed the study, as two patients were non-compliant with this aspect of the study. There were paired data available on 13 patients. The median intestinal permeability (lactulose/rhamnose) ratio on glutamine-supplemented parenteral nutrition was 0.91 (0.37, 1.45) compared to 0.39 (0.18, 0.79) on standard parenteral nutrition. In addition, the mean intestinal absorption index (rhamnose/3-O-methyl-D-glucose) on glutamine was  $0.10 \pm 0.06$  compared to  $0.12 \pm 0.05$  on standard parenteral nutrition. Neither of these results showed a statistically significant difference. Therefore, the intestinal permeability ratio and absorptive index were not affected by the addition of glutamine (Table 5).

### Biochemistry and haematology

The addition of glutamine had no significant effect on any of the variables measured (data not presented). Liver function tests were not significantly affected by the addition of glutamine (Table 5).

**Table 2** Comparison of baseline data of the two groups at randomization (demographics, anthropometrics, oral and parenteral nutrition, plasma glutamine, intestinal permeability and absorption)

	Glutamine-supplemented HPN first (n = 11)	Standard HPN first (n = 11)	P-value
Male/female	5/6	4/7	0.64
Age (years)	51.5 ± 12.1	55.5 ± 12.8	0.46
<b>Aetiology</b>			0.67
Crohn's disease	5	3	
Mesenteric infarct	2	2	
Other*	4	6	
<b>Length of small bowel</b>			0.84
< 50 cm	3	2	
50–100 cm	3	4	
> 100 cm	5	5	
<b>Type of stoma</b>			0.04
Jejunostomy	1	0	
Ileostomy	0	5	
Colostomy	1	1	
Colon in continuity	9	5	
<b>Time on HPN (months)**</b>	51 (11, 99)	28 (13, 83)	0.65
<b>Nutritional status</b>			
Weight (kg)	57.9 ± 11.1	61.7 ± 10.2	0.41
Body mass index (kg/m <sup>2</sup> )	21.1 ± 3.0	22.1 ± 2.5	0.41
Tricep skinfold thickness (mm)	11.2 ± 3.7	14.0 ± 5.7	0.18
MAMC (cm)	21.8 ± 4.0	23.3 ± 2.6	0.30
<b>Oral nutrition</b>			
Energy (kcal)	1244 ± 606	1547 ± 949	0.42
Protein intake (g)	47 ± 28	55 ± 31	0.58
Fat (g)	50 ± 22	73 ± 46	0.19
Carbohydrate (g)	161 ± 92	183 ± 116	0.64
<b>Parenteral nutrition</b>			
Energy (kcal)	1376 ± 511	1204 ± 484	0.43
Nitrogen (g)	9.3 ± 2.1	9.5 ± 3.4	0.83
Lipid (kcal)	202 ± 124	173 ± 163	0.65
Glucose (kcal)	1177 ± 419	1031 ± 426	0.64
Glutamine (g/kg/day)	0.14 ± 0.07	0.15 ± 0.04	0.68
Frequency of HPN (days/week)**	6 (5, 7)	6 (5, 7)	0.95
Plasma glutamine (μmol/l)	481 ± 106	459 ± 90	0.61
Intestinal permeability ratio	0.58 ± 0.43	0.39 ± 0.26	0.32
Intestinal absorption index	0.13 ± 0.06	0.14 ± 0.09	0.81

Abbreviation: HPN, home parenteral nutrition.

\*Includes visceral myopathy, scleroderma, radiation enteritis, pseudo-obstruction, familial adenopolyposis, sclerosing peritonitis and fistulae.

Value presented as mean ± s.d. or \*\* median (IQR).

#### Plasma amino acid concentrations

The concentrations of phenylalanine and histidine were significantly higher during glutamine administration, whereas the levels of serine and proline were significantly

**Table 3** Comparison of baseline data of the two groups at randomization (quality of life and liver function tests)

	Glutamine-supplemented HPN first (n = 11)	Standard HPN first (n = 11)	P-value
<b>SF-36</b>			
Health perception	41 ± 25	40 ± 23	0.90
Physical function	66 ± 32	45 ± 16	0.07
Role limiting physical*	38 (0, 100)	25 (0, 50)	0.34
Role limiting emotional*	100 (0, 100)	100 (67, 100)	0.84
Social functioning	68 ± 30	60 ± 28	0.57
Mental health	72 ± 15	73 ± 16	0.87
Body pain	68 ± 27	56 ± 25	0.30
Energy/fatigue	49 ± 26	44 ± 23	0.62
<b>EuroQol</b>			
Index	0.68 ± 0.21	0.67 ± 0.15	0.87
Visual analogue scale	63.7 ± 18.1	67.4 ± 10.3	0.57
<b>Liver function tests</b>			
ALT (10–50 IU/l)	49 ± 29	43 ± 32	0.64
AP* (40–135 IU/l)	111 (74, 125)	154 (109, 401)	0.11
Bilirubin* (1–17 μmmol/l)	8 (6, 12)	8 (4, 9)	0.25
Albumin (35–50 g/l)	41 ± 4.1	39 ± 2.4	0.18

Abbreviations: ALT, alanine transferase; AP, alkaline phosphatase; HPN, home parenteral nutrition.

Values presented as mean ± s.d. or \*median (IQR).

**Table 4** Complications in the 6-month period on each HPN solution in 22 patients who completed the study

Glutamine-supplemented HPN	Standard HPN	P-value
<b>Infective</b>		
<i>Klebsiella sp</i> (n = 1)	<i>Klebsiella sp</i> (n = 2)	0.67
<i>Staph aureus</i> (n = 1)	<i>Pseudomonas</i> (n = 2)	
<i>Staph epidermidis</i> (n = 2)	<i>Staph epidermidis</i> (n = 2)	
<b>Non-infective</b>		
CVC resistance to flushing (n = 1)	Occluded CVC (n = 1)	1.00
CVC fracture (n = 1)	CVC displacement (n = 1)	
<b>Vascular</b>		
IVC stenosis (n = 1)	SVC stenosis (n = 1)	1.00
<b>Disease related</b>		
Small bowel obstruction (n = 1)	None	1.00

Abbreviations: CVC, central venous catheter; HPN, home parenteral nutrition; IVC, inferior vena cava; SVC, superior vena cava.

higher during standard parenteral nutrition administration as would be expected from the profile of amino acids in the two solutions. Glutamine supplementation had no significant effect on plasma glutamine concentrations (Table 6).

#### Discussion

The debate on the efficacy of glutamine in artificial nutrition continues with many studies and reviews providing conflicting

**Table 5** Treatment effect of the addition of glutamine to HPN on quality of life, nutritional status, intestinal permeability and absorption and liver function tests

Outcome	Treatment effect	95% CI	P-value
<i>Quality of life (n = 21)</i>			
<i>SF-36</i>			
Health perception	2.9	-2.3, 8.2	0.26
Physical function	-2.1	-8.3, 4.1	0.48
Role limiting physical	-6.7	-28.2, 14.8	0.52
Role limiting emotional	4.4	-16.4, 25.2	0.66
Social functioning	1.8	-12.3, 15.8	0.80
Mental health	2.5	-4.4, 9.4	0.46
Body pain	2.8	-7.9, 13.6	0.59
Energy/fatigue	-1.6	-9.5, 6.4	0.69
<i>EuroQol</i>			
Index	-0.02	-0.071, 0.031	0.42
Visual analogue scale	1.04	-6.99, 9.07	0.79
<i>Nutritional status (n = 22)</i>			
Body weight (kg)	-0.95	-2.47, 0.56	0.2
Body mass index (kg/m <sup>2</sup> )	-0.36	-0.84, 0.13	0.14
Tricep skinfold thickness (mm)	-0.36	-1.00, 0.28	0.25
MAMC (cm)	-0.33	-0.87, 0.22	0.22
Intestinal permeability ratio (n = 13)	0.52	-0.06, 1.11	0.07
Intestinal absorption index (n = 13)	-0.008	-0.024, 0.009	0.32
<i>Liver function tests (n = 22)</i>			
ALT	10.9	-2.6, 24.4	0.11
AP	3.5	-19.5, 26.4	0.76
Bilirubin	-0.54	-4.01, 2.91	0.75
Albumin	-0.27	-1.75, 1.2	0.70

Abbreviations: ALT, alanine transferase; AP, alkaline phosphatase; HPN, home parenteral nutrition; MAMC, mid-arm muscle circumference.

results and opinions (Buchman, 2001; Novak *et al.*, 2002; Garcia-de-Lorenzo *et al.*, 2003). Furthermore, in 2003, the Canadian clinical practice guidelines for nutrition support in ventilated, critically ill adult patients were published which recommend the addition of glutamine to parenteral nutrition. However, many difficulties are faced when attempting a systematic review or meta-analyses including the use of a heterogeneous population which may include children or the inclusion of patients after elective surgery who may not be considered critically ill such as the patients in this study (Heyland *et al.*, 2003). Despite studies in animals demonstrating that parenteral glutamine reduces CVC infections (McAndrew *et al.*, 1999) no benefit was observed in the present long-term study ( $P=0.67$ ). The species of infective organisms causing CVC infections (Table 4) were similar to those previously reported in HPN patients (O'Keefe *et al.*, 1994). It is difficult to compare our study with previous studies on the efficacy of glutamine supplementation given that this is the first long-term study of patients on HPN. As can be seen in Table 2, these patients had a mean BMI in the normal range and were stable and living at home. They were not critically ill or undergoing surgical or medical procedures, which may have increased their requirement for glutamine, although some patients had baseline plasma glutamine concentrations below normal and abnormal intestinal permeability (Table 2).

Previous studies have shown both a positive (Detsky *et al.*, 1986) and a negative (Jeppesen *et al.*, 1999) impact of standard HPN on quality of life. In patients undergoing bone marrow transplant a significant improvement in mood with parenteral glutamine supplementation was observed. The authors hypothesized that glutamine may influence patients' feeling of well-being either directly by affecting central nervous system neurotransmitters or through its effect on protein status of patients. However, in the present

**Table 6** Treatment effect of the addition of glutamine to HPN on plasma amino acid concentrations ( $\mu\text{mol/l}$ ) in 22 patients who completed the study

Amino acid	Glutamine-supplemented HPN	Standard HPN	Treatment effect (95% CI)	P-value
Leucine	98.2 ± 23.8	99.4 ± 23.6	-1.27 (-8.47, 5.93)	0.72
Isoleucine <sup>a</sup>	58.0 ± 11.7	58.5 ± 11.7	-0.44 (-4.04, 3.16)	0.80
Lysine	185.7 ± 44.3	172.6 ± 43.4	13.1 (-0.5, 26.6)	0.72
Valine	187.1 ± 37.7	178.4 ± 39.1	8.8 (-6.6, 24.1)	0.25
Phenylalanine	59.8 ± 12.7	54.8 ± 9.2	5.07 (0.7, 9.44)	0.02
Histidine <sup>b</sup>	82.9 ± 17.6	67.2 ± 11.9	31.4 (6.4, 56.3)	0.02
Threonine	131.3 ± 47.7	121.7 ± 47.5	9.9 (-13.1, 32.5)	0.39
Methionine	26.9 ± 9.9	24.5 ± 7.4	2.43 (-0.32, 5.18)	0.08
Alanine	358.9 ± 86.3	375.5 ± 91.8	-16.6 (-16.6, 18.4)	0.33
Arginine	63.5 ± 15.4	68.7 ± 21.9	-5.1 (-13.7, 3.4)	0.23
Glutamine	471.6 ± 75.4	466.3 ± 78.1	5.3 (-30.8, 41.3)	0.76
Glycine	327.3 ± 84.2	355.2 ± 88.3	-27.0 (-64.8, 9.1)	0.13
Proline <sup>b</sup>	205.9 ± 48.8	253.9 ± 75.1	-95.9 (-188.8, -3.4)	0.04
Serine	98.3 ± 23.2	116.2 ± 30.8	-17.9 (-28.0, -7.8)	0.001
Tyrosine	52.4 ± 12.8	50.1 ± 13.6	2.30 (-3.57, 8.16)	0.42
Cysteine	2.48 ± 1.7	2.2 ± 1.3	0.27 (-0.08, 0.63)	0.13

Abbreviation: HPN, home parenteral nutrition.

<sup>a</sup>n = 21.

<sup>b</sup>n = 12.

study, no significant difference was observed in any of the assessed quality of life indices, including mental health, during the two phases of the study. This may have been due to the low dose of glutamine used in this study,  $0.14 \pm 0.04$  g/kg/day in comparison to  $0.57$  g/kg/day, the use of different questionnaires or because different types of patients were studied (Young *et al.*, 1993).

The permeability ratio associated with glutamine supplementation observed in the study is contrary to the findings of van der Hulst *et al.* (1993) who found that glutamine-supplemented parenteral nutrition ( $0.23$  g/kg/day) prevented deterioration of gut permeability compared to standard parenteral nutrition in patients with gastrointestinal disease. There were no significant differences in permeability ratio on glutamine-supplemented or standard HPN. All of the patients in the present study took some form of nutrition orally, and it may be that the provision of parenteral glutamine in this group is not as effective as when patients receive solely parenteral nutrition as often occurs during critical illness and post operatively. It was not possible to calculate the contribution of patients' oral glutamine intake as this was impractical in an outpatient setting. However, as their oral protein intakes were similar throughout the study period it can be postulated that their oral glutamine intake would not be significantly different and would contribute the same effect in both phases of the crossover design. This study may provide evidence that at this dose, glutamine-supplemented HPN does not improve small bowel permeability in stable HPN patients who take nutrition orally. Five patients had undetectable urinary rhamnose concentrations, which prevented calculation of the permeability ratio. The rhamnose concentrations are low in this group of patients as the majority had a short bowel, decreasing the absorption of all four of the test carbohydrates used in the study. This means that lactulose and rhamnose are affected equally and so the ratio should be preserved. Previous investigators have demonstrated that this test can be reliable in patients with short bowel syndrome (D'Antiga *et al.*, 1999). Our results agree with the findings of Ockenga *et al.* (2005) who showed that the addition of  $0.2$  g/kg/day of glutamine to 24 patients with inflammatory bowel disease did not alter intestinal permeability or plasma glutamine concentrations.

Of the five patients who no longer required HPN, four of them continued on IV fluids and electrolytes (three patients with Crohn's disease and one mesenteric infarction) presumably due to intestinal adaptation. Of these four patients, there was no difference between patients randomized to glutamine-supplemented HPN first ( $n=2$ ) or standard HPN first ( $n=2$ ), hence the addition of glutamine had no effect on the intestinal adaptation and has not been reported in the results. One had early surgery to reconnect his remaining bowel that allowed him to be independent from HPN. The level of parenteral glutamine supplementation in the present study was lower than that used in a previous study in which three out of seven HPN patients given  $0.285$  g/kg/day of parenteral glutamine for 4 weeks developed abnormal LFTs

(Hornsby-Lewis *et al.*, 1994). These patients had stable LFTs for one year before the study commenced and had no changes made to their HPN prescriptions during the study with all abnormal LFTs returning to baseline 2 weeks after stopping the glutamine. No biopsy or ultrasound was undertaken and patients were not rechallenged. There have been no further studies with glutamine in patients on HPN as studies have concentrated on acutely unwell patients. It was shown that the level of glutamine administered in our study did not cause an elevation in LFTs and may be given to patients on long-term HPN. However, as a result, it is possible that the dose was not adequate to exert a potential benefit.

It is interesting to note that plasma glutamine concentrations were below normal in some patients at baseline (Table 2) but we were unable to demonstrate a significant difference in the plasma glutamine concentrations during the course of the study (Table 6). This is concordant with the findings from a study by van Acker who studied glutamine-supplemented parenteral nutrition in 18 patients undergoing gastrointestinal surgery. They showed that  $0.21 \pm 0.01$  g/kg/day of parenteral glutamine did not significantly increase plasma glutamine concentrations after 8–10 days of treatment (van Acker *et al.*, 2000). However, in bone marrow transplant patients, Ziegler showed that plasma glutamine concentrations rose by 40% following glutamine-supplemented parenteral nutrition in comparison to standard nutrition ( $P < 0.0001$ ) and concentrations remained elevated while supplementation continued for 21 days (Ziegler *et al.*, 1992). This may reflect the much higher dose of glutamine ( $0.57$  g/kg) used in this study. In the present study, significant differences in the plasma concentrations of other amino acids were observed between the two groups (Table 6) and it seems likely that these differences can be attributed to the different composition of the two amino acid solutions used (Table 1). The higher serine content of the standard HPN probably accounts for higher concentrations in patients while on the standard HPN. Parallel differences may also explain the significant differences in phenylalanine, histidine and proline concentrations. However, this is not seen with glutamine and the explanation for this is not known. It may be that the dose given in this study was inadequate or that the additional glutamine provided was utilized. It was thought that the glutamate, present as a dipeptide with lysine, in the standard HPN (Table 1) could have been synthesized to glutamine via glutamine synthetase, which may have resulted in the maintenance of plasma concentrations of glutamine in patients during the period of standard HPN infusion. It is known, however, that glutamate is not a good substitute for glutamine as it has been shown that glutamate is rapidly metabolized and fails to increase plasma concentrations of glutamine in septic patients and healthy volunteers (Kingsland *et al.*, 1981).

The addition of  $0.14 \pm 0.04$  g/kg/day of glutamine to HPN has been shown to cause no adverse effects in this patient population. There was a numerical reduction in the number

of infective complications during glutamine supplementation, but this did not reach statistical significance. There were no differences in quality of life, plasma glutamine concentration, intestinal permeability or absorption. We recognize that the study is underpowered and that the small number of patients limits the power of detecting significant changes. However, as no changes or trends were observed at this dose of glutamine it appears that glutamine confers no benefit with regards to CVC infections, plasma glutamine concentrations, intestinal permeability or absorption, hence routine supplementation of HPN with glutamine at this dose cannot be currently recommended. Further studies might productively consider higher glutamine doses during an infective episode as part of a multi-centre trial or in patients who experience multiple CVC infections. Studies could be targeted to patients who are known to have depleted plasma glutamine concentrations.

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