A double blind, randomised, controlled crossover trial of glutamine supplementation in home parenteral nutrition.

Alison Culkin[1], Simon Gabe[2], Ingvar Bjarnason[3], George Grimble[4, 5] Angela Madden[5], Alastair Forbes [2, 6]

[1] Department of Nutrition and Dietetics, [2] Department of Gastroenterology, St Mark's Hospital, Harrow. [3]Department of Clinical Biochemistry, King's College Hospital, London. [4]School of Life Sciences, University of Surrey, Roehampton. [5] Department of Health and Human Sciences, London Metropolitan University, London. [6] Department of Gastroenterology and Nutrition, University College Hospital, London.

Correspondence to: Alison Culkin, Department of Nutrition and Dietetics, Northwick Park and St Mark's NHS Trust, Watford Road, Harrow, Middlesex, HA1 3UJ, UK.

Telephone 02088692666

Fax 02088692695

Email alison.culkin@nwlh.nhs.uk

Contributors: AC was the study lead and involved in recruitment, data collection, blood and urine sample collection and preparation, data interpretation and writing the manuscript.

SG was involved in the protocol development, supervision of the data collection and interpretation and writing the manuscript

IB was involved in the protocol development.

GG was involved in the protocol development.

AF was involved in the protocol development and writing the manuscript.

AM was involved in writing the manuscript.

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

Design: A double blind randomised controlled crossover trial.

Setting: National centre for the treatment of patients on HPN.

Subjects: 35 patients on HPN were recruited and 22 completed the study.

Interventions: Patients were randomised to receive either standard HPN or glutamine supplemented HPN. Patients were assessed at randomisation, 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 randomisation. 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.

Sponsorship: Unrestricted grant from Fresenius Kabi

Descriptors: 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 (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 0.57g/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 0.285g/kg/day of parenteral glutamine over four weeks resulted in abnormal liver function tests, which necessitated the discontinuation of glutamine supplementation in two patients (Hornsby-Lewis et al, 1994).

Patients and methods

The study was a randomised, 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 endpoint was infective complications. Our secondary endpoints 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 randomised 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 randomisation 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 blind to the randomisation process. Patients were assessed as outpatients at randomisation, 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 11g 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 ± 0.04g /kg/day of glutamine (range 0.08 – 0.24g/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 $>38^0$ 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 whilst awaiting the results of the cultures. Patients are administered appropriate antibiotics (according to sensitivities) via the CVC for one 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 (MAC), tricep skinfold thickness (TST) and calculation of mid-arm muscle circumference (MAMC). This was undertaken by a trained research dietitian using standardized procedures (Gurney & 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 out patient 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 program was used to calculate the energy, protein, fat and carbohydrate content of the three 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 0.2g 3-O-methyl-D-glucose, 1g L-rhamnose and 5g of lactulose made up to 100ml with tap water. Food and fluids were withheld until 2 hours after ingestion of the solution. Over the next 5 hours, patients collected their urine into containers containing 5ml 10% thyme. The volume of the urine collected was recorded and a 20ml aliquot removed from the final collection and stored at -70^{o}C prior to analysis of urinary sugars by thin layer chromatography (Menses & 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 out patient appointments and so we were unable to standardise the timing of the samples for glutamine analysis but this would have been within 6-8 hours post infusion. An extra blood sample was taken in a heparins tube and spun at 2000*g* for 10 minutes. The plasma was then stored at -70^{o}C prior to analysis of amino acids by high performance liquid chromatography (Sherwood 1990).

Statistics

Statistical analyses were performed at randomisation to ensure that the randomisation process was effective. The statistics reported are mean ± standard deviations (SD) 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) was 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 ± SD together with the P-value for those variables found to be normally distributed. For variables not normally distributed, the median and IQR is 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 two 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 randomised to the standard HPN first (P=0.04) showing that the randomisation 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 3 patients had a subsequent re-infection of the same CVC with the same organism which 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. 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 twenty patients who completed the study, as two patients were non-compliant with this aspect of the study. There were paired data available on thirteen 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 ± 0.06 compared to 0.12 ± 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).

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 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 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 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 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 wellbeing either directly by affecting central nervous system neurotransmitters or through its effect on protein status of patients. However, in the present study, no significant differences 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 ± 0.04g/kg/day in comparison to 0.57g/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 who found that glutamine supplemented parenteral nutrition (0.23g/kg/day) prevented deterioration of gut permeability compared to standard parenteral nutrition in patients with gastrointestinal disease (van der Hulst et al, 1993). 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 out patient 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 who showed that the addition of 0.2g/kg/day of glutamine to 24 patients with inflammatory bowel disease did not alter intestinal permeability or plasma glutamine concentrations (Ockenga et al, 2005).

Of the 5 patients who no longer required HPN, 4 of them continued on IV fluids and electrolytes (3 patients with Crohn's and one mesenteric infarction) presumably due to intestinal adaptation. Of these 4 patients, there was no difference between patients randomised to glutamine supplemented HPN first (n=2) or standard HPN first (n=2) and so the addition of glutamine had no effect on the intestinal adaptation and has not been reported in the results. One had surgery to reconnect his remaining bowel which 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 3 out of 7 HPN patients given 0.285g/kg/day of parenteral glutamine for 4 weeks developed abnormal liver function tests (Hornsby-Lewis et al 1994). These patients had stable LFT's for one year before the study commenced and had no changes made to their HPN prescriptions during the study with all abnormal LFT's

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 LFT's and may be given to patients on long term HPN. However, it is possible that as a result 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 ± 0.01g/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 whilst supplementation continued for 21 days (Ziegler et al, 1992). This may reflect the much higher dose of glutamine (0.57g/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 whilst 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

utilised. 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 ± 0.04g/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 recognise 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 and so routine supplementation of HPN with glutamine at this dose cannot currently be 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.

Acknowledgements

Financial support of this investigation in the form of an unrestricted grant from Fresenius Kabi is gratefully acknowledged. Claire Chadwick and Shola Olusanya, Department of Pharmacy at St Mark's are thanked for performing the randomisation and crossover. We are

grateful to Roy Sherwood, Sue Maestranzi and Kate John from Kings College Hospital for the amino acid and urinary sugar analyses and to Diane Brundrett for dietetic support.
Paul Bassett is thanked for help with statistical analysis.

References

Buchman A. Glutamine: Commercially essential or conditionally essential? A critical appraisal of the human data. *Am J Clin Nutr* 2001;74:25-32.

Calder PC. Glutamine and the immune system. *Clin Nutr* 1994 13;1:1-8.

D'Antiga L, Dhawan A, Davenport M, Mieli-Vergani G, Bjarnason I. Intestinal absorption and permeability in paediatric short-bowel syndrome: A pilot study. *JPGN* 1999;29:588-593.

Detsky AS, McLaughlin JR, Abrams HB et al. Quality of life of patients on long-term total parenteral nutrition at home. *J Gen Intern Med* 1986;1:26-33.

Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQol: Results from a UK general population survey*. York: Centre for health economics, University of York, 1995.

Garcia-de-Lorenzo A, Zarazaga A, Garcia-Luna PP et al. J. Clinical evidence for enteral nutritional support with glutamine: A systematic review. Nutrition 2003;19:807-811.

Griffiths RD, Jones C, Palmer TEA. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997;13:295-302.

Gurney JM, Jelliffe DB. Arm anthropometry in nutritional assessment: Nomogram for rapid calculation of muscle circumference and cross sectional and fat areas. *Am J Clin Nutr* 1973;26:912-915.

Hammarqvist F, Wernerman J, Ali R, von der Decken A, Vinnars E. Addition of glutamine to total parenteral nutrition after elective abdominal surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis, and improves nitrogen balance. *Ann Surg* 1989;209:455-461.

Heyland D, Dhaliwal R, Drover JW et al. Canadian Clinical Practice Guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN* 2003;27:355-373.

Hornsby-Lewis L, Shike M, Brown P, Klang M, Pearlstone D, Brennan M. L-Glutamine supplementation in home total parenteral nutrition patients: Stability, safety, and effects on intestinal absorption. *JPEN* 1994;18:268-273.

Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. *Gut* 1999;44:844-852.

Kingsland PA, Kingsnorth A, Royle GT, Kettlewell MGW, Ross BD. Glutamate metabolism in malnutrition and sepsis in man. *Br J Surg* 1981;68:234-237.

Krebs HA. Metabolism of amino acids. IV. The synthesis of glutamine from glutamic acid and ammonia and the enzymatic hydrolysis of glutamine in animal tissues. *Biochem J* 1935;33:1951-1969.

McAndrew HF, Lloyd DA, Rintala R, van Saene HK. Intravenous glutamine or short-chain fatty acids reduce central venous catheter infection in a model of total parenteral nutrition. *J Pediatr Surg* 1999;34:281-285.

Menzies IS, Crane R. Assessing intestinal absorptive capacity and permeability in vivo. In: Preedy VR, Watson RR, Eds. *Methods in disease: Investigating the gastrointestinal tract*. London: Greenwich Medical Media, 1998:41-63.

Morlion BJ, Stehle P, Wachtler P et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery. *Ann Surg* 1998;227:302-308.

Nelson M, Atkinson M, Meyer J. *A photographic atlas of food portion sizes*. London: MAFF, 1997.

Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: A systematic review of the evidence. *Crit Care Med* 2002;30:2022-2029.

Ogle CK, Ogle JD, Mao JX et al. Effect of glutamine on phagocytosis and bacterial killing by normal and paediatric burn patient neutrophils. *JPEN* 1994;18:128-133.

O'Keefe SJ, Burnes JU, Thompson RL. Recurrent sepsis in home parenteral nutrition patients: An analysis of risk factors. *JPEN* 1994;18:256-63.

Ockenga J, Borchert K, Stüber E, Lochs H, Manns MP, Bischoff SC. Glutamine enriched total parenteral nutrition in patients with inflammatory bowel disease. *Eur J Clin Nutr* 2005;59:1302-1309.

O'Riordan MG, Fearon KCH, Ross JA et al. Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. *Ann Surg* 1994;220;212-221.

Richards DM, Scott NA, Shaffer JL, Irving M. Opiate and sedative dependence predicts a poor outcome for patients receiving home parenteral nutrition. *JPEN* 1997;21:336-338.

Rose WC. The nutritive significance of the amino acids. *Physiol Rev* 1938;18:109-136.

Sherwood RA. Amino acid measurements by high-performance liquid chromatography using electrochemical detection. *J Neurosci Methods* 1990;34:17-22.

van Acker BAC, Hulsewe KWE, Wagenmakers AJM, von Meyenfeldt MF, Soeters PB. Response of glutamine metabolism to glutamine-supplemented parenteral nutrition. *Am J Clin Nutr* 2000;72:790-795.

van der Hulst RR, van Kreel BK, von Meyenfeldt MF et al. Glutamine and the preservation of gut integrity. *Lancet* 1993;341:1363-1365.

Ware J. *SF-36 health survey, manual and interpretation guide*. Boston: Medical Outcomes Trust 1993.

Windmueller HG. Glutamine utilization by the small intestine. *Adv Enzym Relat Areas Mol Biol* 1982;53:201-237.

Young LS, Bye R, Scheltinga M, Ziegler TR, Jacobs DO, Wilmore DW. Patients receiving glutamine-supplemented intravenous feedings report an improvement in mood. *JPEN* 1993;17:422-427.

Ziegler TR, Benfell K, Smith RJ et al. Safety and metabolic effects of L-glutamine administration in humans. *JPEN* 1990;14 (Suppl 4):137S-146S.

Ziegler TR, Young LS, Benfell K et al. Clinical and metabolic efficacy of glutamine supplemented parenteral nutrition after bone marrow transplantation. *Ann Intern Med* 1992;116:821-828

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

Amino acid	Glutamine supplemented HPN (g)	Standard HPN (g)
Indispensable		
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
Dispensable		
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

Table 1 Composition of glutamine supplemented HPN and standard HPN per 500ml (cont).

Energy content (kcal)	270	300
pH	5.80	5.20
Osmolality (mosmol/kg water)	1140	1400

Table 2 Comparison of baseline data of the two groups at randomisation (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
Aetiology			**0.67**
Crohn's disease	5	3	
Mesenteric infarct	2	2	
Other *	4	6	
Length of small bowel			**0.84**
<50 cm	3	2	
50-100 cm	3	4	
>100cm	5	5	
Type of stoma			**0.04**
Jejunostomy	1	0	
Ileostomy	0	5	
Colostomy	1	1	
Colon in continuity	9	6	
Time on HPN (months)**	51 (11, 99)	28 (13, 83)	0.65
Nutritional status			
Weight (kg)	57.9 ± 11.1	61.7 ± 10.2	0.41
Body mass index (kg/m^2)	21.1 ± 3.0	22.1 ± 2.5	0.41

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

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
Oral nutrition			
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
Parenteral nutrition			
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

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

Value presented as mean ± SD or ** median (IQR)

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

	Glutamine supplemented HPN first (n=11)	Standard HPN first (n=11)	P value
SF-36			
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
EuroQol - index	0.68 ± 0.21	0.67 ± 0.15	0.87
- visual analogue scale	63.7 ± 18.1	67.4 ± 10.3	0.57
Liver function tests			
ALT (10-50IU/L)	49 ± 29	43 ± 32	0.64
AP* (40-135IU/L)	111 (74, 125)	154 (109, 401)	0.11
Bilirubin* (1-17µmmols/L)	8 (6, 12)	8 (4, 9)	0.25
Albumin (35-50g/L)	41 ± 4.1	39 ± 2.4	0.18

ALT=alanine transferase, AP=alkaline phosphatase

Values presented as mean ± SD 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
Infective	Klebsiella *sp* (n=1) *Staph* aureus (n=1) *Staph* epidermidis (n=2)	Klebsiella *sp* (n=2) Pseudomonas (n=2) *Staph* epidermidis (n=2)	0.67
Non- infective	CVC resistance to flushing (n=1) CVC fracture (n=1)	Occluded CVC (n=1) CVC displacement (n=1)	1.00
Vascular	IVC* stenosis (n=1)	SVC** stenosis (n=1)	1.00
Disease related	Small bowel obstruction (n=1)	None	1.00

* Inferior vena cava ** Superior vena cava

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
Quality of life (n=21)			
SF-36			
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
EuroQol - index	-0.02	-0.071, 0.031	0.42
- visual analogue scale	1.04	-6.99, 9.07	0.79
Nutritional status (n=22)			
Weight (kg)	-0.95	- 2.47, 0.56	0.2
Body mass index (kg/m^2)	-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
Liver function tests (n=22)			
ALT	10.9	-2.6, 24.4	0.11
AP	3.5	-19.5, 26.4	0.76

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. (cont)

Bilirubin	-0.54	-4.01, 2.91	0.75
Albumin	-0.27	-1.75, 1.2	0.70

ALT=alanine transferase, AP=alkaline phosphatase

Table 6. Treatment effect of the addition of glutamine to HPN on plasma amino acid concentrations (µmol/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*	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**	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**	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

*** n=21 **n=12**

Figure 1

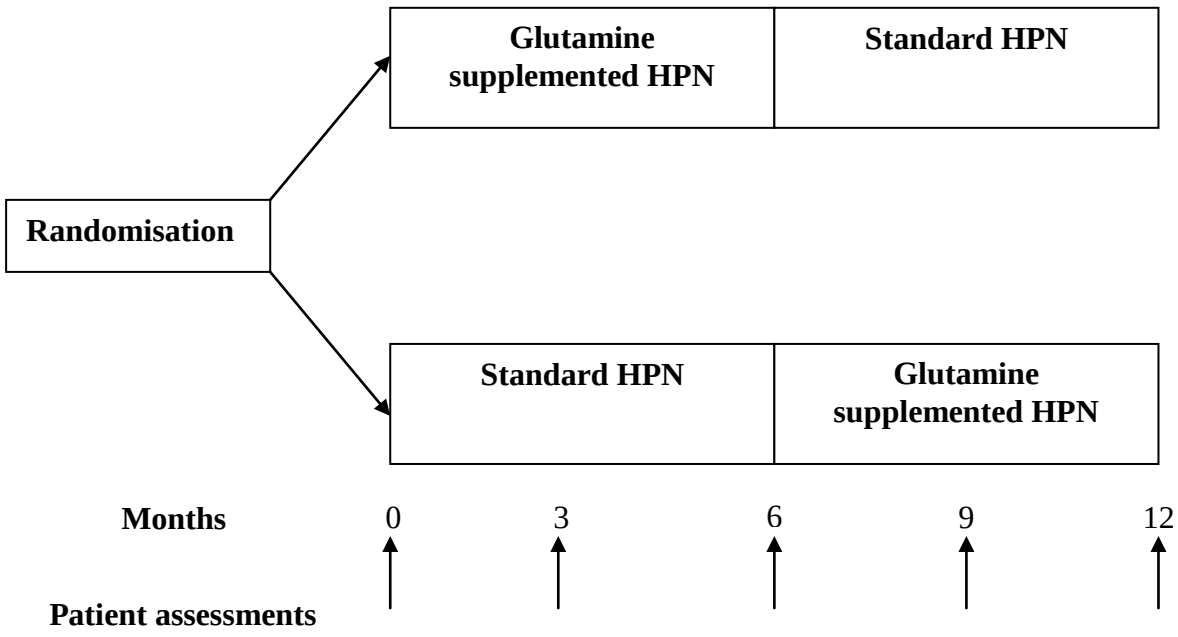

Figure 2