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Factors that impact on the quality of life of intestinal failure patients treated with home parenteral nutrition: protocol for a multicentre, longitudinal observational study

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ABSTRACT

Background Home parenteral nutrition (HPN) refers to the intravenous administration of macronutrients, micronutrients and fluid. The aims of treatment are to increase survival and improve quality of life (QoL). However, patients struggle with physiological symptoms, time-consuming invasive therapy and an increased occurrence of depression and social isolation. Our aim is to understand how HPN impacts the QoL of patients, and the contribution played by the complications of treatment, for example, liver disease.

Methods and analysis A multicentre, longitudinal, observational study will be conducted using routinely collected clinical data. Participants will also be asked to complete three QoL questionnaires (EuroQol-5 Dimensions, Short Form 36 and HPN-QoL) at baseline and 12 months. The primary outcome is mean change in QoL scores over 12 months. Secondary outcomes include how factors including liver function, gut microbiota, number of infusions of PN per week, nutritional composition of PN and nutritional status impact on QoL scores.

Ethics and dissemination Ethical approval was obtained from HRA and Health and Care Research Wales Research Ethics Committee (21/SC/0316). The study was eligible for portfolio adoption, Central Portfolio Management System ID 50506. Results will be disseminated through peer-reviewed scientific journals and presented at national and international meetings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The comprehensive collection of clinical data to accompany the quality of life (QoL) questionnaires will provide a rich data set for exploratory analyses and as a basis for future studies, including intervention studies.
⇒ The study uses routinely collected data which have the advantage of being recorded prospectively and are, therefore, not susceptible to recall bias.
⇒ The longitudinal design of the study may reveal changes in QoL over time and allow us to explore potential reasons for those changes.
⇒ Given its scale and representativeness, the study has national and international relevance, and the resulting dataset will have potential for use for multiple purposes including audits and service evaluation projects.
⇒ The observational design is a limitation of the study. While the recommendations outlined in the STrengthening the Reporting of OBservational studies in Epidemiology statement have been followed, it is still possible that there will be confounding factors that have not been considered.

BACKGROUND

Home parenteral nutrition (HPN) is a life-saving therapy for intestinal failure (IF) patients, when the oral or enteral route is unavailable. It refers to the intravenous administration of macronutrients, micronutrients and fluid.[1] Over 2500 people are treated with HPN in England, with numbers rising by 20% per year.[2] It is costly in terms of National Health Service (NHS) resources (£55 000 per patient/year),[3] impairs quality of life (QoL) for patients and poses a considerable challenge for 21st century healthcare. The biggest area of growth in IF is because of complications following surgery for comorbid health conditions. In an ageing society with increasing multimorbidity, IF almost always coexists with a range of comorbid health problems that affect the older person.

The aims of HPN are to increase survival and improve QoL.[4] However, it is well documented that HPN patients have a decreased QoL, higher rates of depression and anxiety compared with the general population and most are unlikely to return to meaningful employment.[5] Moreover, patients are affected not only by their intestinal disease, but also by decreased physical health due to multimorbidity and the threat of potentially

life-threatening complications, such as intestinal failure associated liver disease (IFALD). IFALD is the most serious complication of HPN and is characterised by steatosis (fat deposition), and cholestasis (bile stasis), progressing to fibrosis and cirrhosis.[6] In most cases, it is preventable and, if diagnosed early, reversible. In contrast, rapid progression leads to hepatic failure, followed by the need for a multivisceral transplant (the simultaneous transplantation of liver, intestine and pancreas) with high morbidity and mortality.

Chronic liver disease is a major cause of poor QoL, a contributor to excess death and a significant concern for patients and the health system.[7] Despite this, we do not understand the aetiology of IFALD specifically nor the extent to which IFALD affects the QoL of patients. Recommendations for the treatment and prevention of the disease are vague[4] and require a better evidence base. Contributory factors may include suboptimal formulation of the HPN solution; however, there is no understanding of which component(s) (calories, glucose, lipid, fatty acids and micronutrients) are present in inappropriate concentrations.

A number of observational studies have reported QoL in HPN patients. Richards and Irving revealed QoL scores significantly lower than population norms in six out of eight domains of the Short Form 36 (SF-36),[8] whereas Blüthner *et al* found QoL scores to be significantly worse across all categories when compared with population norms.[9] However, studies have focused primarily on the impact of HPN programmes and intestinal anatomy on the QoL of patients. Such studies fall short, since QoL is a rich multidimensional concept encompassing mental and physical health, and is likely affected by disease status, treatment, and the associated complications of treatment. To our knowledge, no studies have investigated the association between QoL and the complications of HPN treatment such as IFALD, sepsis, gut dysbiosis, sarcopenia and metabolic bone disease.

Aim

To understand how HPN impacts on the QoL of patients, and the contribution played by liver disease.

Hypotheses

The hypotheses for this project are:

1. QoL scores will improve with the first year of HPN therapy and plateau thereafter.
2. QoL scores will be influenced by gastrointestinal anatomy and HPN regimen.
3. QoL scores will be influenced adversely by comorbidities, for example, the presence of IFALD.
4. Parenteral nutrition causes an upregulation of de novo lipogenesis (DNL).
5. Parenteral nutrition causes alterations in phospholipid metabolism with reductions in plasma free choline.

METHODS

Study design

A multicentre, longitudinal, observational cohort study.

Study setting

Patients will be recruited from three participating centres: Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH), The Leeds Teaching Hospitals NHS Trust (LeedsTH), and Nottingham University Hospitals NHS Trust (NUH). LeedsTH and NUH are tertiary, integrated HPN/IF centres and are of similar size to NuTH in terms of patient numbers. Together, the three centres provide a cohort of patients from a wide geographical area.

Study population

All adult patients treated with HPN for benign reasons from the three participating centres will be invited to participate.

Inclusion criteria

- Adults (>18 years old) treated with HPN.
- Capacity to provide informed consent.

Exclusion criteria

- Malignancy.

Recruitment strategy

Newcastle upon Tyne Hospitals NHS Foundation Trust

Eligible study participants will be identified using a database maintained by the Nutrition Team which includes all patients being treated with HPN from Newcastle Hospitals. One week prior to their routine clinic appointment, a participant information sheet explaining the study, an invitation to participate and the QoL questionnaires will be sent through the post. Participants will receive a follow-up phone call 24 hours prior to their appointment, providing them with an opportunity to ask questions. Participants will be enrolled prospectively on receipt of the signed consent form.

Leeds and NUH

Local Nutrition Teams will assess eligibility and provide a list of patient names and contact details to the primary investigator (PI). As above, the PI will send an information sheet explaining the study, along with an invitation to participate through the post. Eligible participants will receive a follow-up phone call one week later, providing them with an opportunity to ask questions. Enrolment will follow successful screening and receipt of written informed consent.

Study outcomes

The primary outcome is mean change in QoL scores over 12 months. Secondary outcomes include how factors including liver function, gut microbiota, number of infusions of PN per week, nutritional composition of PN and nutritional status impact on QoL scores.

Data collection

Routine data

Data for LeedsTH and NUH patients that is recorded in medical notes during clinic visits will be collected

retrospectively during two research visits to each of the sites. Data collection for NuTH patients will be collected prospectively by the PI, as a member of the clinical care team. Nutritional requirements and the nutritional composition of the patient's oral diet will be calculated using diet histories taken by a registered dietitian. Demographic, socioeconomic and clinical data will be recorded at the time of patient inclusion. Remaining data (anthropometrics, nutritional requirements, dietary intakes, parenteral nutrition prescriptions, blood results liver markers and admissions) will be collected at baseline, 6 months and 12 months. Details of the study measures are provided in table 1.

QoL assessment

QoL for each patient will be evaluated using three questionnaires. The SF-36 is the most frequently used non-disease-specific questionnaire registered in clinical trials. It examines QoL in eight domains, scoring each between 0 and 100, and two summary scales.[10]

The HPN-QoL questionnaire is a disease-specific 48-item instrument that focuses on physical, emotional and symptomatic issues.[11] It contains seven multi-item functional scales and one single-item functional scale. There is also a six multi-item and three-single item symptom scales. The symptom scales ask questions about body image, immobility, fatigue, sleeping pattern, gastrointestinal symptoms, other pain, stoma or bowel management, financial issues and body weight. The questionnaire also has three global health status/QoL numerical rating scales seeking information on the effect of QoL on the underlying illness leading to the need for HPN and the effect of HPN. The two single items relate to nutrition teams and the availability of an ambulatory pump for the infusion of HPN. A high score relates to a good outcome.

The EuroQol-5 Dimensions-5 Levels (EQ-5D) is a generic, self-assessed health-related questionnaire that measures QoL on a 5-component scale: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[12] There are five response levels to each question (no problems, slight problems, moderate problems, severe problems and extreme problems). The EQ-5D also contains a vertical Visual Analogue Scale where the participant rates their overall health. The endpoints are labelled 'the worst health you can imagine' (0) and 'the best health you can imagine' (100). It provides a quantitative measure of health outcome that reflects the participants own judgement.

Experimental data

Lipidomics

To advance understanding of the contribution played by liver disease in QoL impairment, lipidomic analysis will be performed using blood samples from new patients (NuTH only) and an equal number of existing patients (matched by key characteristics). In collaboration with Aberdeen University, blood plasma (obtained at baseline and at 12 months following the infusion of a lipid and glucose-based feed) will undergo lipidomics analysis to elucidate mechanisms underlying specific changes in lipid metabolism.

DNL will be estimated using the lipogenic index calculated as the ratio of palmitic acid (16:0) to linoleic acid (18:2n6). An increase in DNL is indicated by an increased ratio of palmitate to linoleate. In addition, plasma-free choline concentrations of HPN patients will be measured and compared with normal values of 11.4±3.7 nmol/mL.[13]

Microbiota

Intestinal microbes play a fundamental role in the well-being of their host.[14] Gut dysbiosis has been observed in adult and paediatric patients with IF and is associated with impaired outcome.[15–17] To understand whether gut dysbiosis and impaired QoL are linked, either directly, or indirectly through the development of complications, stool or stomal samples will be collected in 3 mL cryovials at baseline, 6 and 12 months. They will be transferred to aliquots at –80°C within 2 hours. 16S rRNA sequencing will be used to identify the microbiome composition of these samples. Volume of stomal output, colour and consistency will also be recorded.

Sample size

Insufficient relevant data for HPN patients are available to inform a formal power calculation. The SF36 user guide[18] provides estimates of sample sizes necessary to detect differences over time within one group of participants, and between two experimental groups (tables 2 and 3). These estimates assume alpha of 0.05 (two tailed), and power of 80%. The SF-36 outcome score ranges from 0 to 100. The sample size needed to detect a 10-point difference varies between each domain and the tables show the largest number of participants required for each domain. For this study, there is an estimated pool of 500 participants from the three centres; however, it is anticipated that 45% will not meet the inclusion criteria. Therefore, the remaining sample size is 275. Based on a previous study at NuTH that evaluated the QoL of adult patients on HPN at a single time point,[19] initial uptake is expected to be at least 80% (n=220).

Given the longitudinal nature of the study and allowing for a 20% drop-out rate at follow-up, 10% of participants stopping HPN, and 10% data attrition, we anticipate complete data for 132 participants. This sample size will provide sufficient power to detect a 10-point difference in all domains of the SF-36.

Statistical analysis

Frequency statistics will be calculated for each variable. QoL scores at baseline and 12 months will be evaluated using analysis of covariance. Differences in means between new and existing patients will be analysed by the Student's t-test for independent samples. Multiple linear regression analysis will be used to explore the relationship between QoL scores, baseline characteristics and the

Table 1 Schedule of study measures

Variables	Baseline	6 months	12 months
Demographic and socioeconomic data			
Gender, year of birth, ethnicity	√		
Postcode	√		
Smoking, activity	√		√
Education, household income, employment status, marital status	√		
Clinical data			
Medical history	√		
Main underlying disease and reason for HPN	√		
Gastrointestinal anatomy and presence of a stoma	√		
Date HPN commenced	√		
Anthropometry			
Weight, height and BMI	√	√	√
MAC, TSF, MAMC and HGS	√	√	√
Presence of oedema or ascites	√	√	√
Body composition analysis	√		√
Nutritional requirements			
Energy, nitrogen and lipid requirements	√		√
Glucose oxidation rate	√		√
Dietary intake			
Oral fluid and diet intake	√	√	√
Diet type	√	√	√
Parenteral nutrition prescription			
No. of weekly infusions	√	√	√
Volume±additional fluids	√	√	√
Nutritional composition±micronutrients	√	√	√
Blood results			
CRP, WCC	√	√	√
Electrolytes (urea, creatinine, sodium, potassium, magnesium, phosphate, calcium)	√	√	√
Micronutrients (vitamin A, D, E, B_{12} and folate, copper, zinc, manganese and selenium)	√	√	√
Iron, transferrin, haemoglobin, transferrin saturations	√	√	√
Cholesterol, triglycerides, HDL cholesterol, total/HDL cholesterol ratio, non-HDL cholesterol	√		√
Liver markers			
IFALD diagnosis (Y/N)	√	√	√
Bilirubin, ALP, ALT, GGT, platelets, albumin	√	√	√
Liver biopsy (Y/N) and result	√	√	√
FibroScan (Y/N) and result	√	√	√
Admissions			
No of admissions and length of stay	√	√	√
Sepsis during admission (Y/N) and CRP level	√	√	√
Experimental data*			
Blood samples	√		√
Stoma samples	√	√	√
QoL measures			
EQ-5D, SF-36, HPN-QoL	√		√

Continued

Table 1 Continued

Variables	Baseline	6 months	12 months

*NuTH patients only.
ALP, Alkaline phosphatase; ALT, Alanine transaminase; BMI, body mass index; CRP, C reactive protein; EQ-5D, EuroQol-5 Dimensions; GGT, Gamma-glutamyltransferase; HDL, High-density lipoprotein; HGS, Handgrip strength; HPN, home parenteral nutrition; IFALD, intestinal failure associated liver disease; MAC, Mid-arm circumference; MAMC, Mid-arm muscle circumference; NuTH, Newcastle upon Tyne Hospitals NHS Foundation Trust; QoL, quality of life; SF-36, Short Form 36; TSF, Tricep-skinfold thickness.

factors likely to affect QoL scores outlined above. This will include assessment of potential confounding and effect modification (ie, statistical interaction) and path analyses will be used to assess potential mediating pathways.

IFALD will be classified as a binary variable to explore whether those patients with the disease have a lower QoL. Additionally, liver enzymes will be used as continuous variables to determine whether those patients with worsening liver function have poorer QoL. Analysis of the lipidomic dataset will be performed in collaboration with Aberdeen University, and the microbiome analysis of stomal samples in collaboration with colleagues in Newcastle University.

Patient and public involvement

Ten patients with IF have been involved in designing the project so that it is relevant to themselves and their families. Six have volunteered to form a patient panel for the duration of the project. Panel members provided suggestions which were implemented throughout the study design. These included changes to the language used in patient information documents, choice of QoL questionnaire and method of administration, and the schedule of assessments. Panel members will also be involved in sharing research findings to benefit patients, their families and the NHS:

- To guide future research aimed at improving the factors that affect QoL.
- To guide future recommendations for HPN services.
- To improve patient experience of nutritional and medical care.
- To support patients to engage in research, increasing confidence and enhancing experience.

Ethics and dissemination

Ethical approval was obtained from HRA and Health and Care Research Wales (HCRW) Research Ethics Committee on 25 October 2021 (21/SC/0316). Site-specific capacity and capability were then obtained for each of the participating sites. Participants were recruited between March 2022 and March 2023. The study remains open until 31 March 2024 and all data will be analysed by the end of 2025. The study was eligible for portfolio adoption, Central Portfolio Management System (CPMS) ID 50506.

A variety of means will be used to ensure that the project and subsequent results achieve maximum visibility. Publication of the study protocol is an important first step in this direction. Similarly, the results of the study will be disseminated through peer-reviewed scientific journals and presented at national and international research meetings.

DISCUSSION

HPN is a treatment that keeps patients with intestinal failure (IF) alive but at a cost to their QoL. HPN patients have higher rates of depression and anxiety compared with the general population and few are likely to return to meaningful employment.[5] Moreover, patients are affected not only by their intestinal disease, but also by decreased physical health due to multimorbidity and the

Table 2 Sample size needed to detect a 10-point difference over time within one group in average SF-36 scores

Domain	Sample size required to detect a 10-point difference
Physical functioning	35
Role–physical	74
Bodily pain	36
General health	27
Vitality	28
Social functioning	33
Role–emotional	69
Mental health	21

SF-36, Short Form 36.

Table 3 Sample size needed per group to detect a 10-point difference in change over time between two experimental groups in average SF-36 scores

Domain	Sample size required to detect a 10-point difference
Physical functioning	55
Role–physical	118
Bodily pain	57
General health	43
Vitality	45
Social functioning	53
Role–emotional	111
Mental health	34

SF-36, Short Form 36.

threat of potentially life-threatening complications, such as IFALD. Despite this, there are currently few clinical studies with well-phenotyped patients on the effects of HPN treatment, the management of complications and how these impact on patient QoL.

This study has been designed to provide a better understanding of the relationship between HPN and the QoL of patients, the factors associated with worsening QoL and the pathways responsible. In the short term, patients identified as having poorer QoL and most in need of support will be identified to clinical care teams. In the medium term, the findings from this study will provide a framework on which to base future intervention studies and will identify those patients who are most likely to benefit from such interventions. The primary outcome of the study is to understand how QoL changes over the first year of treatment and thereafter. In addition, the study will provide data on the potential contributors to poor QoL, and therefore, a starting point for interventions.

The proposed study has several strengths. The comprehensive collection of clinical data to accompany the QoL questionnaires will provide a rich data set for exploratory analyses and as a basis for future studies, including intervention studies. The study uses routinely collected data which have the advantage of being recorded prospectively and are therefore not susceptible to recall bias. The longitudinal design of the study may reveal changes in QoL over time and allow us to explore potential reasons for those changes. Given its scale and representativeness, the study has national and international relevance, and the resulting dataset will have potential for use for multiple purposes including audits and service evaluation projects. A limitation of the study is the observational design. While the recommendations outlined in the STrengthening the Reporting of OBservational studies in Epidemiology statement have been followed,[20] it is still possible that there will be confounding factors that have not been considered.

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Contributors CK designed the study with assistance from JM, NPT, MP and DJ. JM, NPT, MP, DJ are supervising the project. CK will conduct recruitment and data collection. CK will perform data analysis with assistance from MP. CK drafted the manuscript; all authors revised and approved the final version for submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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