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Randomized control trials

A single-blinded randomised clinical trial of permissive underfeeding in patients requiring parenteral nutrition

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SUMMARY

Background & aims: The importance of adequate nutritional support is well established, but characterising what 'adequate nutrition' represents remains contentious. In recent years there has been increasing interest in the concept of 'permissive underfeeding' where patients are intentionally prescribed less nutrition than their calculated requirements. The aim of this study was to evaluate the effect of permissive underfeeding on septic and nutrition related morbidity in patients requiring short term parenteral nutrition (PN).

Methods: This was a single-blinded randomised clinical trial of 50 consecutive patients requiring parenteral nutritional support. Patients were randomized to receive either normocaloric or hypocaloric feeding (respectively 100% vs. 60% of estimated requirements). The primary end point was septic complications. Secondary end points included the metabolic, physiological and clinical outcomes to the two feeding protocols.

Results: Permissive underfeeding was associated with fewer septic complications (3 vs. 12 patients; $p = 0.003$), and a lower incidence of the systemic inflammatory response syndrome (9 vs. 16 patients; $p = 0.017$). Permissively underfed patients had fewer feed related complications (2 vs. 9 patients; $p = 0.016$).

Conclusion: Permissive underfeeding in patients requiring short term PN appears to be safe and may results in reduced septic and feed-related complications.

Trial registration: NCT01154179
Trial registry: http://clinicaltrials.gov/ct2/show/NCT01154179.

1. Introduction

The importance of parenteral nutrition (PN) in patients with temporary or permanent gut failure is well established. However, PN is not without risks, which include hyperglycaemia, fluid overload, electrolyte imbalances, hyperlipidaemia, and septic complications. These complications are a manifestation of the patient's inability to metabolise the macronutrient loads provided inferring that these patients are being "overfed". Overfeeding is now recognised as one of the most common complications of parenteral nutrition, and this probably accounts for the higher incidence of adverse outcomes associated with PN when compared with enteral supplementation noted in some studies. As conventional practice is to estimate macronutrient, and in particular, energy requirements from standard prediction equations, then the implication is that these prediction equations overestimate requirements in some patients. This was recognised many years ago by Zaloga et al.[1] who was amongst the first to propose the practice of intentionally providing less macronutrient supplementation than estimated requirements in some patient groups. This practice is referred to as 'permissive underfeeding'.

The aim of this prospective study was to assess whether or not permissive underfeeding was associated with any change in the incidence of septic morbidity when compared to the standard practice of normocaloric feeding.

2. Methods

This was a single blinded, randomized, clinical trial (trial registration number NCT01154179 at clinicaltrials.gov). The study

Abbreviations: PN, parenteral Nutrition; SIRS, systemic inflammatory response syndrome; WCC, white blood cell count; CRP, C reactive protein; ITU, intensive therapy unit; Kg, kilogram; L, litre; HOMA, homeostatic model assessment; ALT, alanine aminotransferase; ALP, alkaline phosphatise.

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protocol was approved by the North Yorkshire Research and Development Alliance (trial reference number SNE-AO1322) and ethical approval was granted by the Bradford Research Ethics Committee (09/H1302/5). The study was conducted in Scarborough General Hospital (Scarborough, United Kingdom).

Consecutive patients requiring PN support were included in this study, subject to the provision of informed consent and only after a detailed assessment of the nutritional status by professional dieticians. The indication for nutritional support was 5 days or more of actual or anticipated inadequate oral nutrition.[2] The need for nutritional support and the method of feed administration were decided by the attending clinicians together with the hospital multidisciplinary nutrition team and pursued according to strictly enforced local feeding protocols. Only when the decision for PN had been taken on clinical grounds, were patients approached for trial recruitment. Patients were blinded to their intervention. Patients were excluded if they were deemed at risk of refeeding syndrome[3] (or if for any other clinical reason they could not be prescribed 100% of their calculated requirements) or if they required concomitant administration of enteral and parenteral nutrition. Pregnant women and children under the age of 18 year were also excluded.

Patients eligible for the study were then randomised to one of two study arms; the control (normal feeding) group or the intervention (permissive underfeeding) group. In the control group patients were prescribed intakes aimed to meet 100% of estimated requirements as calculated by Schofield's equations,[4] whilst in the intervention group patients were prescribed 60% of their estimated requirements again calculated using Schofield's equations. All patients received TPN as Kabiven or Kabiven Peripheral (Fresenius Kabi ®). Randomisation occurred remotely by phone (by the recruiting physician) and by making reference to a list of computer randomly generated numbers. For purposes of the trial, the start of the study was at the commencement of feeding, and patients were considered to have completed the trial 24 h after the cessation of PN. Morbidity data was recorded until hospital discharge, patient transfer or death.

The primary end point of the study was septic morbidity. This was defined as the clinical evidence of an infection, confirmed by radiological, haematological and/or microbiological evidence. All septic complications occurring after the first 24 h of commencement of nutritional support until 24 h after the cessation of PN were recorded. The number of patients who developed septic complications were compared between the two groups rather the number of septic complications. This was agreed prior to the trial to avoid bias where few patients develop multiple septic complications.

To aid reproducibility, specific sources of infection were strictly defined as follows:

Pneumonia: clinical evidence of a new chest infection supported by radiological and/or microbiological evidence.
Wound infection: isolation of pathogens in either pus or discharge from a clinically infected wound.
Urinary tract infection: presence of positive urine culture together with clinical signs of a urinary infection
Line sepsis: positive culture from the line associated with clinical signs of line sepsis
Intra-abdominal abscess/collection: Clinical and/or radiological evidence of an intra-abdominal collection with signs of sepsis or systemic inflammatory response syndrome (SIRS).

A number of secondary end points were recorded. These included white cell count (WCC) and C reactive protein (CRP), which were both recorded at the beginning and at the end of feeding. Liver function test, renal function tests, and serum electrolyte levels were assessed regularly during the duration of PN, in line with widely accepted practice in such patients. The occurrence of the systemic inflammatory response syndrome (SIRS), defined according to standard criteria[5] at any time during the study was recorded.

The metabolic response was assessed by the homeostatic model assessment (HOMA) as a measure of insulin resistance.[6] This assessment involved measuring overnight fasting blood insulin and glucose levels on the day feeding commenced and again after feeding was discontinued. All feed-related morbidity (such as fluid overload and hyperglycemia), necessitating cessation, suspension, or slowing of the feed by the attending clinician/dietitian as well as the correction of any electrolyte abnormalities (such as hyperkalemia, hypomagnesaemia, and hypophosphataemia) were recorded prospectively. Disease severity was assessed by the Sequential Organ Failure Assessment (SOFA) score.

Patients' nutritional status was assessed at the beginning and at the end of the trial using basic anthropometric measurements including height, weight and body mass index (BMI) assessments. The body composition of participants was recorded at induction and at termination of feeding using multifrequency bioelectrical impedance (QuadScan 4000, Bodystat Ltd, UK operating at 5, 50, 100 and 200 kHz). Because of known technical limitations of this measurement in patients with severe body oedema, morbid obesity or severe chronic obstructive pulmonary disease, these patients were excluded from this assessment. The QuadScan 4000 device has been validated using dual energy X-ray absorptiometry (DEXA) and shows a bias of −0.07% and satisfactory limits of agreement from −7.97% to 7.76%.[7]

3. Statistical analysis

Sample size was estimated from a previous study performed in the authors' institution.[8] Calculations demonstrated that 25 patients would be required in each arm to show a 40% difference in septic morbidity at the 5% significance level with a power of 80%, assuming an incidence of 50% in patients receiving PN.

Results were tabulated on an Excel® spreadsheet (Excel for Windows®, Microsoft Corporation, Redmond, Washington, USA) and then analysed on an 'intention-to-treat' basis using SPSS® for Windows® version 16 (SPSS®, Chicago, Illinois, USA). Results for non-parametric data were expressed as medians and interquartile ranges (IQR). Relationships between groups were assessed using χ^2 test for binary outcomes or Fischer's exact test for small cohorts as appropriate. Continuous variables were compared with the Mann–Whitney *U*-test in the case of independent groups, or the Wilcoxon signed rank test in the case of paired cohorts. Statistical significance was considered at the 5% level. Analysis of data was done on intention to treat basis.

4. Results

Fifty consecutive patients were recruited to the trial, 24 randomised to the control group (normocaloric feeding) and 26 randomised to the study group (permissive underfeeding). After exclusions, data from 22 patients and 24 patients respectively were included in the final analysis (Fig. 1).

Both groups were similar in basic demographic characteristics including disease severity as assessed by SOFA scores. Similarly, the two groups were comparable with respect to the nature of the underlying condition being treated. By study design, there was a significant difference in the median number of calories delivered daily to each group (Table 1).

With reference to the primary end point, 12 patients in the normocaloric feeding group developed 14 septic complications and 3 patients developed 4 septic complications in the permissive

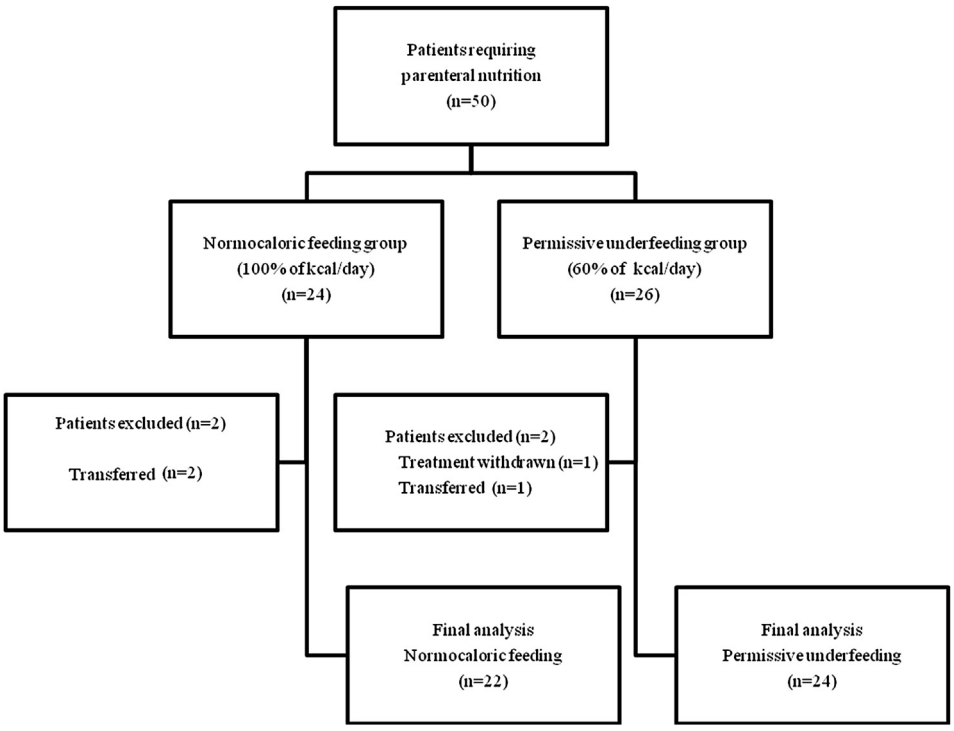

Fig. 1. CONSORT diagram.

underfeeding group ($p = 0.003$). Details of these septic complications are summarised in Table 2.

Nine patients in the normocaloric feeding group developed 12 feed related complications in comparison to 2 patients who developed 2 feed related complications in the permissive underfeeding group ($p = 0.016$). Feed related complications are shown in Table 2. Six deaths occurred in total; 4 patients in the normocaloric feeding group and 2 in the permissively underfeeding group ($p = 0.291$).

Patients in the normocaloric group developed significantly more episodes of SIRS than the patients who were permissively underfed (16 vs. 9 patients respectively; $p = 0.017$). Analysis of WCC and CRP values between the two groups both at the beginning and at the end of the feeding period did not reveal any significant differences. Within group analysis demonstrated that there were no observed differences in WCC at the two time points in either of the groups (normocaloric group $p = 0.153$ and permissive underfeeding group $p = 0.085$) and a significant drop in CRP was observed in both groups by the cessation of feeding ($p = 0.002$ and $p = 0.002$ respectively; Table 3).

Patients in both the normocaloric and the permissive underfeeding group lost weight in absolute terms during the trial, however this did not reach statistical significance in either group (respectively 68.6 (59–82) kg to 67.4 (57–82) kg; $p = 0.124$ and

Table 1
Patient demographics and energy intakes.

	Normocaloric ($n = 22$)	Permissive underfeeding ($n = 24$)	*P*-value
Age (years)[a]	67 (54–74)	69 (53–76)	0.783
BMI	23 (20–28)	26 (22–29)	0.484
Weight	68.6 (59–82)	75.5 (64–90)	0.340
Sex (Male:female)	13:9	19:5	0.124
Number of ITU patients	6	6	0.563
Length of stay (days)[a]	20 (12–27)	17 (14–33)	0.700
Duration of feeding (days)[a]	6 (5–6)	6 (5–7)	0.911
SOFA score	0	0	0.202
Underlying disease			
Colonic resection for cancer	7	6	0.426
Perforated viscus	4	4	0.598
Pancreatic disease	0	4	0.065
Inflammatory bowel disease	2	1	0.467
Ileus post adhesiolysis	4	2	0.291
Upper gastrointestinal bleeding	1	2	0.533
Other	4	5	0.559
Total calories prescribed (kcals)[a]	7815 (6331–9864)	5620 (4990–7660)	0.104
Total calories received (kcals)[a]	6496 (4658–8800)	5330 (4695–6920)	0.244
Energy intake/day (kcals)[a]	1147 (932–1347)	1006 (838–1059)	0.006
Daily energy deficit (kcals)[a]	390 (112–547)	853 (753–965)	0.000

[a] Values are median (Interquartile range); ITU, Intensive Therapy Unit.

Table 2
Septic complications, feed related complications and mortality.

	Normocaloric feeding group	Permissive underfeeding group	*p*-value
Septic complications (number of patients)	14 (12)	4 (3)	0.003
Intra-abdominal collection	3	1	
Line Sepsis	3	1	
Pneumonia	6	2	
Urinary tract infection	2	0	
Feed related complications (number of patients)	12 (9)	2 (2)	0.016
Deranged liver function tests	2	0	
Hyperkalaemia	1	0	
Hypophosphataemia	6	1	
Line sepsis	3	1	
Mortality	4	2	0.291

Table 3
Changes in body weight, body composition, inflammatory markers, renal function tests, liver function tests and HOMA model.

Body composition	First day (median) normocaloric feeding	Last day (median) normocaloric feeding	Wilcoxon test (*P* value)	First day (median) permissive underfeeding	Last day (median) permissive underfeeding	Wilcoxon test (*P* value)
Weight (kg)[a]	68.6 (59–82)	67.4 (57–82)	0.124	75.5 (64–90)	74 (61–88)	0.173
Fat (Kg)[a]	18.3 (13–25)	15.8 (14–26)	0.972	15.1 (9–18)	15.9 (9–19)	0.173
Lean body weight (Kg)[a]	57.3 (52–69)	51.6 (47–64)	0.279	57.6 (45–63)	55.1 (49–62)	0.374
Total body water (L)[a]	44.2 (41–53)	39.6 (37–42)	0.750	46.5 (43–50)	45.9 (41–47)	0.139
Intracellular water (L)[a]	21.5 (19–25)	21 (20–27)	0.875	23.6 (21–25)	22.9 (18–25)	0.258
Extracellular water (L)[a]	18.6 (17–22)	17.8 (16–21)	0.480	21.4 (18–22)	20.6 (17–22)	0.213
HOMA model[a]	0.65 (0.53–1.37)	2.32 (0.5–7.8)	0.086	0.73 (0.5–2.99)	1.7 (0.92–3.33)	0.062
WCC ($\times 10^9$/L)	8.7 (6.7–12.4)	12.4 (7.5–16.5)	0.153	10.8 (8.4–13.4)	11.3 (9.5–15.2)	0.085
CRP	150 (78–266)	79 (42–95)	0.002	188 (103.5–247)	78 (25–113)	0.002
Urea	6.2 (4.775–9.1)	4.95 (3.9–6.1)	0.065	6.6 (4.45–9.95)	5.45 (3.93–8.43)	0.44
Creatinine	57 (42–72.5)	53 (48–64)	0.498	67.5 (54–112)	66 (54–89)	0.543
Bilirubin	8 (6–12)	7 (4.75–7.25)	0.117	10 (6–17.25)	6 (5–13)	**0.023**
ALT	18 (13–27)	21.5 (15–38)	0.079	30.5 (19.25–41.25)	27 (16–34.5)	0.197
ALP	69 (45.75–86)	90.5 (67.25–122.75)	**0.011**	88 (59–109.5)	110.5 (77–155.75)	0.148

[a] Values are median (Interquartile range); WCC, White Blood Cell Count; Kg, Kilogram; L, litre; HOMA, homeostatic model assessment; CRP, C reactive Protein; ALT, alanine aminotransferase; ALP, Alkaline phosphatase.

75.5 (64–90) kg to 74 (61–88) kg; $p = 0.173$). No differences in body composition were recorded within groups for the duration of the trial (Table 3). 7 patients in the normocaloric group and 8 patients in the hypocaloric group did not have a before and/or after body composition assessment as they did not meet the criteria for this assessment. Serum urea and creatinine levels were maintained within groups throughout the study period. The results of these and other serum assays are summarised in Table 3. Similarly, there were no recorded differences in insulin resistance in either of the groups as measured by the HOMA model (normocaloric group, $p = 0.086$; permissive underfeeding group, $p = 0.062$).

5. Discussion

The results of this randomised clinical trial demonstrate that in patients receiving short term PN, permissive underfeeding of 60% of estimated nutritional requirements is safe and is associated with a significant reduction in both septic as well as feed related morbidity when compared to normocaloric parenteral feeding. The most frequently recorded feed related morbidities were hypophosphotaemia and line sepsis. There were no recorded differences in inflammatory mediators, body composition, insulin resistance or electrolyte changes which readily accounted for this observation. Permissive underfeeding was associated with a lower incidence of SIRS, but whether this is simply a result of lower septic morbidity or whether this has a more causal explanation remains unclear.

The term permissive underfeeding was first used by Zaloga et al. in 1994 to describe a feeding strategy which was based on the premise that short term dietary restriction (but not elimination) could possibly limit pathological processes associated with overfeeding while minimally impairing organ function.[1] Since then, several studies have attempted to investigate the various merits or demerits of permissive underfeeding, but to date none have conclusively shown benefits.[9,10,11]

This study was designed to compare two feeding regimens in patients requiring parenteral nutrition only, to the exclusion of patients receiving enteral intake. The underlying assumption that patients who are capable of tolerating their nutritional requirements enterally do so because they have a functioning gastrointestinal tract is central to our decision to limit this study to patients receiving PN only. Previous research from our institution has shown that gut failure is independently deleterious to patient outcome.[12] Since the gut is the largest single immunological organ in the body, and given that the gut has numerous vital homeostatic functions (e.g. barrier function, hormone production etc), it is probable that patients with a working gut may be less prone to septic complications and other negative outcomes purely as a result of an adequately functioning gut. The corollary is that patients with a non-functioning gut are more prone to septic complications and as such represent a better target population to appreciate any value of nutritional manipulation on septic morbidity.

The authors are aware that proponents of permissive underfeeding have advocated such nutritional practices in predetermined patient populations, such as the critically ill or the morbidly obese. It is arguable, however, that if prediction equations overestimate nutritional requirements, then this overestimation might occur in other patient groups as well. An additional intention of the study design was to accurately represent the day-to-day occurrences of PN across a whole nutritional practice. We were specifically interested in assessing the impact of permissive underfeeding on septic morbidity, if any, on all patients requiring parenteral nutrition, and not limit this to a narrow spectrum of patients suffering from predetermined medical conditions. As such, not only was it necessary that the attending clinician should instigate nutritional support by whatever route they considered appropriate (e.g. peripheral vs. central PN) unhindered by a rigid study protocol, but additionally, exclusion criteria were kept to an absolute minimum. This approach also had the added, albeit unintentional advantage of facilitating recruitment. We recognise the inherent limitations of this approach which may render some of our results less relevant to certain specific patient populations. Moreover, from the early stages in the study design we acknowledged that if the benefits of permissive underfeeding were to be limited only to specific patient groups, a methodology of including all patients requiring PN would run the risk of watering down the benefits of such a strategy and in so doing, increase the possibility of observing a type II statistical error. However in the true spirit of a null hypothesis, and given the dearth of high quality evidence in the field; it was our opinion that an overarching assessment of the impact of permissive underfeeding on septic morbidity was more pressing. It is our opinion that the positive findings of this study vindicate this approach and is particularly relevant to those patients outwith the cohorts originally described to possibly benefit from this feeding technique. These results also provide a rationale for more focussed disease-specific trials.

There were no differences between the groups in measures of body composition. This is probably a reflection of the short term nature of this study combined with the well known confounding factors in weight measurement and bioelectrical impedance analyses in critically ill patients.

Like many nutrition teams across the United Kingdom, we employed Schofield's equations to estimate individual patient requirements.[13] We are mindful of the limitations of the Schofield equations, and the fact that these may occasionally overestimate energy requirements.[10,14] This overestimation has been assessed to be in the order of 10–20% surplus to requirements in some cases and may result in overfeeding which, in turn, is known to increase the susceptibility to both septic and non-septic morbidities. The results of this study confirm the propensity of Schofield to result in over estimation of requirements.

We recognise a number of limitations of our study. The small number of patients in this study ($n = 46$) could be perceived as one such drawback; however the difference in complications between the two groups, and the consistency with the limited published literature makes it unlikely that our observations represent a type 1 error. It is noteworthy that the median duration of PN in both groups was only 6 days. However, this is an accurate reflection of TPN practice in the UK.[15] We recognise that the selection of value of 60% of calculated requirements for our study group was arbitrary. However a recent systematic review concluded that energy intakes lower than 60% might be associated with adverse outcomes.[9] As such, we wished to avoid this as a confounding factor.

On the basis of the results from this trial, it is the authors' opinion that lower rates of feeding may indeed decrease complication rates from adjuvant parenteral nutritional support, and increase feed tolerance. Extrapolating from this, permissive underfeeding may maximise benefits from parenteral nutrition.

In conclusion, this study demonstrates that permissive underfeeding, defined by calculation of requirements from standard equations, in patients receiving short term PN appears to be safe and may be effective in reducing both septic as well as feed related complications. Many of the complications associated with normocaloric PN may relate to relative "overfeeding". Further research is required to define the optimal nutritional needs of patients requiring PN.

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Conflicts of interest

None.

Disclosures

None.

Authors' contributions

Anwar Elias Owais: Designing the study, recruiting patients, collecting data, analysing data, writing the manuscript.

Marcel Gatt: Designing the study, analysing Data, writing the manuscript.

Syed Irfan Kabir collecting data, writing manuscript.

Claire Mcnaught: Designing the study, analysing data, writing the manuscript.

John MacFie: Designing the study, analysing data, writing the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.01.005

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