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Use and Tolerance of a High Energy Peptide Based Paediatric Oral Nutritional Supplement: A UK Multicentre Trial

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Abstract

Introduction: Supporting optimal growth is a key responsibility in paediatric care. Oral Nutritional Supplements (ONS) can help achieve nutritional needs in patients with or at risk of disease related malnutrition. Children with Gastro Intestinal (GI) dysfunctions often have a reduced ability to tolerate and accept whole protein-ONS.

Objectives: To assess the tolerance and acceptability of a new high energy peptide-based ONS in children presenting with GI impairment-related clinical conditions.

Research design and methods: This was a prospective, observational study recruiting children from four UK NHS sites who were on an ONS, >12 months age and did not meet any exclusion criteria. Baseline data was collected including demographics, anthropometry, GI symptoms and stool data. The study ONS was a 1.5 kcal/ml peptide whey based supplement. Children took the study ONS for 7 days and recorded GI symptoms and volume consumed. UK Ethics approval was granted.

Results: Twenty one children were recruited. Fifteen children (6 M:9 F, mean BMI Z score -0.55) completed the 7-day trial. At day 7 on completion of the study 21% reported an improvement in a GI symptoms. 85% reported no worsening of GI symptoms. No major or critical GI symptoms were reported during the study period. 57% were able to consume the recommended volume. Overall compliance was satisfactory.

Conclusion: Tolerance and acceptability were positive. The transition and subsequent tolerance to the study ONS was most successful in those historically on an extensively hydrolysed or peptide-based supplement. High energy peptide ONS may prove useful as a clinical option in nutritionally vulnerable patients with GI issues.

Trial Registration: The trial is registered at ClinicalTrials.gov (CT.gov identifier: NCT04515940).

Keywords: Acceptability; Gastrointestinal tolerance; Nutrition; ONS (Oral Nutritional Supplements); Paediatrics; Peptide-formula

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Introduction

Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on body shape, size and composition as well as function and clinical outcome [1]. Malnutrition is a global issue with a 2013 report stating that 165 million children were chronically malnourished worldwide [2].

Broadly, malnutrition can be sub categorised into starvation-associated malnutrition, where food security is the major cause, and disease-related malnutrition where the disease impacts on appetite, energy nutrient requirements, inflammation and absorption or losses [3].

The prevalence and impact of disease-related malnutrition has increasingly been recognised in recent decades. A large multicentre European study reported a percentage of hospitalised underweight children ranging from 4.0% to 9.3% across countries and that this correlates with length of hospital stay [4]. Several

conditions in childhood such as, chronic diarrhoea, Cystic Fibrosis (CF), gastrointestinal surgery and oncology diagnosis are closely associated with disease related malnutrition and are a clinical focus for nutrition teams. Dysfunction of the gut is associated with problems in nutrient absorption and tolerance to feeds that can lead to or exacerbate malnutrition. In turn this may further decrease the integrity of the Gastro Intestinal (GI) system leading to decrease of barrier function [5]. As a result, many diseases impacting on GI function are commonly associated with highest risk for disease-related malnutrition. A range of nutrition support options exist across a spectrum from Oral Nutritional Supplements (ONS) to Parenteral Nutrition (PN). This spectrum is often illustrated as a pyramid with the least invasive, lowest risk, first line options at the bottom (such as ONS) and the most invasive and highest risk at the top (PN). Given the increasing risk there is a clinical emphasis and benefit to, if possible, achieving success with the lowest risk options.

ONS have been identified as an intervention that may reduce the risk and impact of disease-related malnutrition in children, providing cost savings on hospital outcomes [6] as well as in the community [7].

A limiting factor to success with ONS maybe tolerance related to GI dysfunction. GI dysfunction is complex and multifactorial including a range of factors such as motility, immune aspects and gut barrier function. However, certain characteristics of nutrients such as hydrolysed proteins may address some dysfunction aspects. In particular improving digestion [8] and absorption [9] and thereby helping successfully address under-nutrition in those with GI dysfunction.

Another limiting factor to success is compliance. While ONS have been shown to be clinically effective in the management of disease-related malnutrition, it is essential to achieve good compliance for the ONS to be effective and maximise outcomes [10]. Compliance may be based in part by the likeness for the taste. In addition compliance will be poorer if the product is associated with negative GI symptoms. It is therefore necessary to address both taste and minimise any impact on GI symptoms to maximise the potential for positive benefit.

The aim of this study was to evaluate acceptability, tolerance compliance of a whey peptide-based ONS in children with various GI impairment-related clinical conditions.

Patients and Methods

Study design

This was a multicentre, nonrandomised, single-arm, single-treatment, prospective observational study conducted in the United Kingdom (UK). Four National Health Services (NHS) hospital's recruited patients: Royal Alexandra Children Hospitals, Brighton and Sussex University NHS Trust, Birmingham Women's and Children's NHS Foundation Trust; Bart's Health NHS Trust and Mid Cheshire Hospitals NHS Foundation Trust. Patients were recruited from these NHS settings either as inpatients, from hospital clinic appointments, or from community settings. Recruitment took place between November 2019 and April 2020. The study design followed the UK Advisory Committee on Borderline Substances (ACBS) criteria to support the submission for prescription usage in the NHS, as shown in **Figure 1**. Our goal was to recruit 20 children with a target of collecting data from 15. The study protocol and ethical approval was granted by London-Hampstead Research Ethics Committee IRAS ID 264414 and HRA approval by HRA and Health and Care Research Wales (HCRW) 19/LO/0802.

Figure 1: Study design diagram.

Eligibility criteria and administration

All eligible participants were children aged 12 months or over with GI impairment-related clinical conditions, such as neurological impairment, history of liver failure, inflammatory bowel disease, short bowel, and cystic fibrosis. These children were currently taking an ONS along side their regular diet or required an ONS as a bolus *via* a feeding tube as part of their dietary management. Informed consent was obtained prior to the start of the study. Exclusion criteria were food allergies to any ingredient in the ONS, a requirement for a milk-free diet, under the age of 12 months, and children involved in another protocol within two weeks of this study.

The ONS investigated in this study was Peptamen Junior 1.5 (1.5 kcal/ml) (Nestlé Health Science, Switzerland) as a liquid supplement with banana or vanilla flavour. The main characteristics are shown in **Table 1**.

Formula composition	Per 200 ml
Protein	9 g
Carbohydrate	36 g
Fibre	1.4 g
Fat as MCT	8 g
Osmolarity	465 mOs m/l
Osmolality	560 mOs m/kg
Type of protein	Whey

Table 1: Study formula characteristics.

Participants were recommended a volume to consume by the dietitian daily for 7 days. The participant were offered the option of both, however the children did not have prior exposure to the flavours at the start of the trial. The dietitian completed paper baseline forms for each child and collected demographics, including weight, height and BMI z score, diagnosis of allergies, current GI symptoms and stool type (including consistency, and frequency using the Bristol Stool Form Scale 10 (BSFS).

Parents and caregivers recorded GI symptoms and the amount of ONS consumed daily during the 7-day trial period. The questionnaires were then returned to the dietitian the study team and chief investigator collated the data from the 4 sites.

Primary and secondary end points

Primary outcome measures were collected by completing a hard copy of a GI tolerance diary that asked parents, to note any changes in diarrhoea, constipation, bloating, nausea, vomiting, burping, flatulence, regurgitation and abdominal pain or discomfort. Changes were documented by either ticking if the change was seen, followed by an “increase" or “decrease” for each GI symptom.

Secondary outcome measures were of participant compliance measured as volume recommended each day by the health care professional versus consumed volume. This hard copy of the questionnaire was completed by the parents who would indicate the volume or number of bottles consumed per day. Palatability such as taste, texture, smell, and appearance were additional endpoints. Capturing this information was also in a hard copy and illustrated by using sad, neutral or happy faces. Feedback questionnaires were provided by the dietitian and completed at the end of the day by the participant or parent.

Statistical analysis

According to the trial design only descriptive values for each patient are presented. BMI z scores were calculated using the UK RCPCH Growth Chart App 2017.

Results

Patient´s characteristics

Twenty one children were recruited, 15 completed the 7-day’s trial and 6 children withdrew or did not complete the 7 days. The main reason for not completing was patients did not like the trial formula and suspended the trial before the 7days period.

The general characteristics of the study population as well as medical conditions are reported in **Table 2**. Of the total children enrolled in the study, 40% were male and 60% were female. The age ranged from 1 year 11 months to 15 years 2 months. The mean weight was 23 kg (range 8.6 kg–51 kg). The mean BMI

Participant number	Age (years, months)	Gender	Height (cm)	Weight (kg)	BMI z Score	Route of delivery	Medical condition/Medical history
P01-001	12,10	M	153	43. 5	0.296	Feeding tube (PEG)	Liver failure, previous transplant in 2008
P02-003	5	F	103 .5	14. 5	-1.563	Oral	CF screen positive inconclusive diagnosis
P02-004	10	F	144.9	32.9	-0.633	Oral	CF with pancreatic insufficiency Investigations for GORD
P02-005	13	M	136.9	26.7	-2.56	Oral	CD
P02-006	2	M	80	8.6	-2.382	Oral	Global developmental delay, fat soluble vitamin deficiencies
P03-001	2,6	F	89	13.7	1.243	Feeding tube (PEG)	Gastroschisis, intestinal atresia, SBS, liver complications. Stoma bag
P03-003	13,11	F	148	51	1.589	Oral	CF
P04-001	1,11	F	85	13.4	2.034	Feeding tube (PEG)	Intraventricular haemorrhage (grade 4), Premature 29 weeks, fundoplication, GORD
P04-002	3,10	F	95.3	11.5	-2.188	Oral	GORD, food aversion, , slow weight gain, constipation
P04-003	6	F	98	16.6	1.017	Feeding tube (Jejunostomy) and oral intake	Vacterl syndrome, duodenal atresia, oesophageal atresia, recurrent oesophageal structure
P04-004	5,9	M	114	21.6	0.808	Oral	Cerebral palsy, Epilepsy, 29 weeks Gestation
P04-005	6	M	99	16.3	0.678	Oral	Undiagnosed genetic syndrome, global developmental delay, GORD
P04-006	7,11	F	101.5	11.95	-3.338	Feeding tube (PEG) and oral	Cockayne syndrome, GORD, global developmental delay
P04-007	14,5	M	171	49.6	-1.038	Feeding tube (PEG-J) and oral	Eosinophilic oesophagitis, asthma
P04-008	15,2	F	124	26.2	-1.402	Oral	Chromosome Xq22.3 deletion, microcephaly developmental delay, Epilepsy, growth hormone deficiency

Table 2: Baseline demographics and clinical characteristics.

	Pre study assessment	Study formula Day 7 assessment		
	Baseline	No change	Increase	Decrease
No. stools per day		87%	13%	0%
Mean	3.4			
Stool consistency		94%	6%	0%
Type 1-2	26%			
Type 3-4	26%			
Type 5-6	33%			
Type 7	6%			
Vomits		94%	0%	6%
None	73%			
1-2	20%			
3 or more	6%			
Abdominal pain		94%	0%	6%
None	40%			
Mild	40%			
Moderate	20%			
Severe	0%			

Table 3: Caregivers evaluation of GI symptoms (baseline n=15, Day 7 n=14).

Z score was -0.55 (range -3.3 - 2.0). The route of delivery was predominantly orally (60%), 20% had it delivered *via* a feeding tube and the remaining 20% had it delivered both orally and *via* a feeding tube. Regarding medical conditions, an extensive range of GI impairment-related conditions were registered.

Primary outcomes

Tolerance: On completion of the 7 days study ONS, 21% (n=3) reported improvements in GI symptoms. Overall 85% reported no worsening of GI symptoms and 14% reported worsening of GI symptoms.

Evaluation of GI symptoms: By day 7 no change from baseline symptoms were reported in the majority of patients for number of daily stools (87%), stool consistency (94%), vomits (94%) and abdominal pain (94%) see **Table 3**. However in the early days of the study some changes were reported. Participant P02-005 reported abdominal pain until day 7 and flatulence on day 1 lasting for 15-30 minutes. Also, it was reported an increase in retching on day 2 for 15-30 minutes that decreased by day 6. Participant P03-001 presented abdominal pain on day 3 for 15 minutes but decreased the number of vomiting episodes on day 4. By day 6, this child perceived a sense of sickness in the morning, but no vomiting episode was reported. Participant P03-004 showed retching only on day 1, without persistence in the remaining days. Participant P04-005 reduced the frequency of vomiting, bloating and distension but it was reported that these were usual symptoms for this child and no further changes were observed. Participant P04-007 parents' reported abdominal pain only on day 1 and 2, lasting 30 minutes.

Stool frequency and scale: 87% of patients reported no impact on their stool frequency by day 7. In the first days some changes were reported. Participant P04-004 had an increase in the consistency and number of stools, more looser stools on day 3. Participant P04-006 presented a change in stool colour and smell. However it was further reported these symptoms tend to be usual for the child when changing to a different formula. For participant P02-006 the number of stools from day 5 to 7 was reduced from 3 to 1-2 per day. Two patients had stomas and one of these (participant P03-001) reported an increase in volume during the 7-day period.

Secondary outcomes

Formula compliance: A secondary endpoint was to evaluate and compare the amount of ONS intake recommended with the amount consumed during the 7-day period as a marker of compliance. At inclusion, children were on either a standard polymeric or peptide-based ONS with volumes ranging from 200-600 ml/d depending on individual situation.

The volume recommended varied among participants based on the dietitians recommendation. The average volume taken of those who completed the 7-day study period was 293 mL/day. **Figure 2** shows compliance with recommended ONS volumes, 57% of the participants achieved the recommended volumes. Comparing the recommended vs. amount consumed, participants, P01-001, P02-004, P02-005, P03-001, P04-001, P04-003, P04-004 and P04-008 consumed the full amount recommended by the dietitian. None the participants consumed more that the recommended dose.

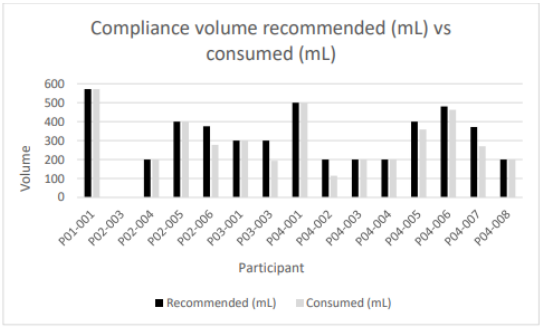

Figure 2: Study ONS compliance presented as recommended volume (mLs) *vs* consumed volume (mLs)

No difference in sex, age or BMI z score between those who complied with the recommended volume versus those who did not was seen. Of the 10 who complied with the full volume, 6 took it orally and 4 via feeding tubes. Of those 5 who were unable to achieve the recommended volume 4 had it orally and 1 had it orally and via a tube. It is important to state that child P02-003 completed the 7-day trial of the ONS but the parents failed to record the daily intake dose and therefore the data is excluded. The most common volume to be recommended was 200 mL (P02-003, P02-004, P04-002, P04-003 and P04-004, P04-008). This volume appears to be most commonly associated with successful compliance. Age ranges for this recommended volume ranged from 5-10 years. P01-001 (age 12 years 10 months, weight 43.5kg, BMI Z score 0.2) was recommended with the highest volume of ONS and *via* a feeding tube.

Palatability feedback: Participant P04-004 appreciated both banana and vanilla flavour in the supplement. Participant P04-008 showed a strong preference for the banana flavour. Some difficulty switching to the new peptide based ONS was experienced by a few children. Participant P03-005 disliked the taste and the dietitian reported this child was previously on a standard ONS. Participant P01-001 disliked the taste however the prescribed volume was achieved *via* a feeding tube. Participant P02-004 added a powdered chocolate flavour to the ONS and found this more palatable. Participant P02-005 expressed a preference for a strawberry flavour but this was not a flavour offered in this trial. Participant P02-005 got used to the taste of the new peptide supplement by day 3. Two recruited participants disliked the supplement after taking 5 mL and withdrew from the study.

Palatability of the new peptide base ONS was evaluated in appearance, smell, taste and texture, as shown in **Figure 3**.

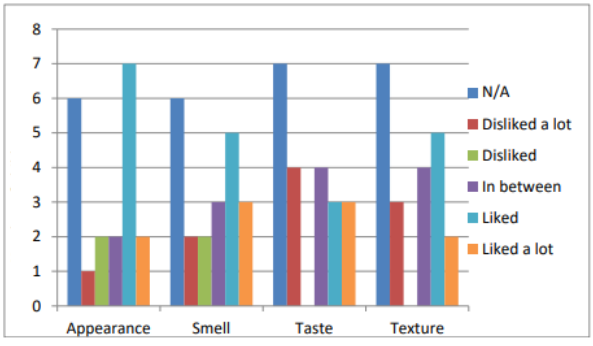

Figure 3: Palatability feedback.

For those where the route of delivery was *via* a feeding tube palatability feedback was not applicable. Regarding the appearance, 7 children liked the ONS, 2 liked a lot and 2 disliked. Very similar results were observed for the smell, with 5 children liking it, 3 liking a lot and 2 disliking it. Four participants disliked the new formula taste a lot, 3 liking it and 3 liking it a lot. Feedback on texture was variable with 5 children liking it, 3 children disliking a lot and 4 children in between.

Discussion

ONS have been identified as an intervention that may reduce the risk and impact of disease-related malnutrition in children and provide cost savings for other medical and nutritional management. Evidence supports an association of ONS to improved intakes and weight across several conditions such as CF, cancer and non-organic conditions [11-14]. However, tolerance and compliance maybe an issue particularly in those with GI dysfunction that may limit their success. In this study we showed encouraging results of both tolerance and compliance of an ONS with characteristics that may be of benefit in those with GI issues. As nearly all participants (85%) reported no worsening of GI symptoms (and in several cases improvements in GI symptoms) the impact of taste preference on compliance is most likely the biggest influencer. This is perhaps to be expected especially in a paediatric cohort. This was further illustrated by the large range of feedback on palatability.

Whey based feeds have long been shown to be associated with better tolerance. Whey-based formulas may induce a shorter gastric emptying time than casein-based formulas and have been shown to reduce the number of episodes and duration of GOR [15]. Gastric emptying times with three whey-based formulas were significantly shorter, and episodes of vomiting significantly fewer when fed with a casein-based formula ($P<0.001$) in gastrostomy-fed children with neurological impairment [16]. The ESPGHAN recommendation is a trial of whey-based formula or feeds in cases of gastroesophageal reflux, gagging, and retching in children with NI [17].

Peptide-based formulas or feeds may have added advantages over whole protein versions. Specifically improving nitrogen retention, improving visceral protein synthesis, improving absorptions, reducing diarrhoea, maintaining, and restoring gut integrity, reducing bacterial translocation and improving outcomes [18]. In addition, work has emerged in critically ill children supporting this concept of better tolerance of peptide based feeds in the most vulnerable patients [19]. Previous work has also shown switching to peptide-based feed has been associated with improved feeding tolerance. Ninety two percent of patients showed improvements within one week of formula switch, in a retrospective chart review of children with developmental delay who failed to reach their nutritional goals using standard polymeric formulas [20].

Specific disease conditions exist where recommendations for management may be theoretically best achieved with such ONS that are peptide based. For example, Short Bowel Syndrome (SBS) is a complex GI condition to nutritionally manage. Guidelines exist that suggest peptide-based proteins are considered most ideal [21]. The same authors also emphasise the importance of promoting and supporting oral intake. This is particularly important in SBS where oral intake may represent an opportunity to progress and advance enteral calories while simultaneously reducing reliance on PN and its associated risks. In addition, as survival improves in this group, there is an increased population of children with altered anatomy who may benefit from nutrition products designed with appropriate characteristics for optimal absorption.

Managing disease related malnutrition goes beyond calories alone. Whilst ONS are dense sources of calories they also represent dense sources of vitamins and minerals which play key roles. Such sources of nutrients are advantageous in many conditions where micronutrient deficiencies are common, such as chronic liver disease [22] or where requirements may be higher, such as in CF [23]. Therefore, developing tolerable and acceptable whey peptide-based ONS for children with various GI impairment-related clinical conditions could be of great clinical use.

Two key learning points from this study stood out. Firstly, during the recruitment phase we identified that ONS were often being used as bolus feeds *via* a feeding tube or interchangeably. For one the recruiting centre (P04) 50% of the participants consumed the majority of the peptide ONS as a bolus *via* a feeding tube. This indicates a multi-usage practice where compliance related to taste is not a factor. There is anecdotal evidence indicating for a greater emphasis on mimicking "normal" physiological feeding patterns such as bolus feeding [24]. This also has the added advantage of allowing increased flexibility for children who are mobile and want less time connected to a feeding pump. This shift in practice has also been reported in an adult study, where ONS were used in 85% of cases for bolus feeds in tube fed patients [25]. In this study 604 patients from 10 centres across the UK demonstrated that bolus feeding is increasing across Home Enterally Tube Fed (HETF) patients. The study went on to find most patients used bolus feeding as their sole feeding method (46%), as a top-up to oral diet, or to mimic mealtimes, due to this method being quick and easy to use.

Secondly, independently of the ONS consumed before the trial the group generally tolerated the product. However those already on a peptide feed transitioned much better to the study. Peptides are recognised to often have a slightly bitter taste [26]. Therefore it is a challenge to develop and balance an ONS with peptide characteristics and good taste. The impact of peptides on taste is particularly noticeable in direct comparison with a whole whey based versions. To improve transition from a standard ONS to a peptide-based, a standard whole protein can be weaned down over a several days and the peptide based ONS volume weaned up. This process may also allow time for the palate change and reduce the slight bitter after taste of peptides.

There are several limitations to this study. Firstly, this is a small heterogeneous cohort of patients; however, the target group for this ONS is quite specific, making recruitment challenging. In addition to this, rates of under-nutrition are improving in several key groups targeted. For example, in CF, where a combination of new-born screening, established MDT working and increasingly effective modulators have proven association with decreased risk and prevalence of under nutrition [27]. In SBS too, improved care in recent decades has been associated with improvements in achieving more optimal weight gain for age [21]. A larger cohort would allow appropriate statistical analysis to be completed as our results show associations and trends but cannot test cause-effect hypotheses.

Secondly, the new peptide based ONS was not associated with any major or critical GI symptoms during the study and tolerance was good. However the time frame was short and further exploration of longer term tolerance would be helpful.

Another limitation is that the study relied on the parental recording of symptoms and therefore could be subject to forms of bias associated with this. To avoid exclusion due to ONS rejection, participants should have had prior exposure to banana or vanilla flavoured ONS before the start of the trial. This is to ensure that they did not have an aversion to the product flavour and a better adjustment when switching to the new flavours. Clearly taste, smell and appearance are subjective and very individual and this was seen in our results. Adding flavours or expanding ranges are possible solutions to address this to maximise compliance further in the future. Finally, due to the COVID-19 pandemic, it was only possible to accomplish some primary and secondary endpoints.

Conclusion

The new peptide ONS was overall well tolerated and accepted by the children involved in this study. The transition to the study ONS appears more successful in those historically established on an extensively hydrolysed or peptide based supplement, when compared to those on a standard whole protein. There is potential application of such a whey peptide based ONS across a wide range of patients with GI dysfunction and disease related malnutrition.

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Authors' Contributions

All authors were involved in the drafting and critical review of the manuscript.

Competing Interests

C. Smith reported personal fees, non-financial support and other from Nestle Health Science, during the conduct of the study.

H. Norton reported financial benefit from Nestlé Health Science UK to Birmingham Woman's and Children's NHS trust, during the conduct of the study.

M. Patel reported personal fees, non-financial support and other from Nestle Health Science UK, during the conduct of the study.

K. Simpson reported that research fees from Nestlé Health

Science UK were paid to her NHS Trust Research and Development department and split with the Nutrition and Dietetic Department as she became the PI for the Trust.

S. Saduera is a Medical Affairs Dietitian employed by Nestlé Health Science UK, and reported personal fees, non-financial support and other from Nestle Health Science, during the conduct of the study; she has also supported the authors writing the publication.

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