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Efficacy of Exclusive Enteral Nutrition in Pediatric Crohn's Disease

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ABSTRACT

Introduction: Exclusive enteral nutrition (EEN) is recommended as first line therapy for mild to moderate Crohn's disease (CD) to induce remission in pediatric patients. It involves the use of a whole protein formula given exclusively for six to eight weeks.

Aims: To report the preliminary experience of a tertiary care center in Portugal, concerning the efficacy and tolerance of EEN in pediatric patients with CD.

Materials and methods: Retrospective descriptive study of pediatric CD patients who received EEN as induction of remission therapy between January/2014 and June/2019. Clinical and laboratory parameters were assessed, including clinical disease activity and nutritional status before and immediately after treatment.

Results: In the study period, 37 patients were diagnosed with CD; 19 were included in the study, 17/19 (89.5%) completed the EEN therapy and 16/17 (94%) achieved clinical remission. Ten patients were male, with a median (IQR) age of 14.2 years (11.8; 16.7 years). The majority of the patients had ileocolonic disease (47.4%) or ileocecal disease (42.1%) and an inflammatory behavior (78.9%). None of the patients had growth delay at diagnosis. All patients received EEN orally for six to eight weeks, 18 used polymeric formulas and one used an elemental formula. Comparing data at baseline and after treatment, significant improvements were observed in BMI Z-score (p=0.002), PCDAI score (p<0.001), erythrocyte sedimentation rate (p=0.002), C-reactive protein (p=0.003), faecal calprotectin concentration (p=0.036), and serum albumin (p=0.020). No side effects were noticed.

Discussion/Conclusion: In this series, EEN therapy was associated to significant improvement of disease activity index, nutritional status, weight gain and decreased markers of inflammation in most patients. Our data are in accordance with previous observations that EEN is an effective and well tolerated treatment for the induction of remission in pediatric patients with CD.

KEYWORDS

Crohn's disease; Exclusive enteral nutrition; Pediatrics.

ABBREVIATIONS

BMI: Body Mass Index.

CD: Crohn's disease.

EEN: Exclusive enteral nutrition.

IQR: interquartile range.

PAL: Physical Activity Level.

PCDAI: Pediatric Crohn's Disease Activity Index.

REE: Resting Energy Expenditure.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition that may involve any level of the gastrointestinal tract from the mouth to the anus[1]. It may present at any age, with up to 25%

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of cases being diagnosed during childhood, with increasing incidence in recent years[2]. The goals of the treatment in pediatric CD are to induce and maintain full remission, to relieve symptoms and to optimize growth, while minimizing side effects[3].

Exclusive enteral nutrition (EEN) is recommended as first line therapy for mild to moderate disease to induce remission in pediatric patients, as it promotes mucosal healing, restores bone mineral density and improves growth. It involves the use of a whole protein formula given exclusively for six to eight weeks[4-6]. In our center, EEN has been increasingly used as induction therapy in CD since 2010.

AIMS

The aim of this study was to report the preliminary experience of a tertiary care center in Portugal, concerning the efficacy and tolerance of EEN in pediatric patients with CD.

MATERIALS AND METHODS

A retrospective study was performed including pediatric patients with CD who were managed with EEN to induce remission between January 2014 and June 2019 in a tertiary care center in Portugal. Inclusion criteria in the earliest treated patients included not only those with mild to moderate disease who started EEN, but also some patients with severe disease and malnutrition, who would benefit from a nutritional intervention. Excluded patients in the study period (16) had moderate to severe active luminal disease and EEN was not a viable option; these patients had either deep ulcers in endoscopy or extensive disease (including upper gastrointestinal and proximal small bowel involvement); they were high-risk patients with severe growth retardation or with severe extraintestinal manifestations. In this subset of patients corticosteroids or anti-TNF therapy was selected as induction treatment.

The diagnosis of CD was performed according to conventional criteria (Porto criteria)[7]. Disease behavior and anatomical location were classified using the Paris classification[8].

Primary endpoints included clinical disease activity, assessed by using Pediatric Crohn's Disease Activity Index (PCDAI) scores (a score of 10 to 27.5 points: mild disease, 27.5 to 37.5 points: moderate disease and >37.5 points: severe disease activity)[9], nutritional status and laboratory examinations of each patient (erythrocyte sedimentation rate, C-reactive protein, faecal calprotectin concentration and serum albumin), assessed at baseline, at two weeks and at six to eight weeks of EEN.

Patients were treated with a whole protein formula (Peptisorb®, Fresubin energy® and/or Fortimel compact protein®) through the oral route. Alternatively, nasogastric tube feeding was proposed if oral route was not feasible. Pediatric dieticians assessed the nutritional requirements and set the feed volume for each child, using the resting energy expenditure (REE) and a physical activity level (PAL) of 1.4. No other food was allowed during the EEN course, with the exception of water and tea (herbal infusion), with no added sugar.

Patients who were unable to consume an adequate amount of the formula or who did not tolerate nasogastric tube feeding, were defined as non-adherent and were excluded from the study. Patients who successfully completed their course of EEN were classified into three groups: those who achieved clinical remission (PCDAI score ≤10 points), which were defined as full responders; those who achieved partial remission (PCDAI score change of 12.5 points), which were defined as partial responders and the non-responders (patients who did not clinically improve or deteriorated within the initial treatment period – two weeks); in these patients EEN therapy was discontinued and an alternative induction treatment was prescribed. Intolerance and adverse side effects during the induction dietary treatment were reported.

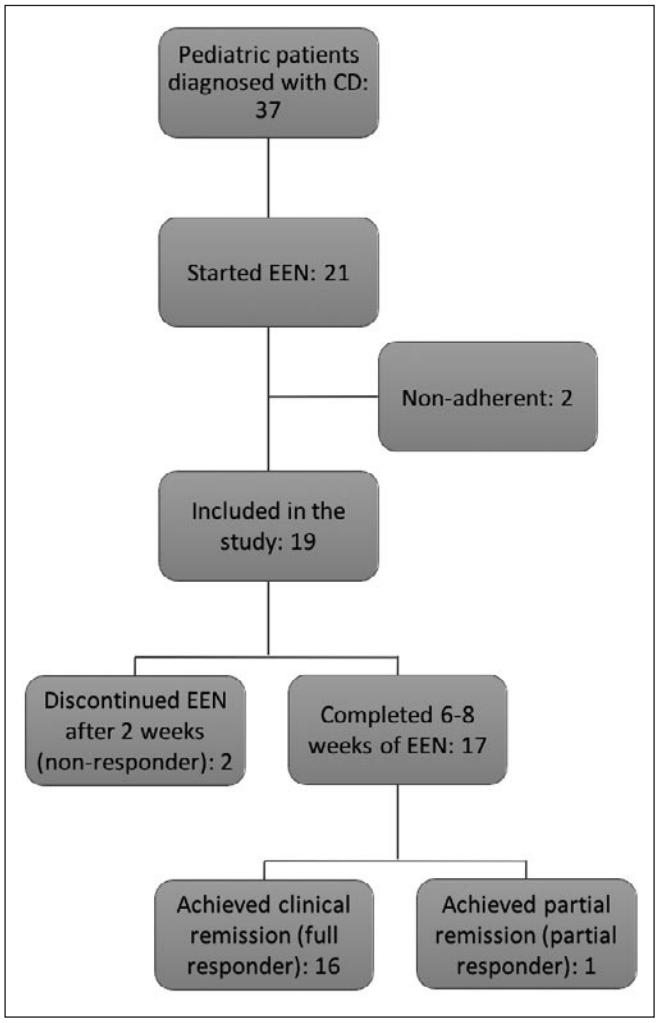
Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations, or as medians and interquartile ranges (IQR) for variables with skewed distributions. Normal distribution was checked using skewness and kurtosis. Appropriate parametric or non-parametric tests were adopted as necessary. Paired Student's t-test was performed for continuous variables with normal distribution and Wilcoxon signed-rank test was performed for ordinal variables and for continuous variables with skewed distribution. All reported P values are two-tailed, with a reported *p*-value of 0.05 indicating statistical significance. Analyses were performed with the use of Statistical Package for the Social Sciences (SPSS®) 23.0 software.

RESULTS

From a total of 37 pediatric patients diagnosed with CD between January 2014 and June 2019 in our center, 21 started the EEN induction course as first therapeutic option. Two patients were not able to continue EEN due to intolerance (nausea and vomiting) and refused nasogastric tube feeding. These patients were defined as non-adherent and were not included in the study. From the 19 included patients, two discontinued treatment after two weeks from initiation (as a result of no improvement/worsening of symptoms – diarrhea and abdominal pain) and were defined as non-responders. Non-adherent and non-responders started corticosteroids as an alternative induction treatment. Seventeen patients (89,5%) completed a six to eight weeks course of EEN and 16/17 (94%) achieved clinical remission after completing the induction protocol (Fig. 1).

Table 1 shows the baseline characteristics of the 19 patients included in the study, according to the Paris classification. Ten patients (52.6%) were male, and the median age (IQR) at baseline was 14.2 years (11.8; 16.7 years). Regarding disease location at diagnosis, eight patients (42.1%) had ileocecal disease, two patients (10.5%) had isolated colonic disease, nine patients (47.4%) had ileocolonic disease and 17 patients

Figure 1. Flowchart of the study.



(89,5%) had upper gastrointestinal involvement (esophageal 5.9%; gastric 47%; duodenal 5.9%; gastric and duodenal 41.2%). Considering disease behavior, 15 patients (78.9%) had inflammatory behavior, two patients (10.5%) had stricturing behavior and two patients (10.5%) had stricturing and penetrating behavior. Only one patient (5.3%) had perianal disease. None of the patients had growth delay at diagnosis. According to PCDAI scores, 10 patients (52.5%) had mild disease, four (21%) had moderate disease and five (26.5%) had severe disease activity. All patients with mild disease achieved clinical remission. Two patients with moderate disease achieved clinical remission and two did not respond (these patients had isolated colonic disease or ileocolonic disease, and both had an inflammatory behavior). Four patients with severe disease achieved clinical remission and one partially responded (this patient had ileocolonic disease, with stricturing and penetrating behavior).

All patients received EEN orally. Fifteen patients completed a six week course of EEN, followed by gradual food reintroduction with concomitant decrease of formula over two weeks;

Table 1. Baseline Characteristics of the Patients Included in the Study (n=19).

Characteristics	N = 19
Sex, male/female	10/9 (52.6%/47.4%)
Age at diagnosis, years	
A1a (<10 years)	3 (15.8%)
A1b (10 to <17 years)	14 (73.7%)
A2 (17 to 40 years)	2 (10.5%)
Disease location at diagnosis	
L1 (ileocecal disease)	8 (42.1%)
L2 (isolated colonic disease)	2 (10.5%)
L3 (ileocolonic disease)	9 (47.4%)
Upper GI involvement at diagnosis	
Presence	17 (89.5%)
Absence	2 (10.5%)
Disease behavior at diagnosis	
B1 (inflammatory)	15 (78.9%)
B2 (stricturing)	2 (10.5%)
B3 (penetrating)	0 (0%)
B2B3 (stricturing + penetrating)	2 (10.5%)
Perianal disease	
Presence	1 (5.3%)
Absence	18 (94.7%)
Growth delay	
G1 (presence)	0 (0%)
G0 (absence)	19 (100%)
Disease activity	
Mild (10< PCDAI ≤27.5)	10 (52.5%)
Moderate (27.5< PCDAI ≤37.5)	4 (21%)
Severe (PCDAI >37.5)	5 (26.5%)

Values are given as n (percentage).

and two patients completed an eight week course of EEN. The median hospital stay was two days (range 0-17 days). Eighteen patients were treated with polymeric formulas (Fresubin energy® and/or Fortimel compact protein®) and only one used an elemental formula (Peptisorb®). Patients have reached a median of 86.1% of their energy requirements, which corresponded to 1901 ± 272 Kcal/day (46 ± 11 Kcal/Kg). The mean protein intake was 72.6 ± 10.2 g/day (1.7 ± 0.4 g/Kg), the mean carbohydrate intake was 237.1 ± 34.2 g/day (5.7 ± 1.3 g/Kg) and the mean fat intake was 73.6 ± 10.5 g/day (1.8 ± 0.4 g/Kg). No side effects were noticed.

Table 2 shows the clinical and laboratory parameters of the patients included in the study who successfully completed their course of EEN (17/19), at baseline and immediately after treatment (six to eight weeks). When comparing data at these two periods, we observed significant improvements in Body Mass Index (BMI) Z-score (p=0.002), PCDAI score (p<0.001), erythrocyte sedimentation rate (p=0.002), C-reactive protein (p=0.003), faecal calprotectin concentration (p=0.036), and serum albumin (p=0.020).

DISCUSSION

EEN is an established first line treatment for mild to moderate pediatric CD and its use is consensual in many centers and countries as the initial therapy following diagnosis, with remission rates of approximately 73% to 85%[4-6]. In this study, we found that EEN induced clinical remission in 94% (16/17) of patients who completed treatment. Current guidelines reinforce the consensus that corticosteroids and/or early immunosuppressive therapy should be reserved for those patients for whom EEN is not an option[4-6]. This is particularly relevant in the pediatric population where nutritional concerns, linear growth deficiency and delayed puberty are currently detected in up to 85% of the patients[10].

In the last 20 years, several studies have compared the efficacy of EEN to corticosteroids in the induction of remission, with an equivalent response but with additional benefits, which included avoidance of all the side-effects of corticosteroids, particularly growth retarding, and providing complete nutritional support to meet growth and development milestones[11-14]. Although the exact mechanism of action of EEN remains unknown, the effect of EEN on systemic/local intestinal immune function and subsequent inflammation (including barrier permeability, direct anti-inflammatory effects and cytokine signaling pathways), alongside with the changes in the microbiome, are becoming clearer in recent years[15]. Recent studies showed that the microbiome can change rapidly in response to short-term dietary interventions, but it typically reverts to its prior composition once the intervention ceases, especially when returning to regular diet following EEN. Given that EEN is highly restrictive and not feasible for long-term maintenance, diets with either partial EEN or mimicking EEN composition with more solid ingredients were studied and were equally effective as EEN in inducing remission in pediatric patients with CD[16-19].

EEN has been increasingly used in our center since 2010. Before 2016 it was used on an individual basis, as there was no government/institutional funding concerning outpatient utilization and it was a relatively expensive intervention. After that, we have used EEN regularly in selected patients with luminal disease, regardless of the site of inflammation. The initiation of EEN can be challenging for the patient and the family and non-adherence occurs frequently, limiting the success of treatment. Some studies showed that older children and females were particularly likely to be non-adherent[20-21]. Similarly, we found that the only two non-adherent patients in our study were older than 14 years of age and both females.

There is conflicting data regarding the efficacy of EEN and CD location, with some studies suggesting better efficacy in patients with ileal involvement compared to isolated colonic disease, and more recent data demonstrating similar rates of remission regardless of the disease location[15,22]. One of our patients with isolated colonic disease achieved full remission and the other did not respond to EEN; furthermore, concerning nine patients with ileocolonic involvement, two did not respond. It is a small sample to elicit any conclusions and in the absence of better scientific evidence, the use of EEN in patients with lu-

Table 2. Clinical and Laboratory Parameters of the Patients Included in the Study Who Successfully Completed Their Course of Exclusive Enteral Nutrition, at Baseline and Immediately After Treatment (n=17).

Parameters	Before EEN	After EEN (6-8 weeks)	*p*-value
BMI Z-score	-1.03 ± 1.01	-0.55 ± 1.12	p = 0.002[a]
PCDAI score	27.50 (20.00; 40.00)	5.00 (0; 10.00)	p < 0.001[b]
Erythrocyte sedimentation rate, mm/h	49.26 ± 29.16	22.37 ± 15.74	p = 0.002[a]
C-reactive protein, mg/dL	1.34 (0.40; 4.72)	0.18 (0.04; 0.81)	p = 0.003[b]
Faecal calprotectin, μg/g	2000 (1249.50; 3427.50)	904 (231.50; 4023.00)	p = 0.036[b]
Serum albumin, mg/dL	3.80 (3.30; 4.15)	4.50 (4.15; 4.85)	p = 0.020[b]

Values are given as mean ± standard deviation or median (interquartile range); [a] Paired Student's t-test; [b] Wilcoxon signed-rank test.

minal disease is currently recommended regardless of the disease location[4-6,22]. A number of recent reports have illustrated that EEN may have a role beyond luminal CD and it has been shown to be beneficial both in penetrating and stricturing CD, either as an adjunctive therapy or as a bridging therapy[23]. In our study, two patients had stricturing and penetrating behavior; one achieved full remission and the other achieved partial remission, suggesting that EEN can also be useful in this setting. Although there are no firm data on the effectiveness of EEN in severe disease to induce remission, we started EEN in these patients because of malnutrition, as they had a low dietary intake due to poor appetite and aversion to food. This therapy offered the advantage of improving patients' nutritional status as well as enabling the mucosa to heal. They started EEN during hospital stay, with clinical response at two weeks of treatment. Four patients with severe disease achieved full remission and one achieved partial remission at six weeks of treatment.

Numerous studies have shown that EEN leads to improved nutritional status and objective measurements have demonstrated improvement in weight and lean mass during the EEN induction period[24,25]. In accordance with previous data, we found significant improvements in BMI Z-score. EEN also leads to rapid normalization of systemic inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, faecal calprotectin concentration and serum albumin[25-26]. Our findings corroborate this data, as all of these parameters significantly improved.

Although elemental formulas were initially used in EEN, several studies have compared the effect of different types of enteral formulas (elemental vs. polymeric) in the management of CD and found no difference between them[27]. As in most centers, polymeric formulas were preferred because they are better tolerated, more cost effective and require nasogastric tube feeding less often, leading to higher adherence. Their safety profile, minimal associated side-effects and being an option for outpatient care, are also known factors increasing acceptability of EEN[28].

Whilst resting energy expenditure is unchanged throughout disease, there is an alteration in total energy expenditure because of low physical activity at diagnosis, so the child's nutritional status needs to be re-evaluated regularly and the prescribed daily volume must be adjusted accordingly[15]. Despite the combination of hypercaloric and hyperproteic formulas, our patients did not reach the energy requirements, even though protein intake was above the recommendation (1.7 g/Kg). A similar study reached a median of 108% of the estimated energy requirements, which could be explained by the different composition of used formulas[29]. However, this approach led to favorable effects on weight gain and body composition, even in patients who have not lost weight at diagnosis. We emphasize that any successful EEN program must include the determination of caloric and other nutrient requirements, determining the best method of administration, specialized nutritional support and education, and addressing expectations around the time to clinical benefits and total duration of therapy, which can only be achieved by a multidisciplinary team (pediatrician, inflammatory bowel disease nurse specialist, dietitian, and psychologist)[30].

The preliminary nature of our report has inherent limitations that include the small sample size (one single tertiary center), the retrospective study design and the fact that not all eligible patients were consistently included before 2016. Furthermore, the inclusion criteria in the earliest treated patients also included cases with severe disease and malnutrition (five patients in the whole sample). Despite these limitations, our preliminary results corroborate scientific evidence, and provide baseline data for further studies concerning the Portuguese pediatric CD population (where similar data have not been previously reported), with a larger sample and longer follow-up period. Questions remain as to the exact mechanism through which EEN acts, which patients are likely to respond best and the potential of new effective dietary therapies for induction of remission and maintenance therapy.

CONCLUSION

In conclusion, the current study confirms previous observations that EEN is a successful treatment for the induction of remission in pediatric patients with active luminal disease, regardless of the disease location and severity. We highlight the benefits of this therapy and the importance of a multidisciplinary team to offer medical and nutritional support throughout the process.

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