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Efficacy of exclusive nutritional therapy in pediatric Crohn's disease comparing fractionated oral versus continuous enteral feeding

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ABSTRACT

Background: Nutritional therapy has an established role as induction therapy in paediatric Crohn's disease (CD). However, compliance is the main difficulty and may be greatly influenced by the administration route.

Aim: To analyse efficiency of exclusive nutrition to induce remission in children with CD comparing fractionated oral versus continuous enteral feeding.

Methods: The medical records of 106 patients treated by exclusive nutritional therapy (Modulen IBD®) by either oral or continuous enteral route were reviewed retrospectively. Comparative analyses of remission rates, changes in anthropometry, Paediatric CD Activity Index (PCDAI), laboratory indices and compliance rates were performed.

Results: On exclusive enteral nutrition, at 8 weeks, 34/45 patients achieved remission in the oral group (75% on intention-to-treat analysis) and 52/61 (85%) in the enteral nutrition group ($P=0.157$). All patients showed a significant decrease in disease severity assessed by PCDAI ($P<0.0001$) and significant improvements in anthropometric measures and inflammatory indices. No difference was observed whether Modulen IBD® was administered orally or by continuous enteral feeding, apart from weight gain which was greater in the enteral group ($P=0.041$). In a subgroup of patients mucosal healing was evidenced on follow-up endoscopies showing a clear correlation to remission. Compliance rates (87 and 90%) were similar. Nevertheless, non-compliant patients had lower mucosal healing and remission rates.

Conclusions: These retrospective data suggest that the use of fractionated oral nutritional therapy might be as efficacious as continuous enteral administration to induce remission and mucosal healing in children with CD. However, appropriate prospective clinical trials are needed to confirm these findings.

Key words: pediatric, Crohn's disease, enteral nutrition, MODULEN IBD ®

INTRODUCTION

Nutritional therapy has a well established place as induction therapy in Crohn's disease (CD) particularly in paediatric practice (1-5). Exclusive enteral nutrition (EEN) does not only alleviate clinical symptoms, but also markedly improves the patient's nutritional status and his quality of life (6). There is good data showing that EEN rapidly decreases CD activity by influencing the underlying mucosal inflammatory process (7-12). It has been shown that EEN can be as efficacious as corticosteroids in inducing remission in children (13-15), without having their numerous adverse effects. In addition, it is well established that nutritional therapy achieves mucosal healing, whereas corticosteroids do not (16,17). Therefore, in many pediatric IBD centres in Europe EEN is frequently chosen as primary induction therapy for CD. In contrast, in North America only few physicians regularly use EEN (18).

While there is no doubt about the efficacy of EEN as induction therapy, there are major concerns about acceptance of EEN and patients' compliance. Many different dietary treatment protocols were used so far, but the ideal formulation and administration route of EEN for CD are still being studied. A major step forward in the understanding of the use of EN was made with the recent data indicating that enteral diet is efficacious as induction therapy only if given in an exclusive manner, (19,20). Thus patients require a large volume of formula every day for several weeks, traditionally by nasogastric tube feeding, while they are not allowed to eat otherwise. These are major drawbacks and therefore several children and adolescents are unable or unwilling to accept this treatment form with the nasogastric tube the most important limiting factor (20,21).

In the paediatric literature, EN was administered by nasogastric tubes in all but three trials (8,14,22). However, no study ever evaluated the benefit of continuous nasogastric feeding compared to oral consumption of enteral formula **on an exclusive basis as induction therapy for pediatric CD. Thus we aimed to compare the efficacy of oral versus continuous nasogastric feeding, both as strictly exclusive nutritional interventions,** to induce remission in children with CD in a homogenous single IBD center cohort analyzing over 100 patients in a retrospective manner.

MATERIAL AND METHODS

Study design

The medical records of patients with active CD treated by EEN by oral route or via continuous nasogastric tube feeding at the Necker Enfants Malades hospital between January 2004 and January 2010 were retrospectively reviewed. The diagnosis of CD was based on conventional criteria (following the Porto recommendation, 23), including clinical, radiological, endoscopic and histological findings. In all patients, infectious causes, including tuberculosis, were carefully ruled out prior treatment. Only patients with newly diagnosed CD or with a first relapse of an established disease on stable medical treatment were eligible. Patients with steroid treatment or therapy modification during the trial period were excluded. The nutritional formula used was exclusively Modulen IBD® (Nestle, Vevey, Switzerland), a specific oral polymeric diet that is rich in transforming growth factor β_2 . All patients were seen and followed by four pediatric gastroenterologists: two of them preferentially prescribed EEN by oral route, whereas two physicians systematically used EEN by nasogastric tube. Patient assignment to one of the prescribing senior pediatric gastroenterologists was completely arbitrary and determined by the initial physician contact. The caloric requirements were calculated for all patients to define the optimal volume of EEN to be taken (calculation of basal caloric requirement plus additional needs for catch-up growth). EEN was given over an eight week period as induction therapy. The amount of formula was stepwise increased over two to four days. EEN was started during the hospital stay in all patients ensuring tolerance as well as compliance. EEN was administered via a nasogastric tube at a constant flow rate over 24h. No cyclisation was allowed beside a maximal 30min break per day (allowing a comfortable shower). Oral ingestion of Modulen IBD was in form of four "meals" per day, also on an exclusive basis, meaning no additional food or liquid intake. Patients were asked to record the daily Modulen IBD intake. In addition, a weekly home visit of a clinical nutritionist was provided to all patients during the 8 week treatment period thus optimizing paramedical support with the aim to increase treatment compliance. Patients were withdrawn from their Modulen IBD® treatment

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3 if they did not tolerate EN or if they did not achieve clinical remission at the clinical
4 week 4 visit. In addition, non-adherence to the exclusive principle of EN was also
5 considered as treatment failure. Non-compliant patients were analyzed separately in
6 the following.
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10 11 12 **Patient assessment**

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14 Prior to treatment children were assessed clinically to document disease activity
15 using the Paediatric Crohn's Disease Activity Index (PCDAI) (24). Anthropometric
16 data were analysed with reference to age and sex as standard deviation scores.
17 Patients were also assessed serologically for evidence of inflammation, with
18 measurements of serum C-reactive protein, erythrocyte sedimentation rate, serum
19 albumin, haemoglobin count, hematocrit, platelet count and fibrinogen. Colonoscopy
20 was performed in all patients before starting treatment. Follow-up endoscopy at the
21 end of induction therapy was proposed to all patients. However, only 18 patients
22 were willing to undergo a second procedure. The laboratory indices and PCDAI were
23 re-evaluated at week 4 and 8 of treatment and at the end of the period of exclusive
24 Modulen IBD® treatment.
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37 **Data analysis**

38 The primary end point was the proportion of patients achieving remission with
39 the assigned treatment at W8. Remission was defined as a PCDAI < 10 at week 8
40 visit. Secondary analyses were performed on changes in anthropometry, PCDAI,
41 laboratory indices and compliance rates.
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46 The results for continuous variables are given as mean \pm standard deviation (SD).
47 The results for non-continuous variables are given as frequency and percentage.
48 Data at baseline and at follow-up were compared with the use of a Wilcoxon signed-
49 rank test for matched pairs. To determine factors that were predictive of
50 improvement at follow-up, we used the Wilcoxon signed-rank test for matched pairs.
51 Comparisons of quantitative parameters between the two patient groups were done
52 with the Mann-Whitney and the Kruskal-Wallis tests for unpaired groups.
53 Comparisons of qualitative parameters were done with the Fisher's exact test. All
54 statistical analyses were performed using Statview® software 5.0 for Windows (SAS
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Institute, Cary, NC, USA). P values below 0.05 were considered statistically significant.

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RESULTS

A total of 106 children were included in this analysis, with 45 patients receiving Modulen IBD® per os, and 61 by continuous enteral route via a nasogastric tube. In both groups Modulen IBD was given as exclusive EN. All patients presented with moderate to severe disease activity (PCDAI > 30), justifying the use of exclusive nutritional therapy (23). 72% of patients were newly diagnosed as having Crohn's disease, whereas 28% experienced a relapse despite stable medication (azathioprine and/or 5-ASA). None of the patients received biologics when included in this study. The characteristics of each patient group are summarized in Table 1.

There was no significant difference between the two groups in terms of anthropometric data, disease severity, inflammatory parameters and associated treatment. Global tolerance of EN at initiation was excellent, but temporary aggravation of abdominal pain and nausea was observed in 8 patients which subsided rapidly within the first week in all but two children. Treatment was initiated in all patients during the initial hospital stay. Patients receiving enteral nutrition via a nasogastric tube stayed significantly longer in hospital compared to CD patients with exclusive oral nutrition (4.4 versus 2.2 days, respectively). Withdrawal from nutritional therapy due to disease aggravation before completion of the intended eight week period was necessary in 3/45 (7%) in the oral route group and in 3/61 (5%) patients in the continuous enteral group: 3 patients were switched to corticosteroid therapy, and 3 further patients needed a surgical intervention for ileocecal stenosis. No change from oral to enteral nutrition or vice versa was allowed in this study.

Induction of remission at Week 8

The primary endpoint of this study was the rate of complete remission at week 8 follow-up visit: 34 patients achieved remission in the oral group (75% based on an intention to treat analysis) and 52 (85%) in the enteral group ($P = 0.157$). Changes in PCDAI, anthropometric data and laboratory test results after eight weeks of treatment compared to baseline are summarized in Table 2. All patients treated with oral or enteral Modulen IBD® showed a significant decrease in disease severity

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3 assessed by PCDAI ($P < 0.0001$) scores, and significant improvement in
4 anthropometric measures and inflammatory serum indices.
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9 To evaluate the relative efficiency of the two administration routes, PCDAI as well
10 as the individual, clinical and biological parameters were compared between the two
11 groups (Figure 1). At week 4 visit, PCDAI was significantly lower in the continuous
12 enteral group compared to the oral route group (8.5 ± 12.8 vs 13.9 ± 11.2 , $P =$
13 0.01). There was also a trend towards lower levels in the enteral versus oral route
14 group in biological levels, in particular in C-reactive protein measures (11.5 ± 17.1 vs
15 18.6 ± 22.9) and haemoglobin increase ($+0.5 \pm 1.0$ vs $+1.3 \pm 1.6$), although these
16 differences did not reach statistical significance. At the endpoint week 8 visit,
17 however, there was no longer any significant difference between patients receiving
18 Modulen IBD® orally and those receiving it by continuous enteral feeding, apart
19 from weight gain which was greater in the continuous enteral group ($P = 0.041$,
20 Table 3).
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33 Treatment failure is sometimes considered to be related to a failure to comply
34 with enteral nutrition. We therefore evaluated and compared the compliance rates of
35 the two patient groups. All patients complied with the prescribed volume of Modulen
36 IBD®. There was no significant difference between the two groups regarding the
37 amount of Modulen IBD taken (mean: 2,3 vs. 2,2l). However, 4 patients in the oral
38 group (13%) and 6 (10%) in the enteral group did not comply with the exclusivity
39 principle as they admitted to eat other foods besides Modulen IBD® during the 8
40 week study period. The compliance rate was not correlated with initial disease
41 severity. After 8 weeks of treatment, patients who lacked compliance had a lower
42 rate of remission (50% vs 75% in the oral administration group and 66% vs 93% in
43 the continuous enteral group), although this did not reach significance ($P = 0.320$),
44 probably due to the small number of patients involved.
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57 The influence of eventual confounding factors on the global remission rate and
58 disease severity outcome was studied. These factors were initial disease severity,
59 disease localization (ileal, colonic, ileocolonic), associated treatment (azathioprine, 5-
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3 aminosalicylic acid compounds), patient naivety for CD and the daily volume of
4 administered formula. The only factor that significantly influenced the disease
5 outcome was the exclusivity and volume of Modulen IBD® intake, which was
6 correlated with remission achievement ($P = 0.0073$) and PCDAI scores at 8 weeks (P
7 < 0.001). However this correlation disappeared when the volume was reported to
8 the patient's weight.
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11 An important point in this study was the link between mucosal healing and the
12 response to enteral nutrition. Unfortunately, only 16 patients (15%) accepted follow-
13 up endoscopy. Seven of 8 children receiving fractionated oral nutritional therapy
14 showed complete mucosal healing of all ulcerative or erosive lesions at W8
15 endoscopy. However, ileocaecal valve fibrosis did not improve in three of them. The
16 eighth patient not in clinical remission showed somewhat improved but still active
17 ileal ulcerations. Among the children treated by continuous enteral nutrition, complete
18 mucosal healing was observed in 5 of 8 patients, with one patient displaying some
19 very mild but persistent rectal aphthous ulcerations. The remaining two patients on
20 continuous enteral nutrition had still active lesions on follow-up endoscopy. There
21 was a clear correlation between remission and complete mucosal healing. All patients
22 with mucosal healing achieved complete clinical remission, whereas the four patients
23 with remaining active lesions were clinically improved but not in remission. In two of
24 these children, insufficient compliance was documented, whereas the two children
25 developed ileocaecal valve stenosis requiring surgery in the following.
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DISCUSSION

There is excellent clinical experience supporting the use of nutritional therapy as primary induction therapy in CD, particularly in paediatric patients. A recent meta-analysis confirmed (13) that efficacy to induce remission in active CD in children is comparable between corticosteroids and **exclusive** enteral nutrition, thus steroids have numerous adverse effects, namely on growth, bone mineral density and body image. The deleterious effects of corticosteroids on growth and on bone mineralisation are particularly harmful in children, whereas EN does not only allow catch-up growth, but also clearly improves bone health (25). In addition, the cosmetic side effects of steroids are particularly poorly accepted by pre- and adolescent patients, presenting nutritional therapy as a real alternative. The exact mechanisms by which exclusive enteral nutrition induces remission are currently unclear. The traditional hypothesis that enteral nutrition works through decreased dietary antigenic presentation and 'relative bowel rest' as a result of a low residue intake and a continuous low-rate infusion might be questioned. Recent data suggest a marked effect of EEN on the composition of the intestinal microflora (26,27) thereby potentially modulating the intestinal mucosal immunophenotype. The avoidance of some pro-inflammatory trigger factors such as food additives present in the patient's normal diet might be another potential mechanism. The good results obtained in some clinical studies by supplemental rather than exclusive enteral nutrition suggest that already the improvement of the nutritional status of the patient is beneficial, via the repletion of nutrient, trace element or vitamin deficiency implicated in tissue repair mechanisms or in immune defences (28).

The arguments supporting continuous enteral administration versus fractionated oral intake in Crohn's disease are based on the hypothesis of a more efficient anti-inflammatory effect and a higher nutritional benefit due to the continuous contact of the formula with the diseased mucosa along with a relative "bowel rest". It is supposed that this improves tolerance of enteral nutrition, allowing higher volumes. In this study, **the use of EEN in form** of fractionated oral and in form of continuous enteral feeding led to a significant reduction in disease activity assessed by PCDAI and biological indices, and improvements in anthropometric measures. The only

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3 difference evidenced after 8 weeks of treatment was on weight gain, which was
4 greater with nasogastric continuous feeding. Unlike the original hypothesis,
5 continuous contact of the formula on the diseased mucosa did not lead to a greater
6 decrease in inflammatory activity, but continuous enteral feeding might act faster on
7 mucosal inflammation.
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12 However, one has to be cautious when interpreting the results of this study.
13 Even, if the study population is of appropriate size, the retrospective character of this
14 cohort analysis carries a high risk of inherent biases. In an ideal study, patient
15 assignment should be random to one or the other treatment option and followed in a
16 prospective manner. Thus, in our retrospective work, there was no randomisation to
17 either treatment approach. Assignment to fractionated oral or continuous enteral
18 nutrition was conditioned by the prescribing senior pediatric gastroenterologist which
19 limits the interpretation of this work. However, this analysis demonstrates clearly that
20 fractionated oral nutrition is efficacious as induction therapy for pediatric CD further
21 encouraging performing a prospective and randomized clinical trial to address this
22 point appropriately. In addition, a prospective clinical trial would also allow to
23 perform an appropriate quality of life assessment which is particularly important
24 when treating adolescent patients; unfortunately in our retrospective analysis a
25 quality of life assessment was not possible.
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39 The choice of oral administration is usually made to avoid the constraints and
40 psychological impact linked to the wearing of a nasogastric tube 24 hours a day (29).
41 This is particularly important as compliance is the main factor that impairs the clinical
42 response to nutritional therapy. In the meta-analysis performed by Griffiths in 1995,
43 21% of adult CD patients allocated to enteral nutrition were noncompliant (30). No
44 data on compliance were available for the recent meta-analysis in a pediatric cohort
45 (13), however, the recent study of Rodrigues et al. (21), showed a non-adherence
46 rate of approx. 15% in children receiving EN orally or by nasogastric tube (whereas
47 the use of polymeric or elemental nutrition did not impact on compliance). In our
48 population, the overall non-compliance rate was with 9% in the same range as the
49 study of Rodriguez. Several factors can account for the higher compliance rate in
50 pediatric CD patients: parental control, regular support and control provided by
51 dieticians and physicians and the evident benefit on weight and height growth in
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3 children that often suffered from severe growth retardation. The main element that
4 militated against successful adherence in our patients was the inability to stay on a
5 solid-free diet for weeks. In our population, the remission rate was lower among
6 non-compliant patients although the difference was not statistically significant. These
7 data are close to the recent report of Johnson et al. (20) who randomised pediatric
8 CD patients to either total or partial enteral nutrition. The remission rate of patients
9 on partial enteral nutrition was with 15% significantly lower compared to patient who
10 received a 6 week exclusive and total nutritional therapy (42% remission rate). The
11 markedly lower remission rate in this study despite exclusive EN compared to our
12 data might be explained by the shorter treatment period (6 versus 8 weeks) as well
13 as the different nature of the liquid formula used. However, it is important to
14 strengthen that a considerable number of patients (18/50) experienced an early
15 withdrawal related to non-effectiveness of induction therapy or unwillingness to
16 continue exclusive EN.
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29 In a subgroup of patients the impact of fractionated oral or continuous enteral
30 nutrition on mucosal healing could be analysed via follow-up endoscopies. There was
31 a clear correlation between mucosal healing and the induction of remission. Both
32 modes of administration allowed obtaining complete healing of mucosal ulcerations in
33 the vast majority of patients, whereas no significant effect on ileal caecal valve
34 fibrosis was seen. In addition, rectal lesions improved but did not completely
35 disappear. Patients with persistent mucosal lesions did not come into clinical
36 remission and had a poorer compliance compared to those with complete mucosal
37 healing. These data are in keeping with the recent report of Borrelli et al. (14) who
38 observed mucosal healing in 14 of 19 patients on polymeric enteral nutrition.
39 However, as already discussed, given the retrospective character of our study and
40 the very limited number of patients with follow-up endoscopies, these data have to
41 be confirmed in well designed and larger studies.
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53 It is often considered that disease localisation influences the efficiency of total
54 enteral nutrition. Afzal et al. (31) evidenced a lower response rate in terms of PCDAI
55 fall, endoscopic and histological mucosal healing among children with isolated colonic
56 CD compared to those with ileal or ileocolonic forms. In our study population
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3 however the site of disease activity had no impact on response to nutritional therapy,
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5 in keeping with the recent data of Buchanan et al (22).
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7 In summary, nutritional therapy **based on the exclusivity principle** is highly
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9 efficacious in inducing remission in pediatric CD. The present study suggests that the
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11 mode of administration does not markedly interfere with its anti-inflammatory
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13 efficacy, however, as shown in previous trials the exclusivity of oral or enteral
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15 nutrition seems to be the crucial and decisive factor for induction of remission. Our
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17 data suggest that oral intake of a solid-free diet for eight weeks **on an exclusive basis**
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19 is a real alternative to rather aggressive enteral therapy via tube feeding to induce
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21 remission in children with CD. However, this has to be validated by a well designed
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23 and powered randomized prospective clinical trial.
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18 **Figure Legends**

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22 **Figure 1:** Efficacy of induction therapy in pediatric Crohn's disease by the use of
23 exclusive enteral nutrition (EEN) comparing fractional oral to continuous enteral
24 feeding. Reduction of the PCDAI scores after 4 and 8 weeks of exclusive Modulen
25 IBD® treatment comparing oral to enteral route of administration. Only at W4 a
26 significant difference was observed (* p<0.01) favouring continuous enteral feeding,
27 no significant difference between the two administration routes was seen at the
28 endpoint W8.
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37 Declaration of conflict of interest

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46 work. The other co-authors do not have any conflict of interest to declare.
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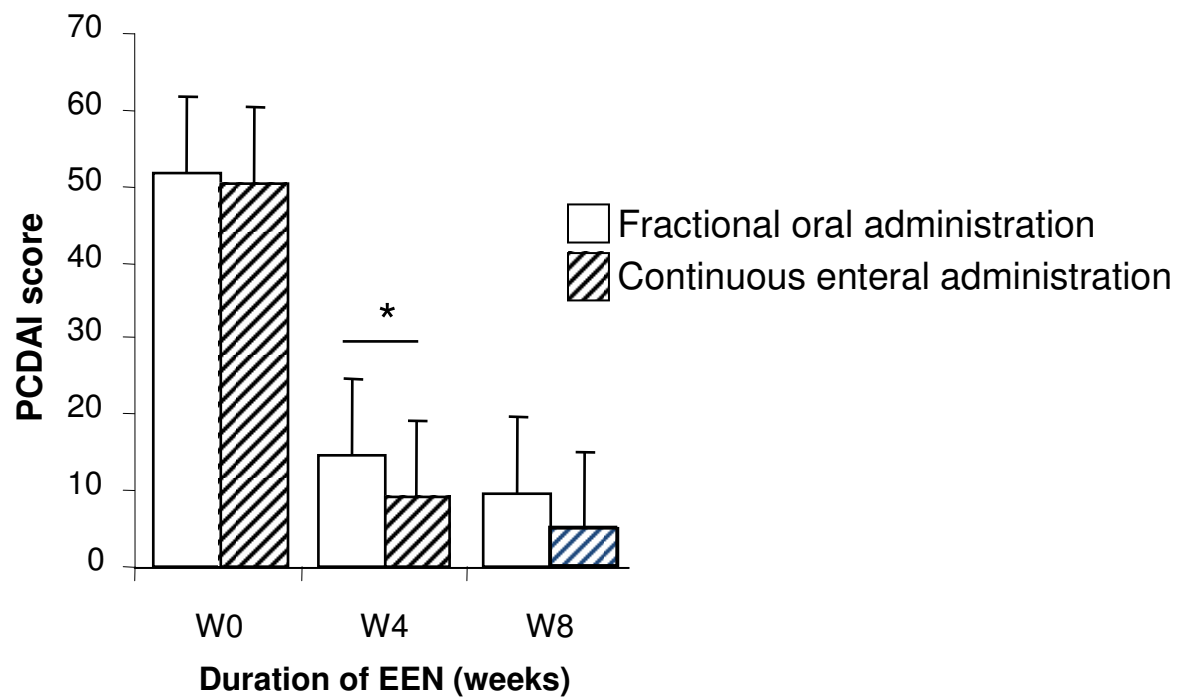
Figure 1

Table 1: Demographic data and disease characteristics of children with Crohn's disease (CD) receiving exclusive enteral nutrition as induction therapy comparing two groups: EEN via the oral route or as continuous enteral feeding (intergroup analysis).

	Oral route (n=45)	Continuous enteral feeding (n=61)	<i>P</i> value
Age at inclusion (yrs) *	11.3 ± 3.4	10.9 ± 3.4	0.202
Gender (% males)	69	64	0.584
Newly diagnosed (%)	76	68	0.701
PCDAI*	51.6 ± 16.3	49.6 ± 15.4	0.661
Weight z-score (SDS) *	- 1.2 ± 1.2	- 1.3 ± 1.3	0.825
Height z-score (SDS) *	- 0.4 ± 1.2	- 0.6 ± 1.3	0.091
Disease localization (%)			
Ileal	28	22	0.076
Colonic	14	12	0.757
Ileocolonic	58	64	0.612
Laboratory indices*			
CRP (mg/l)	59.9 ± 38.8	53.3 ± 37.9	0.927
ESR (mm/hr)	40.2 ± 22.7	37.2 ± 20.6	0.618
Albumin (g/l)	27.9 ± 6.6	27.7 ± 4.6	0.803
Haemoglobin (g/dl)	10.5 ± 1.5	10.6 ± 1.3	0.415
Hematocrit (%)	33.2 ± 3.9	34.2 ± 3.9	0.375
Platelets (x10 ⁹ /l)	503 000 ± 140 000	514 000 ± 130 000	0.732
Fibrin (g/l)	6.1 ± 0.8	5.9 ± 0.8	0.549
Associate medical therapy			
5-aminosalicylic acid compounds	10/45	11/61	0.260
Azathioprine	11/45	15/61	0.619

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; *Values are mean ± SD

Table 2. Changes in disease activity, anthropometry and serum indices after 8 weeks of exclusive enteral nutrition as induction therapy for pediatric Crohn's disease compared to disease onset according to route of administration. (Separate intragroup-analyses for fractionated oral route and continuous enteral feeding analyzing treatment effects between W8 and W0)

	Fractionated oral route (n=45)	<i>P</i>	Continuous enteral feeding (n=61)	<i>P</i> value
PCDAI	- 41.6 ± 20	< 0.0001	- 44.5 ± 16	< 0.0001
Weight gain (kg)	4.6 ± 3.2	< 0.0001	5.9 ± 2.9	< 0.0001
Height gain (cm)	0.7 ± 1.0	0.036	1.2 ± 1.2	< 0.0001
Laboratory indices				
CRP (mg/l)	- 49.0 ± 74.0	0.001	- 42.3 ± 35.9	< 0.0001
ESR (mm/hr)	- 21.1 ± 23.0	< 0.0001	- 27.6 ± 22.6	< 0.0001
Albumin (g/l)	13.4 ± 13.6	0.0001	12.7 ± 6.6	< 0.0001
Haemoglobin (g/dl)	1.2 ± 1.3	0.0001	0.6 ± 1.1	0.0007
Hematocrit (%)	2.7 ± 3.4	0.001	1.0 ± 3.3	0.137
Platelets (x10 ⁹ /l)	- 83 000 ± 130 000	0.004	- 120 000 ± 107 000	< 0.0001

Table 3. Disease activity, anthropometry markers and laboratory tests at 8 weeks of exclusive enteral nutrition as induction therapy for pediatric Crohn's disease comparing the two routes of administration fractionated oral route versus continuous enteral feeding (intergroup analysis)

	Fractionated oral route (n=45)	Continuous enteral feeding (n=61)	<i>P</i> value
Remission	34/45	52/61	0.157
PCDAI	9.6 ± 11.6	5.0 ± 6.5	0.138
HBI	1.0 ± 1.3	0.7 ± 1.5	0.179
Weight gain (kg)	4.6 ± 3.2	5.9 ± 2.9	0.041
Height gain (cm)	0.7 ± 1.0	1.2 ± 1.2	0.105
Laboratory indices			
CRP (mg/l)	12.1 ± 18.3	7.7 ± 8.2	0.812
ESR (mm/hr)	17.1 ± 19.6	10.5 ± 8.8	0.112
Albumin (g/l)	38.2 ± 6.8	39.6 ± 4.7	0.931
Haemoglobin (g/dl)	11.8 ± 1.2	11.6 ± 1.0	0.067
Hematocrit (%)	36.4 ± 3.1	35.2 ± 2.7	0.618
Platelets (x10 ⁹ /l)	407 000 ± 99 000	401 000 ± 96 000	0.845
Fibrin (g/l)	4.6 ± 1.7	3.5 ± 0.9	0.246