Exclusive Enteral Nutrition Promotes Clinical Remission and Mucosal Healing of Southern China Pediatric Crohn's Disease in Short Time

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Abstract

Background: this study aimed to understand the effective of exclusive enteral nutrition on clinical remission and mucosal healing with pediatric Crohn's disease (CD) in a real-world setting in southern China.

Methods: In this prospective disease registry, children (aged between 2 and 18 years) with newly diagnosed luminal CD were recruited from December 2018 to December 2020. Patients were examined at baseline and at weeks 3 and 8 of EEN induction. Logistic regression analysis is used to assess the influencing factors of EEN.

Results: The clinical remission and mucosal healing rate of children is 76.5%–35% separately after 8 week induction. The remission rate of mild CD is higher than that of moderate-severe CD, but it is not statistically significant ($p=0.01$). Disease location–age–the response rate at week 3 all do not predict the effectiveness of EEN treatment.

Conclusions: EEN can effectively promote clinical remission and mucosal healing of southern China pediatric Crohn's disease in short time and is also recommend as the first-line therapy for children with severe luminal CD

Background

Crohn's disease (CD) is a chronic non-specific intestinal inflammatory granulomatous disease of unknown etiology. About 25% of patients are diagnosed before the age of 18 years old(1). The past decade has seen significant advances in the care of children with CD. Compared with adult-onset CD. Paediatric onset CD is a more severe phenotype with the additional issues of growth failure, delayed puberty, poor bone density and psychosocial problems. In recently years, the incidence rate of children in both developed countries and developing countries has increased gradually. Current various drugs for induction of remission include exclusive enteral nutrition(EEN), corticosteroids(CS)and biologic agents. For pediatric patients, therapeutic choices must also take growth and development into account. Voiketal since 1970(2) first report EEN can significantly improve intestinal inflammation in patients with luminal CD, which has been reported in many studies effectively induces clinical remission, improves the nutritional status of children, promotes growth and development, reduces the risk of recurrence, and enables the timely completion of vaccination before immunotherapy(3, 4).

Many meta-analysis reveals that there is no significant difference between EEN and corticosteroids in the efficacy of inducing remission rate of CD in a pediatric population(5, 6). Several reviews also report that EEN provide similar improvement as IFX in clinical symptoms(7, 8), moreover EEN has less side effects. However, there are great differences in the choice of EEN therapy for children with CD in different countries around the world. 62% of gastroenterologists in Western Europe are willing to choose EEN therapy as first-line induction therapy, while only 40% in North America(9) .In Asian countries, 82% of Japanese IBD physicians recommend EEN for the treatment of children with CD at first diagnosis(10).The

guidelines of our country also recommend EEN as the first-line therapy for children with mild-to-moderate luminal CD(11), however the clinical utilization rate of EEN in different regions varies. Recently with an expanding therapeutic armamentarium, there has been a shift of therapeutic goals from symptom control alone towards mucosal and transmural healing with consequent reduction of bowel damage. but the literature of EEN on mucosal healing in CD is scarce, in addition, EEN is mainly recommended as mild-to-moderate patients, so our study aims to assess the early remission and mucosal healing rate of EEN treatment in Chinese southern patients with CD, also concurrent evaluate the effectiveness of EEN in the treatment of severe CD. meanwhile we also analyze the influencing factors of EEN, helps to optimize in clinical application, to increase domestic pediatrician's emphasis on EEN..

Methods

Patients

This is a single-center retrospective cohort study. All patients with Crohn's disease newly diagnosed between December 2018 and December 2020 at Guangzhou Women and Children's Medical Center, a tertiary children hospital, were recruited. Inclusion criteria: Confirmed with luminal Crohn's disease aged 2 to 18 years; EEN treatment for 8 weeks was received and followed up. Exclusion criteria: Combination of other drugs (salicylic acid drugs, corticosteroids, immunosuppressant or biological agent, thalidomide); Recurrent patients. The diagnostic criteria for Crohn's disease refer to the Consensus of Diagnostic Specifications for Inflammatory Bowel Disease in Children(11) .All parents signed the informed consent for treatment.

Data were collected from the electronic medical records of the patients, including demographics, height, weight, clinical manifestations, disease behaviors and locations, compliance to EEN treatment .Laboratory findings and endoscopy were collected before and after induction therapy.

Study design

The primary objectives of the study were to the rate of clinical and endoscopic remission after 8 weeks of induction therapy with EEN. Secondary objectives included influence factors related to EEN treatment. A poly-meric formula had been administered orally or through a nasal feeding tube to induce remission. The formula volume had been based on the estimated energy requirements for an ideal weight, with consideration of height. Clinical remission was defined as a PCDAI (pediatric Crohn' s disease activity index) score ≤ 10 (11). Endoscopic remission was defined as a CD-SES(simple endoscopic score for Crohn's disease) score ≤ 3 (12) .Clinical response: PCDAI score decreased ≥ 12.5 . Endoscopic response refers to a drop in score of one grade, from severe to moderate activity, and so on.

Follow up

All the eligible patients were followed through Medical care network platform. we can monitor the children's daily milk volume, clinical symptoms, adverse reaction, and communicate with the parents.

Statistical analysis

Statistical analysis was performed using SPSS17.0. Data are presented as interquartile range according to distribution unnormality. The difference between both groups was analyzed by The Wilcoxon signed rank test or Fisher's exact test. a multivariable logistic regression analysis was performed to predict remission by week 8 .A p-value ≤ 0.05 was considered statistically significant.

Ethical considerations

All methods were performed in accordance with the Declaration of Helsinki and complied with relevant guidelines and regulations. The Ethics Committee of Guangzhou Women and Children's Medical Center approved the study (No. [2021]148A01). The written informed consent were provided by participant's parents /guardians..

Results

demographic characteristics

During the study period, thirty-four patients completed the registry, thirty-three cases were fed orally, and one case was fed through nasogastric tube. they all came from the southern China, Guangdong and Guangxi, a coastal cities. The mean age at diagnosis was 10 years (range: 7.8 to 13years), nineteen patients (55.9%) were male. Three patients had family history. One of the children had a brother who was diagnosed with Crohn's disease at the age of 10 years and died at the age of 14 years. The child was also diagnosed with Crohn's disease at the age of 10 years and was eventually diagnosed with X-linked inhibitor of apoptosis deficiency (XIAP) by Whole-exome sequencing. The other two patients were siblings in the same family who developed symptoms at the same time and were all diagnosed with Crohn's disease.

Abdominal pain (96.9%), weight loss (81.8%), anemia(58.8%), fever (54.5%), and diarrhea (44.1%) were the most common symptoms of CD. Less common symptoms were bloody stool (21.2%). Oral ulcer (21.2%) were the most common extra-intestinal manifestations. uveitis were relatively uncommon (Fig. 1)

Response and Remission at Week 3

Twenty-eight children (82.4%) had a clinical response at week 3, and Twenty-four children (70.6%) achieved clinical remission.

Remission and Remission at Week 8

Among the 28 diet-responsive patients at week 3, 26 subsequently achieved remission by week 8, clinical remission was 76.5%.The clinical remission rate of children with mild activity was 100%, moderate activity was 66.7%, severe activity was 66.7%, there was no statistical significance ($P = 0.11$).Then we compared the clinical remission rate of different age groups, the remission rate of 2–6 years old was

50%, 7–10 years old was 84.6%, and > 10 years old was 82.4%, the difference was not statistically significant ($P = 0.298$).

The endoscopic response rate and remission rate were 80%(16/20) and 35%(7/20) respectively in 20 CD patients after 8 weeks of treatment. The result showed that CRP, ESR, PCDAI scores and SES-CD scores were significantly decreased and significant increase in albumin, hemoglobin were observed after induction. Weight and height of children increased compared with baseline, with statistical significance ($P < 0.05$) (see Table 1).

Table 1
Comparison between Pre- and Post-induction Variables

Variable	Before EEN	After 8 week of EEN	Statistic	P-value
Hb(g/L)	101(88–109)	115(111–124)	-4.037	0.00
Alb(g/L)	32(29-35.80)	43(40-44.90)	-4.541	0.00
CRP(mg/L)	42.14(22.90-53.08)	0.88(0.30–4.72)	-4.397	0.00
ESR(mm/h)	48(40–72)	12(5–20)	-4.266	0.00
PCDAI	32.5(25–40)	0(0–5)	-4.547	0.00
SES-CD	19.5(12.25-21.0)	4.5(2.25-6.0)	-3.827	0.00
Weight(kg)	25(19.4–36.9)	28(22.5–36.9)	-4.542	0.00
Height(m)	140(121–155)	141(123–156)	-3.666	0.00
EEN: exclusive enteral nutrition, Hb: hemoglobin, Alb: albumin, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PCDAI: Pediatric Crohn's Disease Activity Index, SES-CD: simple endoscopic score for Crohn's disease				

Influencing factors of clinical remission after 8weeks of EEN treatment

26 patients in clinical remission group and 8 patients in non-remission group after 8 weeks induction of EEN. Demographic data (gender, age of onset, duration of symptoms, site of disease), clinical indicators (IBM, HB, CRP, ESR, ALB, PCDAI and SES-CD before treatment) and clinical manifestations were compared between the two groups, the result showed ESR of the clinical remission group was higher than that of the clinical non-remission group. There were no statistical significance in other indicators (see Table 2).

Table 2
Comparison between remission group and non-remission Variables

Variable	Clinical remission(n = 26)	Clinical non- remission(n = 8)	P-value
Gender(male%)	61.5	50	0.667
Age-onset(year)	10.5(7.98-13.0)	9(6.25– 11.90)	0.137
Symptom Duration (month)	3.0(2.0–12.0)	11(5–24)	0.124
Disease location(%)			
Bowel disease	23.1	25	1.0
ileocolonic disease	57.7	37.5	0.429
colonic disease	19.2	25	1.0
BMI(kg/m2)	13.2(12.6– 14.3)	13.8(11.1– 14.5)	0.464
CRP	43.2(22.6– 56.5)	48.1(32.8– 59.8)	0.282
ESR	51(40–75)	28.0(10.5–43.5)	0.025
PCDAI at baseline	32.5(23.8–38.1)	35(30–49)	0.115
SES-CD at baseline	20(13.5–21)	8.5(5–18)	0.082
intestinal symptoms			
abdominal pain	96.15	100	1.0
mild*(%)	92.3	62.5	0.072
moderate*	7.9	37.5	
diarrhea	53.8	25	0.233
hemafecia	19.2	25	0.165
fever	53.8	62.5	1.0
extraintestinal symptoms	30.7	0	0.296
BMI: body mass index, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PCDAI: Pediatric Crohn's Disease Activity Index, SES-CD: simple endoscopic score for Crohn's			
disease.			
* FLACC pain score: 0 for comfort, 1–3 for mild discomfort, 4–6 for moderate pain, and 7–10 for severe pain			

In a multivariable analysis including age of onset (< 10 years), duration of symptoms, ESR and CRP before treat, degree of abdominal pain, clinical response rate at week 3, the results showed that there was no independent influencing factor for clinical remission at 8 weeks in children with CD (see Table 3).

Table 3
Multivariate analysis of EEN therapy

Influence factor	Regression	P-value	OR	95%CI
Age-onset	0.665	0.423	1.944	0.383–9.886
Symptom duration	-0.058	0.09	0.944	0.883–1.009
Degree of abdominal pain	1.974	0.05	7.2	0.944–54.939
ESR	0.037	0.05	1.038	0.999–1.078
CRP	0.002	0.847	1.002	0.978–1.027
PCDAI at baseline	-0.094	0.062	0.91	0.824–1.005
Response rate at week 3	-22.589	0.998	0	0

Discussion

Our study confirm the effectiveness of EEN in the treatment of CD in children. In this study, 26 patients (76.5%) achieve clinical remission. The clinical remission rate reported in most previous literatures was 80%-85%(13), our result is consistent with them. In this study, we find that the remission rate of mild CD is higher than that of moderate-severe CD, but it is not statistically significant. Approximately 25% patients in our study are severe CD, and the clinical remission rate after EEN induction is as high as 67%. Mucosal healing is a new therapeutic goal in recent years. It indicates long-term clinical remission, less intestinal complications (such as fistula formation, enterostenosis) and surgical intervention. Therefore, endoscopic changes are an important indicator to evaluate the therapeutic effect. However, there are very few studies provided information on mucosal healing of patients at the end of induction. Several studies in western countries have found that EEN can induce early mucosal healing rate of 18.9%-58%(3, 14). Studies in Shanghai and Zhejiang in China respectively reported that EEN could induce mucosal healing rate of 67.7%(15) and 71.4%(8). In our study, Among the 34 patients, all the 20 patients underwent endoscopic examination after 8 weeks of induction therapy, except for 6 patients who did not receive endoscopy and 8 small bowel Crohn patients who were not eligible for SES-CD score. 7 patients (35%) achieve mucosal healing, and the endoscopic response rate could reach 80%. It seems that our study was consistent with western studies, but lower than the domestic study significantly. We find that SES-CD ≤ 4 was defined as remission in Shanghai study which may lead to higher mucosal healing rate. Only 7 people in the Zhejiang study completed the endoscopic at 8 weeks, which may lead to a high rate of mucosal healing. Kierkus J and Hu respectively report that early mucosal healing rate of CD treated by IFX is 22.7%(16) and 42%(17). It suggests that EEN can alleviate the clinical symptoms and improve the endoscopic mucosal lesions of CD patients in the short term. After achieving induced remission, patients who received EEN treatment seemed to gain more weight and height, the data are statistically significant. which is consistent with the results of previous studies(18), indicating that EEN can improve the nutritional level and growth of children in a short time in our study.

We also analyze the influencing factors of EEN efficacy. The results show that ESR affects EEN efficacy. In this study, we also observe that patients with colonic CD have a higher clinical remission rate compared with those with small intestine and ileocolonic CD, but no significant difference is reached, which is consistent with the results of Zubin grover study(3). However, the results of a multi-center study in Spain (19) showed that patients with colonic CD had better efficacy for EEN when lesions involved in ileum. Buchanane(20) believed that EEN efficacy was independent of CD site. Therefore, the results of the present study are still controversial and need to be further studied. The early treatment effect can well predict the efficacy of a certain treatment plan. Rotem(21) reported that the remission rate at the 3rd week can predict the efficacy of EEN at 8st week, as to can guide the timely adjustment of treatment plan, and achive individualizad treatment for children. However, our results in this study are inconsistent with it, possibly because the sample size is too small, and we need further clinical studies in the later stage. Lafferty(22) displayed EEN was less effective in patients aged under 10 years, our study show that there is no difference among different ages.

Compliance is often the main reason why parents and children refuse EEN treatment. EEN requires children and parents to strictly administer liquid formula only and avoid any oral food intake for 6 to 8 weeks(23). A questionnaire survey on EEN attitudes of children and their parents in the United States shows that formula milk has poor taste, monotonous variety, high cost and worries about school social interaction are the main obstacles. However, the compliance of the children in this study was very high. All the patients and their parents agreed that EEN was basically fed with formula milk through mouth, and only one person was fed through a nasal feeding tube due to poor nutritional status. We explored the possible reason for such high compliance because we encouraged the children to continue enteral nutrition treatment at home after the condition of the children was stable. In addition, the knowledge of enteral nutrition was publicized to parents through the public network platform of the hospital, and special IBD nurses were assigned to supervise the diet of patients every week, so as to reduce the frequency and cost of hospitalization and soothe the anxiety caused by repeated hospitalization of children.

Our study has several limitations. First, the number of patients were small, which may have caused a lack of observed statistical differences. Second, we did not evaluate mucosal healing in a subset of our patients with small bowel Crohn's disease.

Conclusions

EEN has a good effect on children with CD in South China with high compliance and no drug side effects. EEN can better improve the nutritional level and growth and development, and can be recommended as the first-line treatment for induced remission in children with acute active mild-severe Crohn's disease in China.

Declarations

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Authors' contributions

Liya Xiong and Peiyu Chen participated in the design of the study, selection of the participating patients, analysis, and article writing. Jing Xie, Lu Ren, Peiqun Wu, Linqing Yuan, Huiwen Li, Hongli Wang and Lijuan Wei participated in data collection. Qian Xu participated in data statistics. Lanlan Geng and Sitang Gong participated in the design of the study, and revising the writing on manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki and complied with relevant guidelines and regulations. The Ethics Committee of Guangzhou Women and Children's Medical Center approved the study (No. [2021]148A01). The written informed consent were provided by participant's parents /guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Turunen P, Ashorn M, Auvinen A, Iltanen S, Huhtala H, Kolho KL. Long-term health outcomes in pediatric inflammatory bowel disease: a population-based study. *Inflamm Bowel Dis*. 2009;15(1):56-62.

2. Voitek AJ, Echave V, Feller JH, Brown RA, Gurd FN. Experience with elemental diet in the treatment of inflammatory bowel disease. Is this primary therapy? *Arch Surg*. 1973;107(2):329-33.
3. Grover Z, Muir R, Lewindon P. Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease. *J Gastroenterol*. 2014;49(4):638-45.
4. Cohen-Dolev N, Sladek M, Hussey S, Turner D, Veres G, Koletzko S, et al. Differences in Outcomes Over Time With Exclusive Enteral Nutrition Compared With Steroids in Children With Mild to Moderate Crohn's Disease: Results From the GROWTH CD Study. *J Crohns Colitis*. 2018;12(3):306-12.
5. Swaminath A, Feathers A, Ananthakrishnan AN, Falzon L, Li Ferry S. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2017;46(7):645-56.
6. Yu Y, Chen KC, Chen J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. *World J Pediatr*. 2019;15(1):26-36.
7. Lee D, Baldassano RN, Otley AR, Albenberg L, Griffiths AM, Compher C, et al. Comparative Effectiveness of Nutritional and Biological Therapy in North American Children with Active Crohn's Disease. *Inflamm Bowel Dis*. 2015;21(8):1786-93.
8. Luo Y, Yu J, Lou J, Fang Y, Chen J. Exclusive Enteral Nutrition versus Infliximab in Inducing Therapy of Pediatric Crohn's Disease. *Gastroenterol Res Pract*. 2017;2017:6595048.
9. Stewart M, Day AS, Otley A. Physician attitudes and practices of enteral nutrition as primary treatment of paediatric Crohn disease in North America. *J Pediatr Gastroenterol Nutr*. 2011;52(1):38-42.
10. Ishige T, Tomomasa T, Tajiri H, Yoden A, Japanese Study Group for Pediatric Crohn's D. Japanese physicians' attitudes towards enteral nutrition treatment for pediatric patients with Crohn's disease: a questionnaire survey. *Intest Res*. 2017;15(3):345-51.
11. 中华医学会儿科学分会消化专业组. 儿童克罗恩病诊断与治疗方案共识意见. *中华儿科杂志*. 2019;7(57).
12. Sipponen T, Nuutinen H, Turunen U, Farkkila M. Endoscopic evaluation of Crohn's disease activity: comparison of the CDEIS and the SES-CD. *Inflamm Bowel Dis*. 2010;16(12):2131-6.
13. Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2018;4:CD000542.
14. Tang W, Huang Y, Shi P, Wang Y, Zhang Y, Xue A, et al. Effect of Exclusive Enteral Nutrition on the Disease Process, Nutrition Status, and Gastrointestinal Microbiota for Chinese Children With Crohn's Disease. *JPEN J Parenter Enteral Nutr*. 2021;45(4):826-38.

15. Li Y, Chen B, Gao X, Hu N, Huang M, Ran Z, et al. Current diagnosis and management of Crohn's disease in China: results from a multicenter prospective disease registry. *BMC Gastroenterol*. 19(1):145.
16. Kierkus J, Dadalski M, Szymanska E, Oracz G, Wegner A, Gorczewska M, et al. The impact of infliximab induction therapy on mucosal healing and clinical remission in Polish pediatric patients with moderate-to-severe Crohn's disease. *Eur J Gastroenterol Hepatol*. 2012;24(5):495-500.
17. 李宇, 陈博, 高翔, 胡宁, 黄明, 冉卓, 等. 中国克罗恩病诊断和管理现状: 一项多中心前瞻性疾病注册研究结果. *中华消化杂志*. 2019;2(3).
18. Miller T, Suskind DL. Exclusive enteral nutrition in pediatric inflammatory bowel disease. *Curr Opin Pediatr*. 2018;30(5):671-6.
19. Moriczi M, Pujol-Muncunill G, Martin-Masot R, Jimenez Trevino S, Segarra Canton O, Ochoa Sangrador C, et al. Predictors of Response to Exclusive Enteral Nutrition in Newly Diagnosed Crohn's Disease in Children: PRESENCE Study from SEGHP. *Nutrients*. 2020;12(4).
20. Buchanan E, Gaunt WW, Cardigan T, Garrick V, McGrogan P, Russell RK. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. *Aliment Pharmacol Ther*. 2009;30(5):501-7.
21. Sigall Boneh R, Van Limbergen J, Wine E, Assa A, Shaoul R, Milman P, et al. Dietary Therapies Induce Rapid Response and Remission in Pediatric Patients With Active Crohn's Disease. *Clin Gastroenterol Hepatol*. 2021;19(4):752-9.
22. Lafferty L, Tuohy M, Carey A, Sugrue S, Hurley M, Hussey S. Outcomes of exclusive enteral nutrition in paediatric Crohn's disease. *Eur J Clin Nutr*. 2017;71(2):185-91.
23. Mehta P, Pan Z, Furuta GT, Kim DY, de Zoeten EF. Parent Perspectives on Exclusive Enteral Nutrition for the Treatment of Pediatric Crohn Disease. *J Pediatr Gastroenterol Nutr*. 2020;71(6):744-8.

Figures

Figure 1

intestinal symptoms and extraintestinal manifestations in pediatric Crohn' disease