MANAGEMENT OF PAEDIATRIC CROHN'S DISEASE USING EXCLUSIVE ENTERAL NUTRITION IN THE INDIAN SUBCONTINENT

[1]Lekha Sreedharan, [2] Dhanasekar Kesavelu, [3]Anusuya Devi
[1] Senior Clinical Dietitan, [2] Consultant Paediatric Gastroenterologist , [3]Associate Professor
[1] Department of Dietetics, Apollo Children's Hospitals, Chennai,India

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease that may affect any part of the gastrointestinal tract from mouth to anus. [1] In 1970's, nutritional therapy was first introduced as a treatment for CD.[2]
Nutritional support using enteral nutritional therapy includes the use of formulas and is usually administered in two methods:
1. Exclusive Enteral Nutrition (EEN) where enteral nutrition is used as primary medical therapy to induce remission.
2. Partial Enteral Nutrition where enteral nutrition is given in addition to a diet, with the primary goal to improve nutritional status and to maintain remission.[3]
Some therapies have key roles in inducing disease remission, while other treatments are utilized to maintain remission. One such intervention that is known to induce remission is EEN, which involves the administration of a liquid nutritional product, while excluding normal dietary components.[4] EEN has an anti-inflammatory effect and induces clinical remission after the onset of therapy.[5] Within the gut lumen, EEN modulates bacterial flora and reduces the intestinal inflammation.[6] EEN also has direct anti-inflammatory effects on intestinal epithelial cells by down-regulating mucosal pro-inflammatory cytokines.[7-8] In addition, it is well documented in the literature that EEN helps in mucosal healing whereas the same effect is not exhibited by corticosteroids. [9]
In 2006, the European Society for Clinical Nutrition and Metabolism and the Japanese Society for Paediatric Gastroenterology, Hepatology and Nutrition published guidelines recommending that EEN can be considered as the first-line induction therapy in paediatric CD, followed by same conclusions by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition in 2010.[10-12]
EEN has anti-inflammatory potential when given on an exclusive enteral basis, without any other food.[13]
EEN helps in achieving clinical remission.[14]
Children and adolescents are at the risk of impaired growth and delayed pubertal development due to untreated Crohn's disease. [15] Subsequent to diagnosis, many children have ongoing problems in maintaining weight which is appropriate for their age. The weight loss is due to the anorexic effects of mucosa derived through pro inflammatory cytokines.[16] Hence a therapy that leads to resolution of gut inflammation, improving nutrition and growth could therefore be considered as an best therapy for the management of CD in children and adolescents.[17]
EEN fits into all the above criteria by meeting the nutritional needs, reducing inflammatory response, promoting mucosal healing and more importantly in eliminating the unwanted and long term side effects vis-à-vis with corticosteroids.
Our study is a prototype study and first of its kind in Indian children with CD. We have shown that the data that is available globally can be translated to Indian population and the results are promising. This study describes our experience of treating paediatric CD with EEN.

MATERIALS AND METHODS

Research design

Prospective observational study

Locale

The study conducted in a tertiary level children's hospital in India

Inclusion criteria

1-17 year old children with confirmed diagnosis of CD (as per PORTO Criteria)

Exclusion criteria

- Parent's & care takers who have declined to be part of the study.
- Children less than 1year of age.
- Children on steroid treatment or who have undergone therapy modifications during the trial period was excluded.

Patient and family education

Before the commencement of the therapy, parents and children were counselled by the attending paediatric gastroenterologist and clinical dietician. Along with the child, family were counselled about the treatment and treatment options i.e. the use of oral steroid or the EEN. The benefits versus risks were explained for both the therapies. The cost to be inferred was discussed and patient leaflets were provided for any remaining unanswered questions.

Once the decision was made by the parents / patient, EEN was commenced on outpatient basis. The daily nutritive allowances were adjusted according to the individual needs. Children were allowed to drink water, a can (300 ml) of fizzy drink of their choice and a handful of hard boiled candies on a daily basis to keep them motivated during the period of EEN therapy. This also helped to avoid drop outs. Patients were seen by the dietician and the clinician on a daily basis, during the first week (minimum 5 visits), to ensure compliance to the therapy and to monitor any side effects. In addition, a weekly contact (telemedicine/phone) with the dietician and the clinician was provided to all patients during entire treatment. EEN using polymeric / semi-elemental formula was given over a 6-8weeks period with regular monitoring and ensuring compliance. Key assessments included feed tolerance, achievement of target calorie, weight changes and inflammatory markers. At the end of the EEN therapy, balanced soft diet was introduced slowly with reductions in the formula feeds on an individual basis.

Treatment failures were as follows:

- Patients' intolerance towards enteral nutrition.
- Unachieved clinical remission in the first 15 days after commencement of therapy.
- Non-adherence towards EEN.

Clinical and Nutritional Assessment

PCDAI using the Cincinnati online score [18] was used to monitor disease activity and progress.

Nutritional status was analysed with reference to age and gender using weight for height, height for age and BMI for age percentile using World Health Organization's growth charts.

Laboratory blood investigation included complete blood count, serum C-reactive protein, Serum albumin and Erythrocyte Sedimentation Rate.

Oral Azathioprine (Thiopurine) was started for all patients at the commencement of EEN on day 1. The side effects were monitored specifically for bone marrow suppression and pancreatitis. After the commencement of azathioprine, all the patients had CBC and Amylase for four consequent weeks and monthly every 3 months subsequently. Faecal calprotectin test was also done in few cases by the clinician.

Upper gastrointestinal endoscopy and colonoscopy was performed in all patients before commencement of EEN therapy. Standard mucosal biopsies (10 sites) were obtained for histopathology.

The nutritional status, clinical parameters and PCDAI were re-evaluated at the end of EEN therapy.

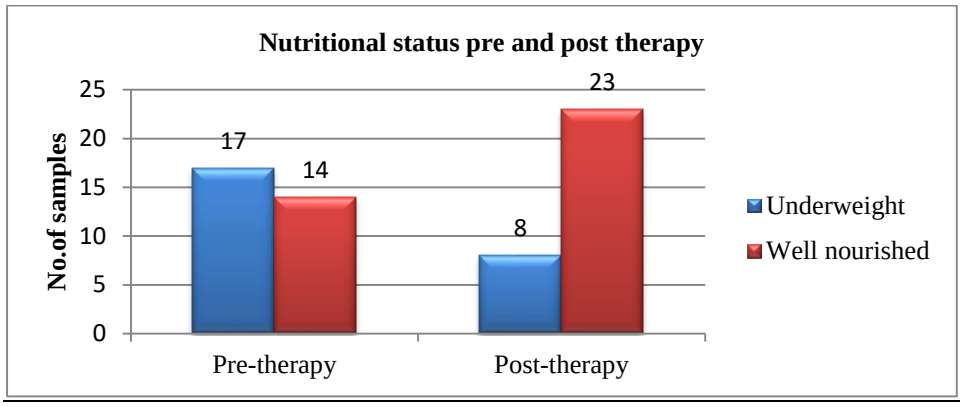
Statistical Analysis

All collected data was transcribed into a Microsoft Excel® database and statistically analysed for descriptive analysis, paired' test and independent't' test using SPSS software version 20.0. A statistical significance was considered at $p < 0.05$.

RESULTS

Thirty three (n= 33) children with confirmed CD were identified. Among that 2 children were excluded as they discontinued EEN during the treatment period. After exclusion, 31 children were included in the study. In the cohort, there were 15 males and 16 females. After counselling, oral azathioprine (Thiopurine) was prescribed at a dose range of 1 mg to 2.5 mg per kg per day to all children.

On classification based on nutritional status, 45.2% children and 74.2 % children were found to be well nourished in the pre and post therapy (Graph 1).



Graph 1 nutritional status during pre and post therapy

Prior to therapy 54.8% children and post therapy 25.8% children were found to be underweight. The sub classification of underweight criteria is shown in Table 1.

Table 1: Sub classification of underweight children

Nutritional Status	Prior Therapy (n=31) n (%)	Post Therapy (n=31) n (%)
Wasting	13 (41.9)	4 (12.9)
Stunting	Nil	3 (9.7)
Wasting and Stunting	4 (12.9)	1(3.2)
Note : Analysed using Water low Criteria (Waterlow.,1972)[19]		

Nutrition Intervention

On the basis of nutritional requirement, the volume and caloric density were planned by the clinical dietician. EEN therapy was continued for 6 weeks in 12 children (38.7%) and for 8 weeks in 19 children (61.3%) based on their PCDAI score and clinical well being.

Weight changes

At the end of EEN therapy, a mean increase of 4.31 ± 2.51kg weight was noted in 31children.

DISCUSSION

Relapse - One child had relapse within one year of completion of EEN (primary course) and the child responded well after the second course of EEN. During the course of EEN, none of the children experienced side effects to the EEN or to the pharmaco-therapy.

The entire cohort demonstrated low PCDAI score pre and post EEN therapy. Mucosal healing could not be demonstrated in all patients because endoscopy and colonoscopy were not performed in all patients at the end of the therapy.

In children who achieved complete remission, nutritional status improved significantly at the end of the EEN therapy. There was significant weight gain ($p < 0.001^{**}$) at the end of therapy and complete remission rates were not affected by gender or age in the study population.

The study demonstrates that 6–8 weeks course of EEN is effective in achieving clinical remission in newly diagnosed paediatric CD, which in turn proves efficacy of EEN in Indian children.

A high response rate was achieved in the patients, including patients with isolated ileal and ileo-caecal disease. We have noted a low PCDAI in our cohort. One child had relapse, despite the use of azathioprine maintenance therapy within the first year after EEN.

Thiopurines were given for all patients at the commencement of EEN. Clinical response to Thiopurines varies among patients and may take up to 4-5 weeks. No untoward effect of drug used was noted in our cohort although the treating clinician will need to have an open eye. Furthermore, all the children had reduced disease activity and inflammatory markers with improved anthropometry. The duration of therapy probably reflects a balance between optimizing anti-inflammatory benefits and the adverse consequences of excluding normal diet for the individual child.

Improved nutritional status is seen with EEN. This hypothesis is strengthened by our observation at the end of the EEN therapy.

EEN does have its pitfall such as the cost. The cost of EEN was approximated around 20000 INR (300 USD) vs. Oral steroids approximated at 500 INR (8 USD). However, clinical remission can be achieved in EEN vs. steroids and the families were ready to pay the price for this novel yet well-established treatment.

Data suggests that mucosal healing and clinical remission may also be achieved with polymeric, semi elemental and elemental formulae.[20] .

Although practically a strict compliance to EEN for 8 weeks is a real challenge for both the child and the family, and there were two children who dropped out due to non-compliance of the EEN therapy. It was also interesting to note that the children who had relapsed a year later, when treated with EEN again, responded well by entering into remission. Moreover, there is an improved quality of life.[21]

We did not note any side effects associated with the EEN or Drug therapy during the entire course of treatment. The study cohort was small and does not reflect the whole panorama of the Indian population since the demographics are different in various parts of the country, which leads to the need for a larger study population to strengthen the data, results and outcomes.

EEN has been shown to be as effective as corticosteroid therapy in inducing remission in paediatric CD.[22] Hence in corroboration with this study; the present research has also accomplished favourable outcomes.

CONCLUSION

Our study has demonstrated the use and effectiveness of the EEN therapy in paediatric CD. EEN therapy was found to be effective in inducing clinical remission in active paediatric CD with no systemic side effects. However, further research with specific EEN formulae, immune-modulators, omega 3 fatty acid and probiotics may also be tried in future. A larger study that may be useful in predicting the routine use of EEN in children with CD should be carried out in the future to assess the extended efficacy of this novel therapy.

Funding: Nil

Conflicts of interest: Nil

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1.Dwarikanth Mahapatra , Peter J Schuffler, Jeroen AW Tielbeek ,Franciscus M Vos, Joachim M Buhmann .Crohn's disease tissue segmentation from abnormal MRI using semantic information and graph cuts .IEEE 10th International symposium on Biomedical imaging ,2013

2. Voitk AJ, Echave V, Feller JH, Brown RA, Gurd FN. Experience with elemental diet in the treatment of inflammatory bowel disease. Is this the primary therapy? Arch of Surg1973 Aug 1; 107(2):329-33.

3.Critch J, Day AS, Otley A, King-Moore C, Teitelbaum JE, Shashidhar H. Use of Enteral nutrition for the control of intestinal inflammation in paediatric Crohn's disease. J Paediatric Gastroenterol Nutr 2012 Feb; 54(2):298–05.

4.Day AS, Whitten KE, Sidler M, Lemberg DA. Systematic review: Nutritional therapy in paediatric Crohn's disease. Ailment Pharmacology Therapy 2007 Nov 27; 27(4):293–07.
5.Ferguson A, Glen M, Ghosh S. 5 Crohn's disease: Nutrition and nutritional therapy. Bailli Clin Gastroenterology 1998 Mar; 12(1):93–14.
6.Day AS, Crone E, Tyrer P, Keenan J. Sa1993 nutritional influences upon CEACAM6 expression by intestinal epithelial cells. Gastroenterology 2012 May; 142(5): S-376.
7.Fell JM, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, Kitching P, et al. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. Aliment Pharmacol and Ther 2000 Mar; 14(3):281–89.
8.Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of elemental diet on Mucosal inflammation in patients with active Crohn's disease: Cytokine production and Endoscopic and Histological findings. Inflammatory Bowel Disease 2005 Jun; 11(6):580–88.
9.Modigliani R, Mary J-Y, Simon J-F, Cortot A, Soule J-C, Gendre J-P,et al. Clinical, biological and endoscopic picture of attacks of Crohn's disease. Gastroenterol1990 Apr; 98(4):811–18.
10.Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schütz T, et al.. ESPEN guidelines on enteral nutrition: Gastroenterology. Clinical Nutrition 2006 Apr; 25(2):260–74.
11.Konno M, Kobayashi A, Tomomasa T, Kaneko H, Toyoda S, Nakazato Y, et al.. Guidelines for the treatment of Crohn's disease in children. Paediatric Inter 2006 Jun; 48(3):349–52.
12.Sandhu BK, Fell JM, Beattie RM, Mitton SG, Wilson DC, Jenkins H. Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. J Paediatric Gastroenterology Nutrition 2010 Feb; 50 (Suppl 1):S1–13.
13.Johnson T. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: A randomised controlled trial. Gut 2006 Mar 1; 55(3):356–61.
14.Pigneur B, Garnier-Lengliné H, Lepage P, Schmitz J, Goulet O, Doré J, et al.. P-107: Effect of exclusive enteral nutrition on the course of CD and intestinal micro biota. J Crohn's and Coli 2014 Sep; 8:S433.
15. L Lafferty, M Tuohy, A Carey, S Sugrue, M Hurley, S Hussey. Outcome of exclusive enteral nutrition in paediatric Crohn's Disease. European Journal of Clinical Nutrition ,2016
16.Walters TD, Griffiths AM. Mechanisms of growth impairment in paediatric Crohn's disease. Nat Rev Gastroenterology Hepatology 2009 Sep; 6(9):513–23.
17. Koletzko B, Koletzko S, Ruemmele F (eds): Drivers of Innovation in Paediatric Nutrition. Nestlé Nutr Inst Workshop Ser Paediatric Program, vol 66, pp 41–54, Nestec Ltd., Vevey/S. Karger AG, Basel, © 2010.
18. Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, et al. Development and validation of a paediatric Crohn's disease activity index. J Paediatric Gastroenterology Nutrition 1991 May; 12(4):449.
19.Waterlow J (1972) Classification and definition of protein calorie malnutrition BMJ.,Vol 3,pp 566-569
20.Tawnya Hansen and Donald R. Duerksen. Enteral Nutrition in the Management of Pediatric and Adult Crohn's Disease, 2018. Nutrients 2018, 10(5), 537
21.Afzal NA, Van der Zaag-Loonen HJ, Arnaud-Battandier F, Davies S, Murch S, Derkx B, Heuschkel R,et al.. Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. Aliment Pharmacology and Therapy 2004 Jul; 20(2):167–72.
22. Dziechciarz P, Horvatha, Shamir R, Szajewskah H. Meta-analysis: Enteral nutrition in active Crohn's disease in children. Aliment Pharmacology Ther 2007 Jul 7;26(6):795–06.