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Meta-analysis: enteral nutrition in active Crohn's disease in children

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SUMMARY

Background
Controversy exists surrounding the optimal treatment for inducing remission in active Crohn's disease.

Aim
To review and update evidence on the effectiveness of enteral nutrition (EN) in treating active Crohn's disease in children.

Methods
MEDLINE, EMBASE and The Cochrane Library (up to February 2007) were searched for randomized controlled trials (RCTs) relevant to Crohn's disease and EN in children.

Results
We included 11 RCTs (n = 394). Seven RCTs (n = 204) compared EN with corticosteroid therapy. On the basis of pooled results of four RCTs (n = 144), we found no significant difference in the remission rates between groups (relative risk, RR 0.97, 95% CI 0.7–1.4, random effect model). Four RCTs (n = 190) compared two EN regimens. One of the four RCTs (n = 50) revealed a significant increase in the percentage of patients achieving remission in the total EN group compared with the partial EN group (RR 2.7, 95% CI 1–7.4). Because of lack of data, formal pooling of results was not possible for many outcomes (e.g., time until remission, duration of remission, growth data).

Conclusions
Limited data suggest similar efficacy for EN and corticosteroids. As the number of patients needed to provide a definite answer is too large, future studies should focus on detailed outcome measurements including growth and quality of life.

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INTRODUCTION

Controversy exists surrounding the optimal treatment for inducing remission in active Crohn's disease (CD). In adults, the most recent meta-analysis showed that enteral nutrition is less effective than conventional corticosteroids.[1] In children, however, current recommendations indicate that enteral nutrition is the first-line treatment in the induction of remission.[2, 3] Chronic malnutrition has long been implicated as a treatable cause of growth failure in patients with inflammatory bowel disease.[4, 5] At diagnosis, up to 85% of paediatric patients with CD and 65% of those with ulcerative colitis have weight loss.[6] Also, 15–40% of children with CD have growth failure.[7] Thus, enteral nutrition may be at the front line of therapy because of its ability to induce remission (decreased disease activity and intestinal inflammation with subsequent improved growth), and its role in the management of malnutrition and its complications.

Its position as first-line therapy to induce remission is mainly based on the results of one meta-analysis[8] and on open trials showing that enteral nutrition leads to endoscopic healing, decreased mucosal cytokine production, and improved quality of life in patients with CD.[9–11] The pooled results of seven studies (five randomized controlled trials, one semi-randomized and one non-randomized trial) showed that there is no difference in efficacy between enteral nutrition and corticosteroid therapy in the treatment of acute CD in children. It was suggested that improved growth and development, without the adverse effects of steroid therapy, make enteral nutrition a better choice for first-line therapy in children with active CD. The limitations of the above mentioned meta-analysis were summarized by Ann Griffiths and include:[12] (i) the inclusion of a limited number of electronic databases; (ii) lack of methodological assessment of included trials; (iii) too small a number of patients from RCTs to detect a significant difference in the effect of the treatment; (iv) pooling the data from RCTs and non-RCTs, which may result in misleading conclusions; (v) inclusion of trials with poorly defined remission criteria as an outcome measure, which can overestimate the positive results; and (vi) lack of subgroup analysis by formula composition and disease location. Partly as a result of these limitations, there is lack of clarity regarding the effectiveness of enteral nutrition resulting in considerable variation in treatment. The objective of this study was to provide some resolution to the uncertainty regarding the use of enteral nutrition by reviewing and updating data on the effectiveness of enteral nutrition for inducing remission in CD in children.

OBJECTIVES

The objectives of this study were: (i) to compare the effectiveness of enteral nutrition and corticosteroids in the treatment of acute CD in children; (ii) to determine which type of enteral formula is most effective, including elemental formula, semielemental formula and polymeric formula; and (iii) to determine short-term and long-term advantages of enteral feeding, if any.

METHODS

We electronically searched MEDLINE, EMBASE and the Cochrane Library (up to February 2007), limiting citations to randomized and quasi-randomized (i.e., allocating participants according to date of birth, the number of hospital records, etc.) controlled trials. We also searched proceedings of major gastroenterological and nutritional conferences (1999–2006) and screened bibliographies of retrieved studies and recent review articles. There were no language restrictions. Studies had to be conducted in children up to 18 years of age, both with newly diagnosed CD and with relapsed disease. Patients in the experimental groups received enteral formula, including elemental (i.e., formulations of amino acids), semielemental (i.e., formulations of amino acids plus oligopeptides), or polymeric (whole protein) formula. Patients in the control group received corticosteroids or other types of enteral nutrition. The search strategy included use of a validated filter for identifying controlled trials,[13] which was combined with a topic-specific strategy. The key words related to the disease included 'Crohn disease' and 'inflammatory bowel disease,' and the key words related to the intervention of interest included 'enteral nutrition.' The complete search strategies are available from the authors on request.

The primary outcome measures were remission (percentage of subjects achieving remission), time until remission, duration of remission or time until the first relapse, and relapse (number of relapses per patient year during follow-up). The secondary outcomes were growth parameters (weight gain, length/height gain), compliance (acceptance of treatment), quality of life and adverse effects.

Methods of review

Included and excluded studies

Two reviewers (AH, PD) independently screened titles and abstracts identified according to the above-described search strategy. All potentially relevant articles were retained, and the full text of these studies was examined to determine which studies satisfied the inclusion criteria. The same reviewers independently carried out data extraction, using standard data extraction forms. Reports in languages other than those familiar to the authors were translated. Discrepancies between the reviewers' findings were resolved by discussion.

Study quality

Two reviewers independently, but without being blinded to the authors or journal, assessed the quality of studies that met the inclusion criteria. Use of the following strategies associated with good quality studies was assessed: methods of allocation concealment; blinding of the investigators, participants, outcome assessors, and data analysts; intention-to-treat analysis; and completeness of follow-up.

Statistical methods

The data were analysed using The Cochrane Review Manager. The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes. The binary measure for individual studies and pooled statistics was reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). The weight given to each study was based on the inverse of the variance. Heterogeneity was quantified by χ^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. If there was heterogeneity, we present results of both random effects and fixed effects models for the main analysis. For simplicity, if heterogeneity was not revealed, we present results of only the fixed effects model. Because of a limited data, we did not test for publication bias.

RESULTS

Description of studies and methodological quality

Table 1 describes the characteristics of the included randomized controlled trials (RCTs),[14–24] three of which were published as abstracts.[22–24] The 11 studies recruited a total of 394 participants (aged 3.8–18.6 years). The excluded studies and reasons for their exclusion are described in Table 2.[9–11, 25–43] The two reviewers completely agreed ($\kappa = 1$) on the selection of the included studies.

Seven RCTs compared enteral nutritional therapy with steroid therapy for induction of remission in CD. Only five were fully peer-reviewed publications,[15, 18–21] while the remaining two studies were published as abstracts.[23, 24] Seven RCTs comprising 204 participants (100 in corticosteroid group, 104 in enteral nutrition group), aged between 4 and 18.6 years, compared elemental,[20, 21, 24] semielemental,[18, 23] or polymeric liquid diets[15, 19] with corticosteroid therapy. There were some differences in the duration of the intervention, which varied from 3 to 10 weeks. Patients included in these studies differed according to disease location, duration of the disease (new onset or chronic disease), additional treatment (allowed in four[18–21] of seven studies; not allowed in one,[15] and not declared in two studies[23, 24]), and route of enteral nutrition administration (nasogastric tube, gastrostomy or oral). Disease activity was defined by the Lloyd-Still index in 2 studies,[20, 21] the Pediatric Crohn's Disease Activity Index (PCDAI) in four studies,[15, 18, 19, 23] and the Crohn's Disease Activity Index (CDAI) in one study.[24] In three RCTs, additional treatment with sulphasalazine[20, 21] or mesalamine[18] was administered to patients in the corticosteroid group. In one RCT,[15] a proportion of patients were treated at baseline (i.e. randomization) with steroids.

The methodological quality of the trials varied (Table 1). Allocation concealment was adequate in one trial[18] and unclear in six of the remaining trials. Although none of the studies was a double-blinded study, in the Terrin *et al.*[18] study, patients were evaluated clinically and also endoscopically by blinded observers. Intention-to-treat-analysis was reported in all seven trials. The completeness of follow-up was adequate in all of the trials reporting it.

Four RCTs ($n = 190$) compared various forms of enteral nutrition (Table 1).[14, 16, 17, 22] Within this group,

Table 1. Characteristics included trials

Study ID	Randomization	Allocation concealment	Blinding	ITT	FU	Number of randomized participants	New/ relapsed disease	Age (years)	Disease location	Clinical criteria	Experimental treatment	Control treatment	Duration of treatment	Additional treatment
Enteral nutrition vs. corticosteroids														
Borrelli *et al.* (2006)[15]	Yes	Not reported	No	Yes	Yes	37	37/0	4–17	All sites	PCDAI	PD	CS	10 weeks	No
Ruuska *et al.* (1994)[19]	Yes	Not reported	No	Yes	Yes	19	9/10	8.5–18.6	All sites	PCDAI	PD	CS	8 weeks	Yes
Sanderson *et al.* (1987)[21]	Yes	Not reported	No	Yes	Yes	17	0/17	8.6–17.2	Small bowel	LSI	ED	CS + sulphasalazine	6 weeks	Yes
Seidman *et al.* (1991) (Abstract)[24]	Yes	Not reported	Not reported	Yes	Yes	19	19/0	<15	Ileitis or ileocolitis	CDAI	ED	CS	3 weeks	?
Thomas *et al.* (1993)[20]	Yes	Not reported	No	Yes	Yes	24	No data	5.7–17.2	All sites	LSI	ED	CS + sulphasalazine	4 weeks	Yes
Seidman *et al.* (1993) (Abstract)[23]	Yes	Not reported	Not reported	Yes	Yes	68	46/22	≥16	¼ small bowel ¾ small bowel + colon	PCDAI	SE	CS	4 weeks	?
Terrin *et al.* (2002)[18]	Yes	Yes	Yes	Yes	Yes	20	No data	7–17 (mean 12.4)	Ileum terminale & colon	PCDAI	SE	CS + mesalamine	8 weeks	Yes
Two enteral nutritional regimens														
Akobeng *et al.* (2000)[17]	Yes	Yes	Yes	Yes	Yes	18	17/1	6–16	All sites	PCDAI	Glutamine-enriched PD	PD	4 weeks	No
Johnson *et al.* (2006)[14]	Yes	Yes	No	Yes	Yes	50	37/13	3.8–16	Small bowel or colon	PCDAI	ED TEN	ED PEN (50% energy)	6 weeks	Yes (?)
Ludvigsson *et al.* (2004)[16]	Yes	Yes	No	Yes	Yes	38	23/10	5–17	All sites	PCDAI	ED	PD	6 weeks	Yes
Griffiths *et al.* (2000) (Abstract)[22]	Yes	Not reported	Yes	Yes	Yes	84		8–18	Small or large intestine	CDAI	ED	PD	20 days	?

CDAI, Crohn Disease Activity Index; CS, Corticosteroids; ED, Elemental Diet; FU, Follow-up >80%; ITT, Intention-to-Treat Analysis; LSI, Lloyd-Still index; PCDAI, Pediatric Crohn's Disease Activity Index; PD, Polymeric Diet; SE, Semielemental Diet; TEN, Total Enteral Nutrition; PEN, Partial Enteral Nutrition.

Table 2. Characteristics of excluded trials

Study	Reasons for exclusion
Afzal *et al.*[9] (2004)	Non RCT; prospective cohort study on quality of life
Afzal *et al.*[25] (2005)	Non RCT
Aiges *et al.*[26] (1989)	Non RCT; long-term study on growth
Akobeng *et al.*[27] (2002)	Part of the other study – Akobeng 2000; no data
Azcue *et al.*[28] (1997)	Non RCT
Bannerjee *et al.*[11] (2004)	Non RCT; uncontrolled case series
Beattie *et al.*[29](1998)	Non RCT; uncontrolled case series
Beattie *et al.*[30] (1994)	Non RCT; uncontrolled case series
Belli *et al.*[31] (1988)	Non RCT; long-term study on growth and prevention of relapse
Breese *et al.*[32] (1995)	Non RCT
Fell *et al.*[10] (2000)	Non RCT; uncontrolled case series
Gailhoustet *et al.*[33] (2002)	Non RCT; prospective cohort study on quality of life
Gavin *et al.*[34] (2005)	Non RCT; retrospective cohort study
Griffiths *et al.*[35] (1993)	Non RCT; long-term study on growth and clinical course of patients with Crohn's disease
Khoshoo *et al.*[36](1996)	Cross over study; No data
Morrin *et al.*[37] (1982)	Non RCT; uncontrolled case series
Morrin *et al.*[38] (1980)	Non RCT; uncontrolled case series, long-term management
Navarro *et al.*[39] (1982)	Non RCT; uncontrolled case series
Nicholls *et al.*[40] (1994)	Non RCT
Papadopoulou *et al.*[41] (1995)	Non RCT; long-term prospective cohort study
Ricour *et al.*[42] (1977)	Non RCT
Stober *et al.*[43] (1983)	Non RCT

RCT, randomized controlled trial.

three RCTs were full publications,[14, 16, 17] and one was published as an abstract.[22] Two studies compared an elemental diet with a polymeric diet,[16, 22] one of which compared polymeric formula with elemental formula enriched with eicosapentanoic acid (n6:n3 ratio 0.86).[22] One RCT compared a standard polymeric diet with a polymeric diet enriched with glutamine,[17] and one compared total with partial enteral nutrition (50% estimated requirement).[14] There were differences in: (i) the duration of the intervention, varying from 20 days to 6 weeks; (ii) disease location and duration; (iii) additional treatment (allowed in two RCTs,[14, 16] not declared in one RCT,[22] and not allowed in one RCT[17]); and (iv) the route of the enteral treatment delivery. Disease activity was defined by the PCDAI in three trials[14, 16, 17] and the CDAI in one study.[22] Regarding the methodological quality of the included trials, allocation concealment was adequate in three trials[14, 16, 17] and unclear in one.[22] Only two trials were double-blind studies.[17, 22] The remaining two trials[14, 16] were open. While intention-to treat-analysis was reported in all four trials, our analysis revealed that the authors performed available cases analysis (i.e., an analysis in which data are analysed for every participant for whom the outcome was obtained[44]). The completeness of follow-up was adequate in all of the trials.

Data synthesis

Efficacy of enteral nutrition vs. corticosteroids

1 Remission rate – four RCTs (n = 144) provided data on the remission rate at 8 weeks,[18, 23] at 9 weeks,[24] or at 10 weeks.[15] We pooled the results of these trials and found no evidence for a difference in the percentage of children achieving remission between those treated with enteral nutrition and those treated with corticosteroids (RR 0.96, 95% CI 0.6 to 1.14, fixed effect model, and 0.97, 95% CI 0.68 to 1.4, random effect model) (Figure 1). The remaining three RCTs did not provide data related to the remission rate.[19–21]

2 Time until remission – two RCTs[18, 23] (n = 88) provided data on the time until achieving remission, although the lack of s.d. did not allow us to pool the results. One of these trials[18] (n = 20) revealed a significantly shorter time until achieving remission in patients treated with enteral nutrition compared with corticosteroids (2.5 vs. 3.7 weeks, $P < 0.05$%). Another

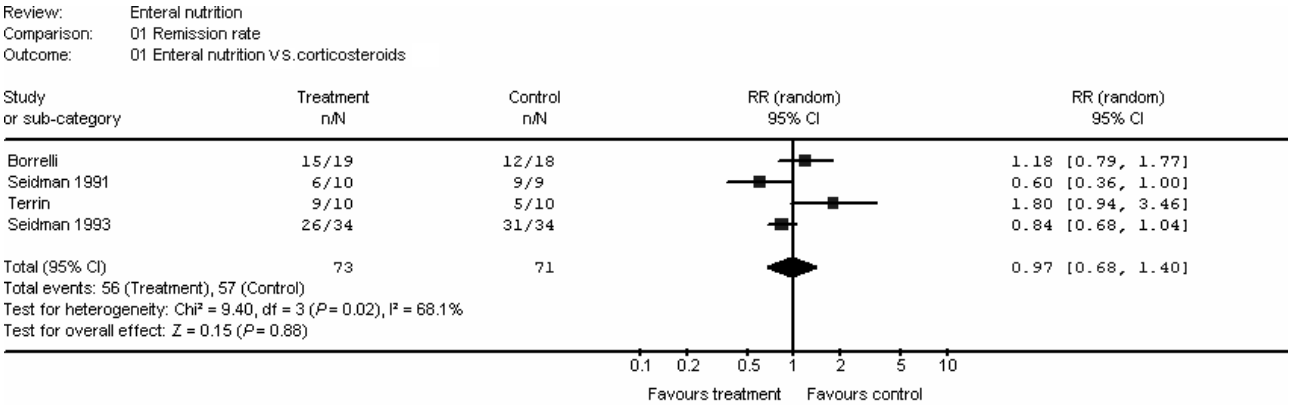

Figure 1. Forest plot showing effect of enteral nutrition compared with corticosteroids on remission rate.

RCT[23] (n = 68) showed an equivalent mean time until achieving remission in those treated with enteral nutrition compared to corticosteroids (11.1 vs. 11.3 days, respectively, significance not given).

3 Duration of remission/time until the first relapse – the duration of remission was reported in two RCTs[20, 24] (n = 43). Only one[24] showed a significant reduction in the time until relapse in the enteral group compared with the corticosteroid group (n = 19, mean difference −0.4 year, 95% CI −0.6 to −0.2). In the second RCT (n = 24), the mean duration of remission was 7 months in those treated with enteral nutrition compared to 10 months in those treated with corticosteroids (s.d. and statistical significance was not reported).[20]

4 Relapse per patient/year during follow-up – patients were observed during the follow-up period in two RCTs[19, 24] (n = 38). Seidman *et al.*[24] reported no significant difference between the two groups in the number of relapses per patient year (1.25 ± 0.25 in the enteral nutrition group vs. 0.88 ± 0.16 in the corticosteroids group; the mean follow-up period was 5.2 ± 0.8 vs. 6.18 ±1 years, respectively). Ruuska *et al.*[19] observed five relapses in the corticosteroid group compared to one relapse in the enteral nutrition group; however, the relapse rate could not be calculated because the authors did not report the follow-up period stately for the two groups.

5 Weight gain – two RCTs[15, 19] assessed weight gain in children fed a polymeric diet vs. corticosteroids (Table 3). In one study (Borrelli *et al.*),[15] weight gain during 10 weeks of the study in those treated with enteral nutrition was markedly higher than that in the corticosteroid group (4.8 ± 0.5 vs. 3.2 ± 0.6 kg, respectively, mean difference 1.6 kg, 95% CI 1.2 to 2, $P < 0.05$). Ruuska *et al.*[19] reported rapid weight gain during the first 4 weeks, but no further weight gain was seen after 8 weeks.

Sanderson *et al.*[21] found reduced weight gain in children fed an elemental diet versus corticosteroids at 6 and 12 weeks (mean difference −1.7 kg, 95% CI −2.98 to −0.4, and −2.1 kg, 95% CI −3.94 to −0.2, respectively). Seideman *et al.*[24] reported a similar weight gain between groups receiving an elemental diet versus corticosteroids (no data provided).

6 Length/height gain – data on length/height velocity are presented in Table 3. During a 10-week follow-up period, Borrelli *et al.*[15] reported larger length gain in children fed a polymeric diet versus corticosteroids (mean difference 0.8 cm, 95% CI 0.6 to 1). Two RCTs[20, 21] provided data about the mean height in children receiving an elemental diet versus corticosteroids. Thomas *et al.*[20] reported the mean height velocity standard deviation score at 6 months in the enteral nutrition group was +0.32 (standard deviation = 3.32) compared with −3.1 (standard deviation = 2.8) in the steroid group ($P < 0.05$). Sanderson *et al.*[21] found that the mean height standard deviation score at 6 months was +0.3 (standard deviation = 2.03) in the enteral nutrition group and −2.8 (standard deviation = 2.50) in the steroid group ($P < 0.05$). Newby *et al.*[7] pooled these results and reported a significant difference in height velocity standard deviation scores (two RCTs, n = 39, WMD 3.25, 95% CI 1.56 to 4.9).

7 Acceptance of the treatment – no data on the acceptance of the treatment were provided in the included trials.

8 Side effects – only one study (n = 32)[15] provided detailed information on adverse events, showing that

Table 3. Effect of enteral nutrition compared with corticosteroids on growth

Study ID	Experimental group*	Control group*	Effect (experimental group versus control group)
Weight gain			
Borrelli *et al.*[15]	PD (n = 17)	CS (n = 15)	MD +1.6 kg (1.2 to 2)
Ruuska *et al.*[19]	PD (n = 10)	CS (n = 9)	Rapid during the first 4 weeks, but after 8 weeks no further gain was seen
Sanderson *et al.*[21]	ED (n = 8)	CS (n = 7)	MD −1.7 kg (−2.98 to −0.42) at 6 weeks (end of intervention) MD −2.1 kg (−3.94 to −0.25) at 12 weeks
Thomas *et al.*[20]	ED (n = 12)	CS (n = 12)	No information
Seideman *et al.*[24] (1991)	ED (n = 10)	CS (n = 9)	Weight gain similar (no data provided)
Seideman *et al.*[23](1993)	SE (n = 34)	CS (n = 34)	No information
Terrin *et al.*[18]	SE (n = 10)	CS (n = 10)	No information
Length/height gain			
Borrelli *et al.*[15]	PD (n = 17)	CS (n = 15)	MD +0.8 cm (0.6 to 1)
Ruuska *et al.*[19]	PD (n = 10)	CS (n = 9)	No information
Sanderson *et al.*[21]	ED (n = 8)	CS (n = 7)	MD 3.42 s.d. scores (0.96 to 5.88)
Seideman *et al.*[24] (1991)	ED (n = 10)	CS (n = 9)	No information
Thomas *et al.*[20]	ED (n = 12)	CS (n = 12)	MD 3.1 s.d. scores (0.77 to 5.43)
Terrin *et al.*[18]	SE (n = 10)	CS (n = 10)	No information
Seideman *et al.*[23] (1993)	SE (n = 34)	CS (n = 34)	No information

CS, Corticosteroids; ED, Elemental Diet; MD, Mean Difference; PD, Polymeric Diet; SE, Semielemental Diet.
* Number of participants for whom outcome data were available.

the overall frequency of side effects was significantly lower in those treated with enteral nutrition compared with those treated with corticosteroids (4/17 in polymeric diet group vs. 11/15 in corticosteroids group, RR 0.32, 95% CI 0.12 to 0.7, number needed to treat (NNT) 3, 95% CI 2 to 7). In particular, in children treated with enteral nutrition, there was a reduced risk of abdominal pain (RR 0.18, 95% CI 0.03 to 0.98); however, the risk of diarrhoea, flatulence, nausea and vomiting did not differ between groups. The most common adverse events attributable to corticosteroid treatment (n = 15) were a cushingoid appearance (67%), acne (47%), skin striae (27%), hirsutism (20%), myopathy (13%) and depression (7%).

9 Quality of life – no data about the quality of life were provided by the authors of the identified RCTs.

Comparison between two enteral nutrition regimens

Remission rate

Three RCTs[16, 17, 22] did not reveal a significant difference in remission rates. In contrast, one trial[14] (n = 50) showed a significant increase in the percentage of patients achieving remission at 6 weeks in those treated with total enteral nutrition compared with partial enteral nutrition group (10/24 vs. 4/26, RR 2.7, 95% CI 1 to 7.4).

Time until remission / Duration of remission / Relapse per patient/year during follow-up

No data were provided for the other primary outcomes (time until remission, duration of remission, relapse per patient/year during follow-up).

Growth parameters

Three RCTs (n = 96) assessed growth (Table 4).[14, 16, 17] Children treated with a polymeric diet gained significantly more weight than those treated with an elemental diet (mean difference 2.5 kg, 95% CI 0.9 to 4.1, P = 0.004).[16] However, there was neither a difference noted in weight gain between children treated with a polymeric diet versus those treated with a glutamine-enriched polymeric diet[17] nor in patients treated with partial enteral nutrition and total enteral nutrition.[14]

Table 4. Effect of two nutritional regimens on growth

Study ID	Experimental group*	Control group*	Weight (kg)	Weight for height SDS	Triceps skin fold thickness	Mid-upper circumference (mm)	Subscapular skin fold	Length/ height gain
Johnson 2006	Total enteral nutrition (n = 24)	Partial enteral nutrition (n = 26)	NS	NS	NS	NS	NS	NS
Ludvigsson 2004	Elemental diet (n = 14)	Polymeric diet (n = 16)	Children treated with a polymeric diet had more weight gain than those treated with an elemental diet (mean difference 2.5 kg, 95% CI 0.9 to 4.1; P = 0.004) Patients who gained more than 3 kg during the 6-week period in the polymeric diet group versus the elemental diet group (56% vs. 14%, RR 4, 95% CI 1.2 to 15) Patients who lost weight during the 6-week period in the polymeric diet group versus the elemental diet group (6% vs. 64%, RR 10, 95% CI 2 to 59)	–	–	–	–	–
Akobeng 2000	Glutamine-enriched polymeric diet (n = 7)	Polymeric diet (n = 9)	NS	–	–	–	–	–

NS, not significant; SDS, standard deviation score.
* Number of participants for whom outcome data were available.

One RCT[14] (n = 50) did not disclose any significant differences between the groups in relation to gain in other anthropometric parameters (e.g., weight/ height, triceps skinfold, subscapular skinfold, mid-arm circumference).

Acceptance of the treatment

Data on the acceptance of the treatment were not found in any of the included studies.

Tolerance

No data about tolerance were provided in any of the included studies.

Side effects

One study[16] assessed in detail the frequency of side effects and revealed adverse events in three patients treated with an elemental diet (pneumonia, intra-abdominal abscess, perianal abscess) and in two children treated with a polymeric diet (pyelonephritis, thalassemia minor).

Quality of life

The 'well being' score was assessed in only one trial.[14] No difference was found between the groups; however, the authors did not define what parameters were included in the 'well being' score.

DISCUSSION

Principal findings

The objective of this study was to provide some resolution to the uncertainty in the literature regarding the usefulness of enteral nutrition for treating active CD in children. Our review shows that on the basis of evidence available, it is not possible to evaluate the effectiveness of enteral nutrition compared to corticosteroids as well as the type of enteral feeding used. This is mainly because of the lack of high-quality studies (small sample size, missing data) and the heterogeneity of study designs, treatment regimens, outcome measures, and follow-up. Adverse events have been reported in some but not all studies. In addition, side effects may not have been thoroughly investigated. Also, some of reported adverse events from the use of polymeric diet (e.g. thalassemia minor) cannot be considered to be related to the study intervention.

Previous research

More than a decade after the publication of the first meta-analysis in adults,[45] there is still insufficient information to delineate the exact role of enteral nutrition in children with CD. The most cited meta-analysis of the effectiveness of enteral nutrition is by Heushkel *et al.*[8] That review, however, as discussed in the Introduction, used a limited search strategy, combined observational studies and trials, and had limited assessments of methodological quality. While physicians should base their practice on evidence-based medicine,[46] one should keep in mind that previous studies found inadequate for this current systematic review, as well as data from animal models, may be used to plan adequate future studies. For example, regarding the site-specific effect of enteral nutrition, Afzal *et al.*[25] have demonstrated in a prospective, but not randomized trial, that polymeric enteral nutrition-induced endoscopic and histologic colonic mucosal improvement in ileocolonic disease; this suggests that well-designed RCTs may demonstrate the usefulness of enteral nutrition in treating ileocolonic disease rather than diseases involving the colon only. Similarly, the same group has shown that 23 out of 26 children achieved a clinical remission at 8 weeks with improvement in their quality of life (QoL) scores; they also showed that the change in the QoL score after treatment was predictive of achieving a clinical remission, but not of histological improvement.[25] Again, the study design does not permit any conclusions to be drawn pending further well-designed studies. In addition, one must keep in mind that data from recent retrospective studies (enhancing the urgent need for adequate RCTs) suggest that in newly diagnosed patients in whom enteral nutrition was used as the primary therapy (44 children), 90% responded to enteral nutrition (median time until remission of 6 weeks); although 62% relapsed (median duration of remission of 54.5 weeks, range: 4–312), 38% of the cohort have not relapsed, 47% have not received steroids, and in those who eventually required steroids, their use was postponed for a median of 68 weeks (range: 6–190).[47]

Another major area of interest is the effect of nutrition on inflammation and growth. As to the role of enteral nutrition in inducing remission in acute CD, almost 20 years ago, Belli *et al.*[31] demonstrated that chronic intermittent nasogastric infusion increased

caloric intake and improved weight and height gain in patients with inflammatory bowel disease. Since then, studies on the effect of enteral nutrition on growth and inflammation, recently reviewed by Shamir *et al.*[5], have suggested a positive effect for enteral nutrition on reduced intestinal inflammation and improved growth, as well as a positive effect of enteral nutrition compared to corticosteroids on these outcome measures.[5, 15, 20, 21] These finding are consistent with our findings in the small number of available RCTs; they are also in agreement with the recent Cochrane review which established that despite the paucity of well-designed controlled studies, current evidence indicates that enteral nutrition may be superior to corticosteroids for achieving an increase in height velocity.[7]

Strengths and limitations

The strengths of this review lie in its use of rigorous systematic review methodology. We used several methods to reduce bias (i.e., comprehensive literature search, duplicate data abstraction, pre-specified criteria for methodological assessment and analysis). However, there are some limitations. First, there was no attempt to identify unpublished studies. Based on our previous experience with systematic reviews, it is usually ineffective; however, lack of such data could skew results. Second, the methodological quality of included trials was not high, and most of the trials had small sample sizes. Additionally, there was a lack of standardization of outcome measures and marked clinical heterogeneity, variation in the length of the trials (follow-up) and in the duration of the intervention. Some trials allowed the use of concomitant treatment, increasing the risk of bias. These limitations altogether may explain why we were unable to provide definitive information on the actual effects of enteral nutrition.

Unanswered questions and future research

Research efforts should now be concentrated on higher quality, more rigorous, randomized trials comparing enteral nutrition with corticosteroid therapy to help clarify the exact potential of enteral nutrition to induce remission in children with CD. At a minimum, these RCTs should use predefined ideally standardized measures of outcome and be multi-centred to ensure that the studies give sufficiently precise estimates of the various outcomes.

CONCLUSIONS

Corticosteroids are associated with severe side effects and are not associated with mucosal healing. However, corticosteroid administration involves a simple explanation to the family and a prescription. On the other hand, enteral nutrition is associated with improved growth[5, 7] and reduced inflammation,[10, 11] making it a potential candidate for being the first-line therapy. However, compliance is problematic (palatability, insertion of the nasogastric tube, gastrointestinal side effects) and the treatment is demanding for physicians, families and patients alike. Our current work suggests that if we seek answers for the definitive role of enteral nutrition in the treatment of children with CD, a very large study is needed; an estimated sample size required to detect significant difference in the remission rate between patients treated with corticosteroids or enteral nutrition (80% power at 5% significance level) should be 3000 children per group! Thus, although larger studies are needed, these should focus on employing unified methodology while looking not only at previously explored questions such as the remission rate and occasional growth but also at less explored questions such as the QoL.

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