Clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in Crohn's disease: a systematic review and meta-analysis

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Declared competing interests of authors: Aileen Clarke is a member of the NIHR HTA Editorial Board.

Published March 2015
DOI: 10.3310/hta19260

Scientific summary

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Health Technology Assessment 2015; Vol. 19: No. 26
DOI: 10.3310/hta19260

NIHR Journals Library www.journalslibrary.nihr.ac.uk

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Background

Crohn's disease (CD) is a relapsing–remitting condition that causes chronic inflammation of the gastrointestinal tract. Frequent symptoms of CD include malnutrition, abdominal pain, diarrhoea and weight loss. The objective of CD management is to induce and maintain remission of disease by controlling inflammation, reducing clinical symptoms and preventing complications. The management of children with CD involves additional goals to promote normal growth and pubertal development. The choice of therapy depends on the extent of inflammation, the disease severity and complications.

None of the currently available therapeutic options, including medical (e.g. corticosteroids, biologics, antibiotics), surgical (e.g. bowel resection) and nutritional (e.g. enteral/parenteral feeding, restricted diet), lead to complete cure of CD. Although corticosteroids are the most widely used drugs for the treatment of active CD and their use has been shown to be associated with short-term remission, they are also associated with steroid dependency, impairment in growth and risk of infection. Tumour necrosis factor inhibitors are also utilised but there are safety concerns with their long-term use.

Recently, enteral nutrition has been shown to be a viable treatment option in the management of active forms of CD. But evidence regarding the efficacy of an enteral nutrition relative to standard treatment (i.e. steroids) has been inconsistent. For example, one meta-analysis found that enteral nutrition was at least as effective as steroids in inducing remission in children and young adults with active CD. In contrast, a more recent meta-analysis indicated that enteral nutrition is less beneficial than steroids in inducing remission in adults with active CD. In Japan, enteral nutrition is recommended as the first-line treatment in the management of active CD.

Evidence for the efficacy of different types of enteral nutrition (i.e. elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and is less clear. Most of the comparative evidence on the maintenance of remission rests on a few retrospective observational cohort studies and prospective non-randomised controlled trials (nRCTs). If enteral nutrition proves to be as effective as conventional medications, its use might minimise or replace the use of conventional drugs (e.g. steroids).

Objectives

This review aimed to evaluate clinical effectiveness and cost-effectiveness of elemental nutrition (a type of enteral nutrition) for the maintenance of remission in CD. The specific aims of this review were to explore:

- the clinical effectiveness and cost-effectiveness of elemental nutrition compared with other interventions (e.g. placebo, unrestricted diet, standard drug treatment or other types of enteral nutrition such as polymeric and semi-elemental) in maintaining remission in patients with quiescent CD
- whether or not the treatment effect of elemental nutrition on the maintenance of remission varies across groups defined by dose/duration of elemental nutrition, gender (males, females), age (adults, adolescents and children) and type of induction therapy (medically, nutritionally and surgically induced)
- additional outcomes for patients with CD: adherence to elemental nutrition, Crohn's Disease Activity Index (CDAI), incidence of mucosal healing, quality of life (QoL), adverse events, gain in body weight [or body mass index (BMI)], growth and pubertal development.

Methods

Search strategy and data sources

Electronic searches were carried out in MEDLINE (Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), EMBASE (Ovid), The Cochrane Library – all sections (Wiley Online Library), Science Citation Index and Conference Proceedings (Web of Knowledge), World Health Organization International Clinical Trials Registry Platform, and UK Clinical Research Network Study Portfolio from inception to August/September 2013. The searches were not limited by study design, language or publication date. The websites of relevant organisations as well as references of included studies were checked for relevant studies. All the retrieved records were collected and then deduplicated using a specialised database.

Study eligibility criteria

English publications of randomised controlled trials (RCTs) and nRCTs comparing clinical effectiveness and/or cost-effectiveness of elemental nutrition to no intervention (restricted/unrestricted diet) or other types of treatment (e.g. placebo, semi-elemental/polymeric nutrition, standard drug therapy) in patients with CD in remission at baseline were eligible for inclusion. Cost-effectiveness modelling studies of observational design were also eligible for inclusion. Reviews, meta-analyses, observational cohort studies, case reports, case series, editorials or comments were excluded.

Outcomes of interest

Primary review outcomes were maintenance of remission (per cent of patients maintaining remission, cumulative probability of remission and duration of remission), development of relapse (per cent of patients developing relapse, time to relapse) and incidence of mucosal healing (per cent of patients with endoscopic mucosal healing). Secondary outcomes were adherence to elemental nutrition, need for surgery, withdrawals from steroids, CDAI score, QoL, gain in body weight or BMI, pubertal development, adverse events and complications.

Study selection and data extraction

Two independent reviewers used a pre-piloted form to screen the identified records for title/abstract. Afterwards, full-text reports of all potentially relevant abstracts were retrieved and examined independently. Disagreements were resolved via discussions and consensus agreement.

Two reviewers using a pre-piloted form independently extracted relevant data on study (e.g. author, country, design, sample size), participant (e.g. age, gender, type of induction therapy), intervention (e.g. type, mode/dose of administration, concomitant diet or medications) and outcome characteristics (e.g. scale of measurement, assessment timing, definition of CD relapse). The extracted data were cross-checked by second reviewer and any disagreements were resolved by discussion.

Risk of bias assessment

Two reviewers independently assessed risk of bias (RoB) of individual studies. We used the Cochrane Collaboration RoB tool to assess RCTs, which rates RoB (high, low and unclear) across selection, performance, detection, attrition and reporting domains. nRCTs were assessed using a modified Cochrane RoB tool in which the domain of selection bias was evaluated in regards to baseline between-group imbalance for important prognostic factors. Disagreements on extractions were resolved by a third reviewer through discussion.

The quality of economic analyses of the included studies was planned to be assessed using the Drummond 10-item checklist.

Data synthesis and overall quality of evidence

Study, treatment, population and outcome characteristics were summarised in text and summary tables. The data on effectiveness of elemental nutrition for each outcome of interest were compared qualitatively and quantitatively in text and summary tables. Results for each outcome were stratified by a comparison of elemental nutrition to no intervention (i.e. restricted/unrestricted diet), drug alone, combination of elemental nutrition and drug, and other types of enteral nutrition.

The decision to pool data was based on a degree of similarity with respect to methodological and clinical characteristics of studies. Post-treatment mean differences (MDs) for continuous and risk ratios (RRs) for binary measures were planned to be pooled using a DerSimonian and Laird random-effects model. The degree of heterogeneity was determined through inspection of the forest plots, Cochran's Q and the I^2 statistics. The heterogeneity was judged according to pre-determined levels of statistical significance (chi-square-based $p < 0.10$, and/or $I^2 > 50\%$). Study-level clinical and methodological sources of heterogeneity was planned to be explored through a priori defined subgroup (i.e. age, gender, induction therapy) and sensitivity analysis. Publication bias was planned to be assessed through visual inspection of funnel plots for asymmetry and use of linear regression tests.

Results were rendered inconclusive in cases of missing/partially reported data [undetermined effect measures, 95% confidence intervals (CIs)] or statistically non-significant effect estimates with great uncertainty (i.e. sufficiently wide intervals that include moderate to large effect size treatment effects in both directions compatible to either benefit or harm of elemental nutrition).

The overall quality of evidence (high, moderate, low, very low grade) for pre-selected gradable outcomes (e.g. maintenance of remission, risk of relapse) was assessed using an approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (www.gradeworkinggroup.org).

Results

A total of 630 records were identified and screened, of which 594 were excluded at title/abstract level. Of the remaining 36 records screened at full-text level, 12 were included in the review (representing three RCTs and five nRCTs).

Out of eight studies, six were conducted in Japan and two in the UK. The sample size ranged from 33 to 95 participants. The mean age ranged from 22 to 44 years and length of follow-up from 12 to 48 months. Type of induction therapy in most studies was medical (standard drugs, enteral or parenteral nutrition). Elemental nutrition was given in addition to unrestricted/restricted diet through tube infusion and/or oral intake. Participants in the control groups received either unrestricted diet (no intervention), standard drug (e.g. 6-mercaptopurine, infliximab, prednisolone) or polymeric nutrition.

Randomised controlled trials indicated a significant benefit of elemental nutrition compared with no intervention (unrestricted diet) in maintaining remission after 24 months of follow-up (one RCT; RR 2.06, 95% CI 1.00 to 4.43; very low-grade evidence) and preventing relapse at 12–24 months of follow-up (two RCTs; pooled RR 0.57, 95% CI 0.38 to 0.84; $I^2 = 0\%$; high-grade evidence). The 6–12 month maintenance rate was not significantly different (RR 1.37, 95% CI 0.86 to 2.17; very low-grade evidence; inconclusive result owing to wide 95% CIs).

Similarly, three nRCTs showed significant benefits of elemental nutrition over no intervention (unrestricted diet) in maintaining remission and preventing the occurrence of relapse at 12 months. In one nRCT, the use of elemental nutrition was associated with a significantly longer time to relapse than no intervention (MD 1.20, 95% CI 0.35 to 2.04). The incidence of mucosal healing between elemental nutrition and no

intervention (unrestricted diet) groups at 12 months was not significantly different (inconclusive results; RR 2.70, 95% CI 0.62 to 11.72).

The 12-month adherence rate was found to be significantly lower for elemental nutrition than for an unrestricted diet in in two nRCTs, one of unclear RoB (RR 0.81, 95% CI 0.65 to 0.99) and one of low RoB (RR 0.80, 95% CI 0.64 to 0.99). Similarly, one RCT of unclear RoB demonstrated that the 12-month adherence rate for elemental nutrition was lower than that for polymeric nutrition (RR 0.68, 95% CI 0.50 to 0.92).

In general, effects of elemental nutrition compared with active treatments (medications, polymeric nutrition or combination) yielded statistically non-significant results across outcomes with wide 95% CIs, including moderate to large treatment effects in both directions and compatible with both benefit or harm of elemental nutrition (inconclusive results). Data on complications and adverse events were too sparse (e.g. zero events, low counts) to derive effect estimates and 95% CIs or to permit any meaningful comparison between the treatments.

There was no evidence for children with CD. Likewise, none of the studies reported cost-effectiveness of elemental nutrition. Owing to scarcity of data, subgroup and sensitivity analyses could not be performed to explore methodological and clinical sources of heterogeneity.

Discussion

Evidence from two RCTs and three nRCTs demonstrated short-term benefits of elemental nutrition for the maintenance of remission and prevention of relapse compared with no treatment (i.e. unrestricted diet). Adherence rates, as shown in one RCT and two nRCTs (unclear RoB), were lower in the elemental group than in the no intervention and polymeric nutrition groups. This finding may be explained by the inconvenience of nasogastric feeding and the poor palatability and/or high cost of elemental nutrition compared with an unrestricted diet or polymeric nutrition. One RCT found no difference in QoL between elemental nutrition and no intervention (unrestricted diet).

Generally, differences across outcomes between elemental nutrition and active treatments (i.e. medications, polymeric nutrition or combination) were not statistically significant. These results should not be interpreted as the treatments being equivalent (or the absence of effect of elemental nutrition). The associated 95% CIs were wide and uninformative, suggesting both benefit and harm of elemental nutrition. Therefore, these results are inconclusive.

The data on complications and adverse events were too sparse to permit any meaningful comparison between the treatments. The scarcity of reported adverse events and complications could be due to small samples, short-term follow-up, rarity of these events and/or under-reporting of such events.

In general, the review findings warrant cautious interpretation given the limitations of evidence in terms of methodological quality (small samples, short follow-up) and RoB in individual trials (lack of blinding, confounding). For example, the lack of blinding of participants, study personnel and/or outcome assessors in the RCTs may have led to systematic differences in care giving, administration of co-interventions and outcome assessments across the compared treatment groups. Patient-reported outcomes (e.g. abdominal pain, number of soft stools, QoL or clinically defined remission/relapse) are especially prone to bias. Findings from one RCT may have been affected by selective outcome reporting bias. nRCTs, in particular, may have been biased because of the possibility of uneven distribution of known (e.g. location of the lesion, disease duration) or unknown prognostic factors between groups. In some non-randomised trials, patients with ‘good compliance’ were assigned to elemental nutrition and those with ‘poor compliance’ to the control treatment. It is hard to predict the direction of bias (if any), if good and poor compliers differed systematically.

Large long-term follow-up RCTs are needed to fill in the gaps in evidence identified in this review (e.g. studies in young adolescents and children, effects of exclusive elemental nutrition, effects of elemental nutrition in subgroups). The reporting practices in relation to trial methodology and completeness of data should also be improved for better interpretability of evidence. More research exploring better tasting elemental nutritional formulas to maximise the adherence rate to elemental nutrition is also warranted.

Conclusions

There is limited evidence indicating benefits of elemental nutrition in the maintenance of remission and prevention of relapse in adult patients with CD. There was a lack of, or insufficient, evidence on adverse events and complications. Methodological shortcomings of individual studies and gaps in evidence have been identified. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

Trial registration

This study is registered as PROSPERO CRD42013005134.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/08/01. The contractual start date was in July 2013. The draft report began editorial review in January 2014 and was accepted for publication in August 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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