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The role of Exclusive Enteral Nutrition in the pre-operative optimisation of adult patients with Crohn's disease. A Systematic Review.

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Short Title: EEN in elective adult Crohn's disease surgery

Abstract

Aim: To conduct a systematic review in order to bring together the current knowledge about the use of exclusive enteral nutrition (EEN) in the pre-operative optimisation of adult patients with Crohn's disease undergoing intestinal resection.

Methods: We searched Pubmed, Cochrane Library, ClinicalTrials.gov and the EU clinical trial register to identify experimental and observational studies on the effect of pre-operative EEN on nutritional and clinical outcomes of patients undergoing surgery. Methodological quality was assessed using the Downs and Black checklist.

Results: Seven studies were included in the final analysis. Of these 5 were retrospective cohort studies and 2 were retrospective case- control studies. There were 4 ongoing RCTs , however they have not reported data to analyse. Overall the 7 retrospective studies, support that with EEN; body mass index (BMI) does not increase, C-reactive protein decreases (CRP), albumin usually increases and haemoglobin does not significantly change. There were fewer infectious complications in patients who had taken EEN. There was a trend towards fewer stomas but only one of the studies was powered enough to demonstrate significance. There was no significant difference in recurrence rates of Crohn's disease at 12 months in any of the studies. Quality of the studies were either medium or poor.

Conclusion: The current data on the use of EEN in pre-operative optimisation is of poor quality and underpowered to demonstrate significance. Randomised controlled trials are needed to demonstrate whether or not EEN can improve outcomes and reduce stoma formation in adult patients undergoing intestinal resection.

Background

It is estimated that at least 115,000 people suffer from Crohn's disease (CD) in the UK(1). Of patients diagnosed with Crohn's disease, 70-74% will require surgical resection by 10-13 years from diagnosis with those with ileocolic disease being the most likely to require surgery (2,3). Complications of surgical resection are common, and includes surgical site infection which may be associated with sepsis and these complications are higher in those with low albumin, low haemoglobin and high C-reactive protein (CRP)(4). Stoma rates are high, with one study citing 40% rate of temporary stoma formation and 14% rate of permanent stomas at 20 years (5).

Exclusive enteral nutrition (EEN) is widely used in children with Crohn's disease, and is successful as first-line therapy, inducing remission in 60-80% of cases without the use of steroids (6–8). In adults, EEN can be used as an alternative to steroids, usually for a period of 3-6 weeks, but the evidence is weak and this is likely to be due to tolerability and acceptability (9). Steroids are often used as first-line therapy for adults presenting acutely with active small bowel Crohn's disease. However, this causes a problem if the patient then requires surgery as steroids significantly increase the risk of anastomotic leak, delayed wound healing, surgical site infection, pneumonia, myocardial infarction, renal insufficiency, prolonged intubation, cardiac arrest, longer hospital length of stay and mortality(10,11). Therefore, for adults who require an operation for Crohn's disease, managing them with EEN instead of steroids to downstage their disease, followed by a planned, semi-elective operation in an optimised state could lead to improved surgical outcomes.

Our aim was to assess with a systematic review of the current evidence whether there is benefit in the use of exclusive enteral nutrition in adult patients undergoing elective surgery for Crohn's disease.

Method

We performed a systematic review of the literature and have reported in accordance with the PRISMA guidelines (12). The research protocol along with the search strategy is registered on the PROSPERO database for systematic reviews (PROSPERO CRD 42020221761).

Eligibility Criteria

Eligibility criteria were guided by the PICO (Patients, Intervention, Comparison, Outcomes) approach.

The inclusion criteria where: Original studies where they reported the use of EEN as an approach to analysing its impact on the surgical management of adult patients with Crohn's disease, prospective observational and experimental designs were considered eligible, including randomised control trials (RCTs) as well as prospective and retrospective studies, irrespective of geographical location, number of patients, duration of intervention or follow up, any formulation administered as EEN to patients, adult patients only and English full text articles.

The exclusion criteria were: studies in the paediatric population, diseases other than Crohn's disease, studies that did not involve surgical management of Crohn's disease, Stuides not published in English , if the full text was unavailable, where EEN was not analysed as a separate entity even when used in combination with other modes of nutrition.

Search Strategy

A literature search was conducted on PubMed and Cochrane Library electronic databases from inception until August 2020. We also searched two clinical trial registers: clinicaltrial.gov and EU clinical trial register. The search strategy used MeSH index terms and free-text restricted to titles and abstracts.The search was initially developed for PubMed by two researchers (ARAA & JGR) and then adapted to other databases. Retrieved records were imported into Rayyan for removal of duplicates, screening and blinded screening of relevant literature by 2 independent reviewers.

Study Selection

Rayyan was used for this review's selection and data processes. For quality control, two reviewers (CEG & AGD) independently screened 100% of titles and abstracts for full-text review against the inclusion/exclusion criteria. Any differences in study inclusion/exclusion was discussed with the aim of reaching consensus. After the screening process full-text versions of selected articles were assessed. The search and selection process were documented and presented as a PRISMA flow-chart (Figure 1) showing numbers of articles excluded at each stage and reasons for exclusion of each of the articles obtained at the full-text stage.

Data extraction

Data were extracted into standardised pilot tested forms by two reviewers (JGR and CG). Firstly, the details about the individual studies including author, year, location, number of patients, exclusion criteria, type of EEN used, duration and comparision or control groups were recorded. Secondly, information about nutritional and biochemical data including body mass index (BMI), haemoglobin, albumin and CRP measurements were extracted. Finally, clinical data including complication rates (specifically anastomotic leak and infectious complications), stoma creation/ avoidance, hospital length of stay, readmission and recurrence were recorded. A meta-analysis was not conducted. A narrative synthesis was performed.

Quality Assessment

The methodological quality of included studies was assessed by a two reviewers (RH and CEG) using a modified Downs and Black checklist designed specifically to appraise both experimental and observational studies(13). The checklist is composed of 27 questions (Yes, No and Unable to determine) which are divided into five sections: Reporting; External validity; Internal validity - bias: Internal validity - confounding; and Power. The checklist provides both an overall score for each study quality and a specific score for each section. Studies were classified into three groups: high (22 points or 80% of the total), medium (≥ 14 and < 22 points or ≥ 50 % and < 80 %) or low quality (< 14 points or < 50%).

Results

Out of 3520 papers initially identified, 1097 were excluded due to duplication, then 2409 excluded due to irrelevant titles and abstracts, leaving 14 full text articles for full text

assessment (Figure 1). Fourteen full-text articles were assessed for eligibility of which 7 were excluded, mostly because they were not studies that specifically analysed EEN as an independent factor in the pre-operative optimisation of elective patients undergoing surgery. Seven studies were included in the final analysis of which 5 were cohort studies and 2 were case-control studies (Tables 1 and 2). Of note 4 ongoing RCTs were found, which have relevant protocols and would have been included in this review except the data of these trials are not yet available (14–17).

All studies included used a retrospective design with regards to collection of data. Four of which were from China, 1 from the UK, 1 from France and 1 from Japan. Of the 7 studies included, two used Peptisorb liquid (Nutricia, Amsterdam, Netherlands) as EEN, two used Peptison liquid (Nutricia, Amsterdam, Netherlands and Shanghai, China) two used Modulen IBD (Nestle, Vevey, Switzerland) and one used Elental, Ajinomoto Pharmaceuticals, Tokyo, Japan. Pre-operative duration of administration was between a minimum of two weeks and three months. The number of patients included in each study who had been treated with EEN pre-operatively varied between 24 and 219.

Pre-operative impact on Body Mass Index (BMI) and biochemical tests

Four of the studies reported data on the impact of EEN on pre-operative body mass index or weight and biochemical tests (Table 2). Only 1 reported a significant increase in BMI ($p=<0.01$) and the others non-significant increase in BMI ($p= 0.17$) or weight ($p=0.92$) and decrease ($p=0.63$)(18–21). Two studies reported a significant increase in pre-operative haemoglobin and four reported a significant increase in albumin with a $p <0.05$ (18,21). Five studies reported a significant decrease in CRP (see table 2).

Post-operative outcomes

Various post-operative outcomes were reported: Five studies reportied an overall complication rate (Table 3) . One study reported an infectious vs non-infectious complication rate (18). others reported rates of specific infectious complications using various terminology including anastomotic leak, surgical site infection (SSI), incisional SSI, organ or space SSI and intra-abdominal abscesses. In all included studies, the EEN group had a lowered overall complication rate, the difference was more likely to be significant when the outcome of interest was defined as a specific infection related complication, such as abscesses and anastomotic leak (Table 3) (18-19,21-23, 25). Six studies reported a significantly lower rate of infection related complications.Three studies reported stoma creation rates of which only one study showed significant results ($p<0.05$)(23). It is worth noting that this study had the largest sample size (n=219 for the EEN group). Hospital length of stay was reported by two studies and was 7.5 and 9.4 days respectively (20,21). Two studies reported re-admission rates which were 3% and 7.8% (22,23). Recurrence rate was analysed in 3 studies. Two of the studies reported a significant difference in the rate of endoscopic recurrence at 6 months ($p=0.044$ and $p=0.03$) (21,18). However there was no significant difference in the recurrence rate of Crohn's disease whether clinical or endoscopic at 12 months in the three studies that reported this outcome (18,21,22).

Quality Assessment

None of the studies were of high quality (Figure 2). Five studies were of medium quality and two of low quality. None had performed a power calculation to detect a clinically important effect of EEN pre-operatively. None of the studies was blinded or randomised.

Discussion

This is an up to date systematic review , aiming to improve the current understanding of the role of EEN in the pre-operative optimisation of adult patients undergoing elective surgery for Crohn's disease. The results suggest that EEN may have a role in pre-operative optimisation by improvement of nutritional status and reducing inflammation as reflected by decreasing inflammatory markers such as the CRP. Nutritional status does seem to have some correlation to the improvement in the pre-operative albumin levels which tend to increase with EEN. BMI itself doesn't seem to be reflective as the patients generally have better outcomes with EEN even though there is no evidence ot support that EEN increases the BMI. EEN may have a role in reducing post-operative complication rates and stoma creation rates. The largest study by Li et al in 2015, with 219 patients in the EEN/immunosuppressant free interal group, was likely to be adequately powered to assess the efficiacy of the intervention, and found the rate of overall complications was lower, particularly those of an infectious nature. This is a promising results as preventing an anastomotic leak is a critical outcome regarding a life threatening complication (23). Overall, the current evidence to date is generally of medium to poor quality, and is retrospective in nature with inadequate controls.

Discussion over the role of EEN in the pre-operative management of Crohn's disease can be fraught with difficulties because of the variable nature of the disease and it's severity, and multiple other factors that impact on nutritional markers, stoma creation and infectious complications. These include patient factors such as frailty, comorbidity, steroid and immunosuppressant use, smoking status and surgeon related factors such as decision-making around the timing of surgery and opting to create a stoma.

EEN has been extensively trialled in the paediatric population in the context of Crohn's disease and the efficacy of EEN is reported to be equivocal to steroid therapy with regard to inducing remission. EEN improves nutritional status, weight and induces mucosal healing in children whilst avoiding the side effects of corticosteroid therapy(24). EEN is considered the first-line management option in children with CD and data albeit weak evidence suggest that this may be extrapolated to adults (6,22) .

Strengths and Limitations

We conducted a systematic review that specifically targeted EEN as a sole mode of nutritional support. This is advantageous in achieving the aim of this review however may have excluded clinically relevant studies which have incorporated other means of supporting the patients such as partial enteral nutrition or TPN- EN coadministration which may be beneficial in certain circumstances. More research on this topic is needed, and the RCTs considered the gold standard of evidence are still ongoing to allow what would have been meaningful incorporation into this review. As such cautious interpretation of the findings of this systematic review is warranted.

Conclusion

There is inadequate evidence currently for the use of EEN in adult patients with Crohn's disease. The limited evidence that exists suggests that there may be a significant role for pre-operative EEN in downstaging disease by reducing inflammation, improving nutritional and

biochemical markers, reducing infectious post-operative complications and reducing stoma formation. Randomised controlled trials of EEN in comparison to standard care are required to understand what role EEN has in optimising outcomes for adult patients with Crohn's disease for surgery.

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Data availablility: The data underlying this article are available in the article and in its online supplementary material.

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