Leading article

Total parenteral nutrition as primary treatment in Crohn’s disease – RIP?

The unpredictable course of Crohn’s disease presents the clinician with many questions concerning therapy, most of which remain unanswered. Ideally prospective, controlled, randomised trials can indicate optimal methods of treatment, but the clinical variability of this disease of unknown aetiology has made such trials difficult to design and to undertake. Since Crohn’s disease was first described over 50 years ago, the aims of therapy have remained the same, to stop the acute attack swiftly and then delay relapse for as long as possible, preferably without recourse to surgery. Several trials of medical treatment have been reported. Two controlled prospective randomised studies indicated that steroids and sulfasalazine were the best drugs in the treatment of the acute attack. Steroids and sulfasalazine together would maintain remission in up to 40% of patients over two years, compared with only 10% on placebo. Azathioprine 2.5 mg/kg/d has been shown to have a significantly beneficial effect in maintaining patients in remission. Metronidazole has also been reported to have a place in the treatment of active disease. None of these treatments, however, is without a substantial incidence of side effects.

In the late 1960s and early 1970s interest focused on total parenteral nutrition (TPN) when various reports indicated that the nutritional state of severely ill patients could be maintained, or even improved, whilst allowing more time for medical therapy to induced remission of the acute attack. TPN could be used in patients in whom medical therapy had failed to improve their general condition before surgery. It was observed that TPN obviated the need for surgical intervention in some patients. It was postulated that the ‘bowel rest’ achieved as a result of the TPN might be in itself of primary importance in the treatment of inflammatory bowel disease. The principle of ‘bowel rest’ using surgical techniques such as ileostomy to divert intestinal contents from the inflamed bowel and thus allow healing, had been suggested before, although such diversion was applicable only when the disease was confined to the colon.

One of the great problems in judging published results of TPN in Crohn’s disease has been that interpretation of the benefits and mechanisms of action have been confused by the differing aims and methods by which data have been collated in various studies. Examples of these pitfalls include studies which examine both Crohn’s disease and ulcerative colitis; studies which are uncontrolled and/or non-randomised and retrospective reviews. ‘Drug resistance’ and ‘failure of medical therapy’ are often not formally defined. The importance of clearly defining such terms has been emphasised elsewhere.

In this issue of Gut Greenberg et al, report a prospective, randomised, controlled trial of bowel rest and nutritional support in the management of Crohn’s disease. Patients with Crohn’s disease ‘unresponsive to medical
management' (with steroid doses before entry stated) were randomised to 21 days of nutritional support in three groups: TPN with nothing by mouth, a nasogastrically administered, defined formula, whole protein containing diet, or partial parenteral nutrition supplying some of the nutritional requirements with ad libitum oral food. Remission of disease was defined as a modified Crohn's Disease Activity Score of less than 150 on day 21. All patients who remitted were maintained on a dose of 15 mg steroids daily and followed up at one year. There was no significant difference in outcome between the three groups with respect to the number of remissions of acute disease (58–71%), or the number of patients still in remission at one year (42–56%). This new study thus dispels the idea that 'bowel rest' plays an essential part in the induction and subsequent maintenance of remission in active Crohn's disease and this is in accordance with the earlier work of Lochs et al. It must be emphasised, however, that this report specifically shows that 'bowel rest' in the conventional sense of withholding nutrients from the intestinal mucosa, is not a prerequisite to achieving remission in those patients who are also receiving medical treatment. The authors record the daily doses of steroids in each group before entry into the study (TPN 24±3 mg; defined formula diet 23±3 mg; partial parenteral nutrition 21±3 mg). Some might argue that higher doses could have induced remission without nutritional support.

The case for TPN as a primary therapy in Crohn's disease is thus confused in this and other studies by either prior, or concurrent administration of standard medical treatment. So far there is no prospective randomised controlled trial comparing TPN alone with standard medical therapy in acute Crohn's disease. The data of Greenberg et al., indicate that such a trial is not needed because the premise that bowel rest (as achieved by TPN) is essential, or beneficial in achieving remission of acute Crohn's has now been shown to be invalid.

Specific ways in which bowel rest can promote healing of affected bowel have been proposed. It has been postulated that bowel damage occurs in relation to the antigenicity of intraluminal contents, possibly in association with disordered immunological function which is secondary to the disease and may be associated with malnutrition. It would follow that improvement of nutrition with a resultant normalisation of immunological function and withholding of antigenic food proteins, or decreased intraluminal concentrations of bacteria might directly benefit the gut. It is also reported that administration of TPN may result in functional change of the intestinal microflora, although the clinical significance of such changes is unclear.

The potential disadvantages of TPN and 'complete bowel rest' must be considered. Even in specialised centres there is a small, but definite morbidity associated with this technique, whatever the indications for using it. The theoretical disadvantages of using TPN as primary therapy for Crohn's disease must be borne in mind. There is now much evidence that glutamine is essential for the normal structure and function of the intestine. Commercial TPN solutions do not contain glutamine and villous atrophy is well recognised in patients receiving TPN. There is increasing evidence that fermentable fibre within the gut lumen may stimulate epithelial cell proliferation in the small and large intestine, possibly by a mechanism involving production of volatile fatty acid and release of plasma enteroglucagon. Glutamine and fibre therefore may promote gut healing.
Treatment with TPN and ‘bowel rest’ denies the acutely inflamed intestine these substrates.

These considerations are important when considering enteral diets as primary therapy in Crohn's disease. The potential benefits of elemental diets have been reported by several investigators. More recent controlled studies have confirmed the efficacy of this treatment. An elemental diet may supply glutamine at the same time as improving nutritional status, but lacks fermentable fibre. It would be interesting to determine whether a fibre supplemented, glutamine rich, chemically defined elemental diet has any additional therapeutic advantage in Crohn’s disease.

The evidence at present indicates that TPN in Crohn’s disease should be restricted to supportive, rather than used as primary therapy. It is undoubtedly useful in some circumstances, particularly in the treatment of specific complications of Crohn’s such as intestinal obstruction related to stricture formation, or short bowel syndromes following repeated resection. Available data seem to suggest that most of the benefit of TPN is related to the improvement of nutritional state. Theoretical and practical reasons dictate that the way forward in the development of more effective (and perhaps safer), alternatives to drugs in the treatment of acute Crohn’s disease must be the evaluation of enteral diets in prospective, randomised controlled trials. There have been many opportunities for evaluation of TPN in this disease, but its advocates have taken too long to achieve positive results. The report of Greenberg et al may be a nail, if not the final nail, in the coffin of TPN as primary therapy in the treatment of acute Crohn’s disease.

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