

Current and novel treatment modalities for chronic idiopathic constipation

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Patients referred for hospital assessment of chronic constipation have usually already failed attempted treatment with dietary and lifestyle modification together with a variety of laxatives. The patients who are referred tend to be young or middle aged women often with a long history stretching back into childhood. Other terms for this group of patients include functional constipation, refractory constipation or constipation predominant irritable bowel syndrome (IBS-C). Widely accepted consensus definitions have been developed (ROME III)¹. Audit of patients attending specialist constipation clinics show that 70% of patients fulfil IBS-C criteria, while the majority of the remainder fulfil functional constipation criteria². Management of these patients is hampered by a lack of understanding of the condition, by likely heterogeneity of the underlying pathophysiology, and by a paucity of high quality comparative research trials regarding the best forms of assessment and treatment. Patients with this condition often suffer very significantly and the effects on quality of life are greatly underestimated. Large-scale community studies show that even patients with community based constipation who do not seek medical attention have a significant reduction in their overall quality of life³. Surveys of patients with functional bowel disease often indicate a significant degree of dissatisfaction with medical care⁴.

The basic treatment of this condition, with dietary modification and laxatives has remained unchanged for many decades. In the last ten years however, we have seen the introduction of a number of novel therapies including biofeedback and behavioural therapies, rectal irrigation, anal sphincter injections with

botulinum toxin, ante-grade continence enema (appendicostomy) surgery, percutaneous colostomy, sacral nerve stimulation, and a new generation of pro-motility drugs.

Standard Therapies

A high fibre diet increases stool weight and speeds colonic transit in normal individuals; a low fibre diet causes constipation. Many patients presenting to primary care services with constipation have the disease because of a lack of fibre in their diet, and replenishing dietary fibre leads to resolution of their symptoms. This has led to many patients with chronic idiopathic constipation being repeatedly asked by their physicians to increase the fibre in their diets. We have been forced into looking at whether chronic functional constipation is caused by low fibre and all of these studies have unequivocally shown that this is not the case⁵. When supplemental fibre is added to diets of normal individuals a marked increase in stool weight can be seen, but studies in patients with chronic constipation show only a 20% increase in stool weight and this is at the expense of significant additional gas production through fermentation. The excess gas leads to increased abdominal bloating and pain and overall symptom profiles of patients with chronic functional constipation on supplemental fibre show deterioration rather than an improvement. Furthermore, the repeated advice to patients that their symptoms would improve if only they could manage the correct diet, compounds an already difficult situation by leading to feelings of frustration and failure.

Laxatives are readily used in the short-term but long-term use is restricted because of

unjustified concerns about safety. These concerns have become ingrained in medical teaching despite being based on circumstantial evidence. Laxative use should be encouraged and many patients will only find satisfactory relief with higher than usual doses or even combinations of laxatives. Laxative effect will wear off over a period of a year to 18 months due to changes in bacterial flora. Thus it is important for patients to recognise this and be ready to experiment with other laxatives when this occurs.

When initial treatments have failed and symptoms are severe and incapacitating some patients turn to colectomy as the ultimate answer. The efficacy of colectomy is hard to judge as studies are usually small (median number of patients 35), uncontrolled, short-term, retrospective, and often performed by the surgeons who performed the operation. Meta-analysis of 17 studies comprising 538 patients showed that 403 (75%) had a good early outcome (unpublished). Mortality is between 1 and 2% with major morbidity of 10% and further surgery or stoma formation may be as high as 10%. In the Durham constipation clinic we see 130 new patients per year and have a further 200 under follow-up. We perform about 5 colectomies per year and believe that long-term satisfaction rates are around 50%. Patients with severe pain as a predominant feature or significant psychiatric disturbance seem to fare badly.

Specialist and novel therapies

Biofeedback has become established as an effective risk-free treatment for chronic constipation when traditional treatments have failed. The goals of biofeedback are to teach diaphragmatic breathing exercises, teach anal sphincter and pelvic floor relaxation, improve rectal sensation, eliminate sensory delay, and improve recto-anal co-ordination⁷. There have

been over 20 studies of biofeedback for the treatment of chronic constipation since 1988, with a total of around a 1000 subjects having between two and 14 treatments. Follow-up in these studies has varied between one month and three years and overall 62% of patients improved (range 22% to 100%). Long-term efficacy has been established. The very large range in success rates between units, and indeed between individual therapists within a single unit remains unexplained. It is likely that biofeedback is a complex therapy involving not only true biofeedback but also elements of behavioural therapy produced by a strong rapport between therapist and patient.

Rectal irrigation involves the use of a small electric pump, or gravity fed system, to instil up to 1 litre of water into the rectum through a soft nozzle. This is performed by the patient on an as-required basis. Results show 50% success rate with no significant complications. Patients need to be highly motivated, but many feel empowered by the self-control they have using this treatment. Rectal irrigation is particularly useful for patients who have both constipation and faecal incontinence⁸.

Anal sphincter injection with botulinum toxin was first reported in 1988 and since then few reports have appeared in the literature, but once again these studies have tended to be retrospective and small. The largest study⁹ described the use of this treatment in 50 patients with whom 49 responded and few complications are reported. The mechanism of action may be more than just reducing outlet obstruction, and may involve improvements in colonic transit as a whole. Anal sphincter contraction may produce an inhibitory reflex on the colon, and abolition of contraction may remove this inhibitory response. It may be that the positive reports in the literature are an overestimate, and certainly there has not been widespread take up of this treatment. Our experience in Durham has been quite

disappointing with only 20% of patients (unselected) obtaining benefit and a 10% rate of significant anal pain or faecal incontinence. This treatment is therefore reserved for those patients with definite anismus, or those who have failed medical treatments, biofeedback and rectal irrigation and are not willing to consider surgical options.

For those patients failing non-surgical treatments three minimally invasive procedures can be considered. The first of these is an appendicostomy, usually performed laparoscopically, allowing the cecum to be intubated and an ante-grade enema used to clear out the colon. The efficacy of the procedure is initially very high and it is an excellent bridge to further therapy, but the volumes of liquid required to clear out the whole colon are considerable and the time involvement with each treatment is therefore significant. Most patients find the process rather cumbersome and many will be satisfied for only the first year because of this. Other problems include recurrent leakage from the stoma site. In the last few years a refinement of this idea has been developed using a gastrostomy feeding tube placed in the left colon as a percutaneous endoscopic colostomy (PEC). In Durham we have recently published the largest series worldwide of this treatment (28 patients)¹⁰. The efficacy is excellent and the volumes of liquid required to stimulate defecation can be very small. Rapid distension of the rectum by installation of just 200 ml of water into the left colon can result in an urge to defecate, and usually passage of a normal motion, within minutes. However, whilst the overall efficacy both in terms of symptoms and quality of life seems very good for this procedure, it suffers from recurrent infections of the tract which does not become epithelialised. Further work is required to prevent these infections before this can become a standard therapy.

Sacral nerve stimulation has become a popular

treatment modality for patients with fecal incontinence as well as bladder dysfunction^{11,12}. Recently the technique has also been studied in patients with chronic functional constipation in a multi-centre study showing good early response. Long-term follow-up and further studies may be necessary before this treatment can be offered widely to such a large group of patients in view of the cost involved. In Durham we are currently recruiting to a study of sacral nerve stimulation in constipation caused by neurological disease. Theoretically efficacy should be better, and there may be additional benefits from improvements in bladder and sexual function.

There is great interest in the development of novel drugs for the management of gut-motility disorders. Two drugs were recently licensed for the treatment of constipation by the American FDA; tegaserod a partial 5HT₄ agonist, and lubiprostone a chloride channel activator. Tegaserod increases colonic motility and may have effects on visceral hypersensitivity as well. Through its action on 5HT₄ receptors, Tegaserod stimulates the peristaltic reflex, increases colonic motility, decreases visceral hypersensitivity and facilitates secretion into the colon^{13,14}.

A large number of well-controlled large-scale studies have been performed around the world. Typical response rates are 40% with a 25% placebo effect. Responders have been determined either by an improvement in global rating scale, or by an increase in bowel movements of one stool per week. A necessity for large studies to produce statistically significant response rates highlights the fact that the magnitude of effect is limited. The drug was refused licence in Europe because of this, and in March 2007 at the request of the FDA, the manufacturer of Tegaserod agreed to stop selling the drug¹⁵. Analyses of 29 studies suggested an increase risk of cardiovascular and cerebrovascular events in those treated with

Tegaserod, compared to placebo. Tegaserod is therefore off the market for general use. In the USA the FDA has approved its use in special cases where alternative therapies are not possible for patients with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation.

Lubiprostone is a chloride channel activator which improves bowel function by increasing secretion within the small bowel¹⁶. There have been fewer studies of this drug and it is possible that the efficacy would be similar to that seen with an osmotic laxative. Naloxone and derivatives of naloxone are currently in late stage trials and many other pro-motility agents are being studied. In addition there is very important work in the understanding of visceral hypersensitivity and agents which affect the neurological pathways and receptors responsible for functional gut pain are being developed. In the next decade it is likely that a number of new drugs will be released providing an armoury of new medical treatments for this condition.

Concluding Remarks

The therapies described above are all currently available, but providing them all on one site requires a large patient throughput, particularly to allow adequate skills for those techniques that are used infrequently. Furthermore, we need to develop algorithms for the order in which treatments should be used, ideally based on comparative studies and high quality audit. Thus, it seems sensible to develop regional centres specialising in this condition.

Finally, patients with functional bowel disorders need to be treated holistically and on an individual basis, and we have found that the use of nurse consultations, by a dedicated and multi-skilled specialist nurse, acts as the centre-point of management.

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