WHEN ALL SEEMS LOST: MANAGEMENT OF REFRACTORY CONSTIPATION – SURGERY, RECTAL IRRIGATION, PERCUTANEOUS ENDOSCOPIC COLOSTOMY, AND MORE

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Short title: PEC and other options for refractory constipation

Abbreviations: **CC** Chronic Constipation

IBS-C Irritable Bowel Syndrome with Constipation Predominant Symptoms

DD Defecatory Disorders

NNT Number needed to treat

TAI Trans-anal Irrigation

RCT Randomised Controlled Trial

STC Slow Transit Constipation

PEC Percutaneous endoscopic colostomy

MACE Malone antegrade continence enema

CIPO chronic intestinal pseudo-obstruction

SV Sigmoid Volvulus

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Abstract:

While the pharmacological armamentarium for chronic constipation has expanded over the past few years, a substantial proportion of constipated patients do not respond to these medications. This review summarizes the pharmacological and behavioural options for managing constipation and details the management of refractory constipation. Refractory constipation is defined as an inadequate improvement in constipation symptoms evaluated with an objective scale despite adequate therapy (i.e., pharmacological and/or behavioural) that is based on the underlying pathophysiology of constipation. Minimally-invasive (i.e., rectal irrigation and percutaneous endoscopic colostomy) and surgical therapies are used to manage refractory constipation. This review appraises these options, and in particular, percutaneous endoscopic colostomy, which as detailed by an article in this issue, is a less invasive option for managing refractory constipation than surgery.. While these options benefit some patients, the evidence of the risk: benefit profile for these therapies is limited.

Keywords: refractory constipation, PEC, rectal irrigation, surgery

Introduction

Chronic constipation (CC) and constipation-predominant IBS (IBS) are defined by symptom criteria. The majority of patients with CC and IBS probably self-manage their constipation, mainly using lifestyle (dietary) adjustments and over-the-counter osmotic and/or stimulant laxatives[1]. For those who seek medical attention, current guidelines also initially recommend laxatives, followed, if necessary, by assessment, initially of, anorectal functions and thereafter when necessary, colonic transit[2]. Both CC and IBS-C can be associated with slow colonic transit[3], which can be readily identified with available techniques. Newer prescription medications are recommended for patients in whom normal or slow transit constipation do not respond to laxatives. Defecatory disorders (DD), which are diagnosed by symptoms of CC or IBS and abnormal anorectal tests, are appropriately managed with pelvic floor biofeedback therapy. It can be challenging to diagnose defecatory disorders in some patients because the results of anorectal tests may be equivocal. The proportions of patients with slow colon transit and DD varies among series[1,2]. Some constipated patients also have visceral hypersensitivity, which is more common in IBS-C than CC[4].

Currently available prescription drugs for constipation include lubiprostone and linaclotide, which are approved for treating CC and IBS-C in Europe and the United States, plecanatide, which is approved for treating CC in the United States, and the selective 5-HT4 receptor agonist prucalopride, which is approved for treating constipation in Europe and several other countries but not in the United States. In clinical trials, all these agents were better than placebo. In CC, the number needed to treat (NNT) ranged from 4 (95% CI 3-7) for lubiprostone to 6 (5-8), for linaclotide and 6 (5-9) for prucalopride [5]. For IBS-C, the NNT was 13 for lubiprostone and 7 (5-8), for linaclotide; prucalopride has not been studied in IBS-C. Of note, the NNT for polyethylene glycol in CC is 3 (2-4). Colonic transit was not evaluated in any of these trials. Hence, the efficacy of these drugs in slow transit constipation is unknown. Since placebo, not over-the-counter laxatives, were the comparator in all studies, head-to-head comparisons of these drugs versus simple laxatives are unavailable. Finally, failure to respond to over-the-counter laxatives was an eligibility criterion for studies with prucalopride but not for studies with lubiprostone, linaclotide or plecanatide. Hence, the incremental utility of these agents over traditional laxatives is unknown. While pelvic floor biofeedback therapy is beneficial for defecatory disorders, the technique is operator dependent and not widely available. Indeed, even in a clinical trial from an experienced centre, the response rate was only 61%[6].

Hence, a substantial proportion of patients have refractory constipation, which we define as an inadequate improvement in constipation symptoms evaluated with an objective scale, despite adequate therapy (i.e., pharmacological and/or behavioural) that is based on the underlying pathophysiology of constipation. A practical definition of adequate duration is a minimum of 4 weeks for each drug and 3 months for pelvic floor biofeedback therapy. The clinical decision-making tool proposed by an international consensus statement provides a simple and effective approach for evaluating the response to therapy[7]. The four week criterion is underpinned by the recognition that most patients who response to medications for constipation generally do so within 4 weeks[8].

In clinical practice, currently, a colectomy is the next step for patients with refractory slow transit constipation who do not have a DD. Before surgery, a colonic manometry with or without barostat testing should be performed, where available, to identify colonic inertia, which is defined by impaired responses to a meal and pharmacological stimulation with bisacodyl or neostigmine[9]. However, by comparison to children with chronic constipation[10], there is limited data on the clinical utility of colonic manometry/barostat testing in adults with refractory constipation[1]. Before a colectomy, gastrointestinal transit should also be assessed when the clinical features suggest an upper gastrointestinal motility disorder. In the present issue of *Neurogastroenterology and Motility,* Strijbos

et al suggest that percutaneous endoscopic colostomy (PEC) is perhaps a less invasive option for refractory constipation as compared to surgery[11]. This review appraises the current options for these patients.

The available treatment options for refractory constipation:

The role of rectal irrigation:

Trans-anal irrigation (TAI), also known as rectal irrigation, involves the instillation of water into the rectum to facilitate a washout of the rectum and sigmoid colon. The volume of water may vary (typically between 70ml and 1000ml) and there are now a variety of devices that can be used to achieve this[12]. While the initial and most subsequent reports were in patients with neurogenic bowel dysfunction[1314,15], it has also been studied in patients with non-neurological chronic constipation (CC) and faecal incontinence[16]. It is increasingly used in units that manage patients with CC. Since these are uncontrolled, mostly small and retrospective reports, its true efficacy is not understood.

A recent systematic review and meta-analysis of TAI in CC[17] identified seven studies including a total of 254 CC patients. All studies were uncontrolled and all but two were retrospective. The proportion of patients reporting a positive outcome of therapy varied from 30% to 65%. A fixed effect analysis of proportions gave a pooled response rate of 50% (95% CI 44-57%). Since most studies were retrospective, the true response rate may be lower. Nonetheless, this response rate is meaningful since patients treated with TAI have usually failed all other conservative options.

Since that review, another large retrospective report[18] in which outcome questionnaires were available in 102 of 148 consecutive patients has been published. The patients reported 21,476 irrigations over 119 patient years, with a mean duration of therapy use of 60.5 weeks. The proportion of patients in whom symptoms improved were as follows: general well-being (65%), rectal clearance (63%), bloating (49%), abdominal pain (48%), and bowel frequency (42%). When asked about overall satisfaction, 67% of patients were “moderately better” (39%) or “very much better” (28%). However, baseline characteristics (i.e., age, duration of constipation, proctographic findings of obstructive defaecation, and colonic transit time) did not predict the response to TAI.

Conceivably, large and small volume TAI may work via different mechanisms. Small volumes may wash-out stool in the rectosigmoid colon, whilst larger volumes may also induce a more proximal colonic contraction that enables colonic evacuation. A scintigraphic study observed anterograde propulsion throughout the colon after TAI[19]. Anecdotally, some patients report an improved urge to defecate after TAI.

TAI is contra-indicated in early pregnancy and where there is an increased risk of perforation (e.g., colitis, cancer, recent resection). Rectal perforation is uncommon (i.e., approximately 1 in 500,000 irrigations) and has been mostly reported in in bedridden patients.[20], [21]. Over 50% of patients who discontinue therapy do so because they find it too inconvenient or because they experience technical difficulties (e.g., water leakage, catheter expulsion, a burst balloon, and peri-anal discomfort) [22]. While TAI is relatively expensive, it reduces the cost of care and is cost-effective in patients with spinal cord injury and constipation [23].

In summary, TAI is useful for managing some patients with refractory chronic constipation. However, prospective studies are required to assess its efficacy, identify predictive factors, determine the

relative value of different methods of irrigation (eg low volume versus high volume), and evaluate the cost-effectiveness. A current multi-centre UK study (CAPACITY 2) is designed to answer some of these questions[24].

The role of surgery:

Exemplifying *primum non nocere*, surgery is reserved for a carefully selected, small proportion of patients with medically-refractory chronic constipation (Table 1). Surgery can restore anatomy, but not, with the possible exception of neural implants, modify neuromuscular functions. In contrast to other therapies, surgery has the potential for irreversible harm.

The outcomes of all main procedures for CC were systematically reviewed in 2017[25-31] (*all full open access*) [Table 1]. In brief, the evidence is very poor. In 113/156 (72.4%) studies, the evidence was rated as level IV; only 4 level I RCTs were included[25,31]. Poor quality observational data are the Achilles heel of surgical research and must be acknowledged to suffer from almost every known source of bias. Further, the use of global satisfaction ratings to judge outcome acknowledges the limited use of validated outcomes in all but a few studies. A recent, large, US retrospective cohort study of over 2000 patients[32] reported high complication rates and greater long-term post-procedural health utilization (ambulatory care, hospital admissions, radiology etc.) after than before surgery. By contrast, a systematic review of 40 observational studies reported a global satisfaction rate of 86% after colectomy for slow-transit constipation, This is the highest of all procedures in Table 1. These differences underscore the differences between global satisfaction ratings and rigorous validated outcomes, which were only used in a few studies. Similarly, the beneficial outcomes of sacral neuromodulation for CC, claimed on the basis of observational data, have been completely refuted by 2 subsequent RCTs that both show no benefit of this procedure over sham stimulation[33,34].

Detailed summary evidence statements derived from these reviews were used to develop (by European expert consensus) a series of graded practice recommendations that address patient selection, procedural considerations and patient counselling[31]. Counselling should consider the balance between benefits and harms, as underscored by recent media reports of the uncommon but significant harms caused by placement of pelvic mesh during rectopexy (infection, erosion and chronic pain) [35,36] and to a lesser extent, the use of stapling devices to excise the rectal wall (STARR procedure) (chronic pain, urgency and incontinence)[36].

Over and above the introduction of enhanced consent processes for such procedures[35], it simply cannot be stressed enough that the selection of patients for potentially harmful surgery must be made with the expectation that their symptoms will be improved by surgery. This should focus the surgeon well beyond sight of the 'structural problem' and requires an understanding of the patient's perception of success as well as a degree of certainty that the evident structural problem is in fact the cause of their symptoms. These points are again illustrated by considering colectomy for STC. Many, if not nearly all, patients with STC have abdominal pain, and many have bloating. If these are the main symptoms, then colectomy is unlikely to help since surgery if anything worsens rather than improves these symptoms[26] accounting for much of the post-interventional health utilisation observed by Dudekula et al[32]. Prior to colectomy, a temporary loop ileostomy may help ascertain whether symptoms emanate from the small intestine or colon. Similarly, the criteria for operating on a rectocele must consider whether symptoms are those typical of a rectocele i.e. vaginal bulging with obstructed defecation and partial resolution with splinting, and whether a large rectocele is both clinically evident and confirmed by diagnostic radiology. If such criteria are met, and relative

contraindications are absent e.g. smoking and obesity, then a reasonable chance of success can be anticipated. This will not however be true of a patient with chronic pelvic pain and dyssynergia who happens to also have a rectocele. A further point in relation to pelvic organ prolapse syndromes is that the 3 organs that immediately depend for their anatomical disposition on the pelvic floor (bladder, vagina and anorectum) should not be addressed by a silo approach between surgical specialities. To neglect the opportunity to correct anatomy of multiple pelvic compartments e.g. synchronous sacrocolpopexy and rectopexy may unnecessarily subject patients to further, more complex, re-operative surgery.

These points, taken together, reaffirm the need for great caution when recommending surgery for chronic constipation. They also underscore the importance of a meticulous assessment of clinical features supplemented, as appropriate, with physiological and radiological tests, followed by multidisciplinary coordination of management preferably in accredited specialist units[35] before surgery is contemplated.

The role of PEC:

Percutaneous Endoscopic Colostomy (PEC) is a variation of the percutaneous endoscopic gastrostomy technique. First proposed in 1986 by Ponsky et al.[37], it is currently used as a less invasive alternative to surgery for patients suffering with sigmoid volvulus (SV) or chronic intestinal pseudo-obstruction (CIPO). More recently, is also used to manage patients with chronic constipation.

The procedure itself involves the insertion of a tube through the abdominal wall into the colon, assisted by colonoscopy. The tube is used to provide antegrade colonic irrigation and lavage. This is similar in theory to the Malone antegrade continence enema (MACE) procedure, commonly performed in patients with faecal incontinence.

The evidence for PEC is limited to retrospective reports. In 2007, a case report and review of 60 patients who underwent PEC for constipation, sigmoid volvulus, chronic intestinal or acute colonic pseudo-obstruction observed 'clinical improvement' in all patients. [38] However 42% (25 of 60) of patients had complications, ranging from mild local infection to faecal peritonitis. Thereafter, there were 2 reviews of PEC in 76 patients with sigmoid volvulus (56 patients) or chronic intestinal pseudo-obstruction (20 patients) . [39] [40]. In these reports, the outcomes evaluated qualitatively were good with relatively low morbidity (21 % for sigmoid volvulus, 30% CIPO), and mortality (5% for both).

Strijbos et al.[11] reviewed their experience with this procedure. Their experience and other reports are summarized in Table 2. The procedure was successful in 122 of 127 patients with refractory constipation. These studies included patients with spinal cord injury and opioid use. Some studies categorized patients into slow –transit constipation or a defecatory disorder. During the follow up period, which ranged from 1 – 89 months, 14 of 122 patients (11%) died. However, none of the deaths seemed directly attributable to the procedure. In one study, 7 of 27 patients (26%) died after PEC[41]. However this report included patients with constipation or sigmoid volvulus or chronic intestinal pseudo-obstruction; 5 of these 7 patients died due to unrelated causes (i.e., pneumonia and cancer) and the remaining 2 patients developed faecal peritonitis after the procedure. Both, these patients had sigmoid volvulus or chronic intestinal pseudo-obstruction, not isolated constipation.

Among these 122 constipated patients, less severe complications were higher (56%) than reported in sigmoid volvulus or chronic intestinal pseudo-obstruction The most common issues were chronic

pain (18/122 patients, 15%), formation of granulation tissue at stoma site (15/122, 12%) and local site infections (12/122, 10%). In the report by Strijbos et al 33% of patients had complications; all were considered to be minor. Among 122 patients, only one had peritonitis. At follow up, 59% of the tubes were still in place, with a good outcome reported at medium-long term follow up in 51%.

Similar to the surgical literature, data on the efficacy of PEC are limited. Indeed, even the definition of what constitutes a good outcome after PEC varies among studies. Some cases report that symptoms improved either with or without the tube. Other reports indicate that the tube was removed without recurrent symptoms. Most tubes were removed shortly after the procedure. Hence, long term follow-up is limited; only 5 of 122 patients with PEC still in situ were followed for more than 3-4 years[42] (maximum median follow up was 43 months among all other studies). In this study of 21 patients who had PEC between 1997 and 2006, 52% of tubes were removed by 2014[42]. Only 5 patients were alive with the tube with follow up between 11-17 yrs. In another large series, the tube remained in situ in only 2 of 27 patients, with these patients only followed up for 7 and 10 months. [41]

How does PEC compare with surgical interventions for constipation? A systematic review of the latter suggested that 86% of patients were satisfied after surgery, [26] 20-30% had complications, and 13% required re-operation. By comparison, 30% of patients have complications after the Malone procedure[11].

Since PEC can be performed under local anaesthesia and conscious sedation, it might be preferred to surgery in patients who have a higher surgical risk due to co-morbidities. Also, PEC is reversible. More evidence is required to weigh the risk: benefit profile of PEC alone and versus surgery.

Conclusions

While newer pharmacological options and pelvic floor biofeedback therapy are effective for chronic constipation, a substantial proportion of patients are refractory to these therapies. A majority of patients report high global satisfaction rates after colectomy for slow transit constipation. However, few studies of colectomy, and other options, including PEC and rectal irrigation, used rigorous validated outcomes. Indeed, the evidence for PEC and rectal irrigation is mostly based on retrospective case reports. Hence, rigorous, evidence-based trials of minimally-invasive, and surgical approaches for refractory constipation are necessary to assess the risk: benefit profile of these approaches and to identify the factors that predict the response to treatment. These studies should include patients who satisfy the criteria for refractory constipation as proposed in this review, and in whom the results of prior therapies have been documented. Until then, clinicians should apply the current evidence to use pharmacological and behavioural treatments, utilising rectal irrigation in patients not responding to these treatment, reserving surgery to selected cases identified in referral centres. While PEC may work for some patients, it should, pending further studies, only be considered in the context of clinical trials.

Table 1: Comparison of Surgical Options for Chronic Constipation

Patient group	**Procedure**	**Number of studies**	**Number of patients**	**Follow up (months) ***	**Global satisfaction†**	**Main harms ∞**
Highly selected cases with STC	Colonic resection	40	2045	47 (12-132)	86 (81-89)%	Adhesional small bowel obstruction
Defecatory disorder with pelvic organ prolapse	Rectal suspension e.g. rectopexy	18	1238	25 (12-72)	83 (74-91)%	Mesh infection, erosion, and chronic pain
	Rectovaginal reinforcement e.g. posterior repair	44	3499	25 (12-74)	72 (67-77)%	Dyspareunia
	Rectal wall excision e.g. STARR	47	8340	23 (12-66)	76 (73-80)%	Chronic anal pain and faecal urgency
Intractable chronic constipation	Sacral neuromodulation	7	375	27 (20-51)	73 (57-87)%	Requirement for device removal

KEY: * mean and range of means; † pooled estimates based on random effects models with (95% CI); ∞ = numerous other harms are listed in full reviews (see also text); STC = slow-transit constipation; STARR = stapled trans-anal rectal resection.

Table 2. Review of currently published literature regarding use of PEC in constipation disorders.

Paper	Type of paper	No. of Patients	Patient diagnosis	Age/Sex	Site of PEC	Type of device	Tubes removed	Follow up	Reported Outcome	Complications	Later required surgery (if known)
Heriot 2002[43]	Case report	1	Obstructed defecation	52, Male	Sigmoid	14ch gastrostomy tube	Nil	6 month	Good - improved QoL at 6months	Faecal leakage, resolved after replacement of tube with flat Mic-Key tube	
Wills 2003[44]	Case report	1	Constipation due to spinal cord lesion and opioid use	35, Female	Caecum	24F gastrostomy tube	Nil	1 month	Good with resolution of constipation symptoms until death from unrelated cause	no complications from procedure, however passed away from respiratory distress 3 weeks later	
Lykke 2006[45]	Case report	1	Faecal incontinence	52, Male	Caecum	Percutaneous gastrostomy set (Freka Pexact CH 15, Fresenius Kabi, Bad Homburg, Germany)	Nil	4 months	PEC still in place with no recurrence of symptoms	none	
Lynch 2006[46]	Retrospective case series	2	Chronic refractory constipation	51, Male; 35 Female	Caecum	20F gastrostomy tube (Microvasive Endoscopy, Boston Scientific Corp, Natick, Mass)	1	1 month	1 Patient deceased at 1 month and other removed at day 4.	1 patient died shortly after placement due to known terminal malignancy, other patient developed peritonitis and PEC removed day 4	
Uno 2006[47]	Retrospective case series	15	Chronic severe constipation	67 (range 26-96), 75% male	Caecum	Introducer method (IM) with 10 F Chait Trapdoor cecostomy catheters	1 accidental removal by patient (dementia), reinserted immediately	median 8.8 (1 to 18 months)	11 surviving patients showed improvement in their ACE regimen after a follow-up, 3 lost to follow up	5 patients had granulation tissue , 1 death due to unrelated disease	
Baraza 2007[48]	Prospective	10	Idiopathic slow-transit constipation	51 (range 36-77)	7 Sigmoid/descending, 3 caecum/ascending colon	Corflo® 20 Fr gastrostomy tube	6	median 35 months (21-89)	Satisfactory outcome in 4/10	1 faecal urgency after enema , 1 chronic site pain	2
Cowlam 2007[41]	Retrospective case series	17	11 functional constipation, 6 neurological constipation	44 +/- 2.7, 5 male and 13 female	Left side of the colon, 3 unable to be sited	14F or 20F gastrostomy tubes (Corflo PEG kit, Merck Pharmaceuticals, West Drayton, UK) or specifically designed 12F PEC tubes (Corflo PEC kit) were used.	13	mean 20.4 +/- 1.0 months	Success in 1 /14	13 removed due to infection and pain as well as faecal leakage	10

Ramwell 2011[49]	Prospective	25	Neurological disease with delayed transit constipation	53 (range 18-78)	Sigmoid	Standard 16-Fr gastrostomy kit (Corflo; Viasys MedSystems, Wheeling IL, USA) was used. Subsequently, a specifically designed 12 Fr Corflo-PEC kit was used	6	median 43 months (6–83 months)	Long term Success in 19/25	Minor complications in 6 patients (site infection, bumper migration), 1 pressure sore. 5 patients died of their neurologic disease, no deaths related to procedure.	2
Duchalais 2015[50]	Prospective	21	Refractory constipation - 12 slow transit,2 neurological, 2 anorectal malformation, 1 scleroderma, 1 opioid induced	47 (range 20–71), 17 female	Caecum, 2 unable to be placed	Chait TrapdoorTM caecostomy catheter (Cook Medical, Bloomington, IN, USA)	7 (1 accidental)	1 yr	Considered successful in 11/18. 87% improved KESS score and 93% GIQLI score at 1 year. During period of ACE 14 stopped laxatives / retrograde irrigations	1 post op painful pneumoperitoneum, 10 minor granulations at site, 9 chronic pain, 7 leakage, 2 minor wound infection. 1 death due to unrelated cause	
Moriwaki 2015[51]	Case report	1	Slow transit constipation	92, Male	Sigmoid	Funada percutaneous endoscopic gastrostomy (PEG) kit	not reported	not reported	not reported	not reported	
Lehto 2016[42]	Retrospective case series	21	Colorectal dysfunction, primarily neurological followed by outlet obstruction and faecal incontinence.	53 (range 29–79), 18 female and 3 male	11 Sigmoid, 9 left transverse, 1 caecum	Percutaneous endoscopic gastrostomy (PEG) size 14 Ch tubes were used (Flocare, Nutricia, Netherlands).	11	median 14 years	Of 5 alive with tube in place 4 still using with good/excellent effect, 4 had tube in place until unrelated death	1 fascial dehiscence, 1 stricture of the tunnel, 1 inflammation around the tube, 5 fecal leakage, 6 pain. 5 passed away unrelated to procedure (4/5 with tube still in place, remaining no data on tube)	6, 1 planned
Strijbos 2017[11]	Retrospective case series	12	Refractory constipation	56 (range 28-70yrs), 75% female	Ascending colon	Freka®PEG (Fresenius Kabi AG, 61352 Bad Homburg v.d.H. Germany), pull technique	6	mean follow-up 3.3 yrs (range 1-7rs)	At 6 weeks eight patients reported a good effect (GPA =1), four patients reported a moderate effect (GPA=2), Six are still in use at long term follow up. 2 were removed due to spontaneous resolution of symptoms	3 site infection, 1 abscess, 2 persistent pain, 1 buried bumper with subsequent abscess	3

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