Quality of Life, physiological evaluation and novel treatment in refractory constipation:

A study of patients from a specialist clinic in the North East of England.

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MAIN ABSTRACT

Background Severe idiopathic constipation is a disorder that can significantly impair Quality of Life (QOL). Idiopathic constipation refers to the situation where no organic, biochemical, structural, endocrine or neurological explanations can be found to account for symptoms.

Little is known about the factors that predict poor QOL in such patients. The pathophysiological processes involved are not fully understood, particularly with reference to subsets of patients defined by their symptoms (such as the urge to defecate). A proportion of patients remain unresponsive to treatment with life style changes, high fibre diet, laxatives and non-invasive therapies. They can be regarded as having severe refractory idiopathic constipation. They may ultimately be considered for surgical intervention.

The main aims of this thesis were to examine three key themes regarding severe refractory idiopathic constipation;

1) To identify factors that can predict disease-specific QOL.

2) To explore the pathophysiology of the urge to defecate and determine whether there are differences between patient groups defined by this symptom.

3) To prospectively evaluate the efficacy of a novel therapy that is a potential alternative to surgery.

Predictors of Disease specific QOL: This study involved gathering data with QOL questionnaires (PAC-QOL and SF-36). Before identifying predictors, it was necessary to evaluate the psychometric properties (validity and reliability) of the QOL measures. It was important to confirm that their use was appropriate in patients with severe refractory idiopathic constipation. Confirming the psychometric properties of the measures was a prerequisite secondary aim of the study.

Determining predictors of poorer QOL could enable clinicians to identify patients in whom the impact and severity of constipation is greatest. Predictors could be used to target therapies to those with greatest need. The relationships between demographics,

symptoms assessed by clinician, symptoms assessed by the patient, results of objective tests and the patient's perception of health were studied.

Psychometric testing of the QOL and health perception measures validated their use in patients with severe refractory idiopathic constipation. Multiple linear regression suggested that symptom intensity assessed by the patient and patient perception of mental health were the main predictors of disease specific QOL. With these results in mind, it is possible that therapeutic strategies that reduce symptoms and address problems of mental health may improve QOL.

Pathophysiology of the urge to defecate: Approximately 60% of patients with idiopathic constipation have a reduced rectal urge to defecate (RRUD). They may represent a distinct group with differences in the properties and motility of the ano-rectum including a reduced frequency of the sampling reflex. This reflex describes relaxation of the anal sphincter allowing rectal contents to come into contact with sensory receptors in the proximal anal canal prior to defecation.

The frequency of sampling events in patients with reduced urge and normal rectal urge to defecate (NRUD) was measured in a prospective comparative study using solid state, semi-ambulatory continuous anorectal manometry. The mean frequency of sampling events was 8.91/hr (sd 5.9) in the normal rectal urge group and 8.77/hr (sd 7.2) in the reduced urge group (NS). No differences in anorectal sensation or colonic transit time were found.

The explanation for the noticeable division of patients into those with NRUD and RRUD remains unclear. Frequency of sampling is no different between the groups and is unlikely that sampling dictates a RRUD. Further study is required to evaluate the role of other potential determinants such as rectal compliance, rectosigmoid motility and central processing of sensory perceptions.

Evaluation of a novel therapy: Percutaneous Endoscopic Colostomy (PEC) in the left colon is a minimally invasive endoscopic technique that can be used to irrigate the left colon and relieve constipation. The technique offers a potential alternative to

surgery in severe cases. The aim was to perform a prospective efficacy study in refractory idiopathic constipation.

The initial step was a retrospective data analysis of patients who had PEC inserted at our unit over a four year period. This is presented in the thesis. The results were to be used to inform the design of a prospective study. Over the 4 year period 31 patients attended for PEC. Indications included idiopathic constipation, recurrent sigmoid volvulus, colonic pseudo-obstruction and neurological constipation. Although symptoms were improved in the majority of patients and recurrent sigmoid volvulus prevented, complications were common. Infection and abdominal pain necessitated the removal of PEC in the majority of patients. Patients with refractory idiopathic constipation were particularly susceptible to these complications. Two deaths occurred due to faecal peritonitis occurring after insertion.

Insertion was associated with significant morbidity and mortality. The widespread use of PEC is not recommended and insertion should be restricted to specially selected cases. The results did not support the initiation of a prospective study of efficacy. Consequently, this aim of the thesis was not fulfilled.

Conclusions By producing this thesis, predictors of disease specific QOL have been identified. These predictors could be studied in future hypothesis testing studies of QOL. Experience has been gained in the use of physiological techniques that could be utilised in further studies of pathophysiology in idiopathic constipation. Evaluation of PEC has added valuable information to the existing literature and has directly influenced clinical practice.

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1 THESIS INTRODUCTION

1.1 Background

Constipation is a common but heterogeneous digestive disorder defined by the presence of symptoms. These symptoms can include infrequent defecation, passage of hard stool, straining, sensations of incomplete evacuation, using manual manoeuvres to facilitate defecation and abdominal fullness or discomfort [1-3].

In Europe the prevalence in the self reported adult population is between 6 and 23% [4]. Hanay described an "iceberg of symptoms" where the majority of gastrointestinal symptoms experienced by individuals do not become the subject of medical consultation [5]. However, a proportion of patients with constipation will present to primary care with an estimated 3 million consultations to general practice per annum in the UK [6].

A proportion of these patients remain refractory to treatment with life style changes, high fibre diet and laxatives. Causes of refractory constipation include mechanical obstruction, neurological disease, anatomical abnormalities of the anorectum, idiopathic constipation, systemic diseases or adverse effects of medication. Such patients may be referred to secondary / tertiary care, either because of the condition precipitating constipation (such as neurological disease e.g. Multiple Sclerosis) or because of the burden of constipation symptoms and the affect this has on quality of life.

In an audit of new referrals to the specialist constipation clinic at University Hospital North Durham, constipation was found to be idiopathic in 79% of cases [7]. The clinic was established to deal with cases of refractory constipation referred from the North Eastern region. The referrals represent a distinct group compared to those whose symptoms can be self controlled or managed within primary care or less specialised secondary care clinics.

The clinic provides an opportunity to study refractory idiopathic constipation and to explore several key areas. These include; the effect of symptom intensity and pathophysiological factors (such as colonic transit) on constipation severity and its impact on quality of life; the pathophysiology of the condition in subgroups defined by their urge to defecate and finally; the role of Percutaneous Endoscopic

Colostomy. This is a novel treatment that may represent an alternative to surgery in refractory idiopathic constipation.

1.2 Definition of constipation

In 1982, Drossman et al proposed a general definition of constipation that refers to two or fewer stools per week and / or straining at stool more than 25% of the time [8].

In a recent review the American College of Gastroenterology described constipation as "a symptom based disorder defined as unsatisfactory defecation and is characterised by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard /lumpy stools, prolonged time to stool or need for manual manoeuvres to pass stool" [9].

Definitions for idiopathic or functional constipation (where no organic, biochemical, structural, endocrine or neurological explanations can be found to account for symptoms) are enshrined in the Rome criteria for Functional Gastrointestinal Disorders. These criteria were initially proposed at the 13th International Congress of Gastroenterology in Rome, Italy in 1988. They have been refined over time; 1999, Rome II criteria [10] and more recently 2006, Rome III criteria [11]. These criteria have been applied in research settings but it is recognised that in the clinical setting they can have limitations[12].

In this thesis the Rome II criteria were utilised because recruitment of subjects began before the release of the Rome III consensus document. The Rome II criteria recognise symptoms of constipation occurring in three categories of functional gastrointestinal disorders including; Constipation predominant Irritable Bowel Syndrome (IBS-C), Functional Constipation (FC) and Pelvic Floor Dyssynergia (PFD), (Figure 1).

It has been suggested that in practice a clearly delineating patients with Irritable Bowel Syndrome (IBS-C) and Functional Constipation (FC) can be difficult because of symptom overlap between these categories [9,12,13].

Figure 1: Rome II diagnostic categories with constipation

Diagnostic criteria for Constipation predominant Irritable Bowel Syndrome (IBS)
At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two or more of three features; (1) Relived with defecation; and / or (2) Onset associated with a change in frequency of stool; and / or (3) Onset associated with a change in form (appearance) of stool With one or more features supportive of constipation predominance; Fewer than 3 defecations per week Lumpy or hard stools Straining during bowel movement

Diagnostic criteria for Functional Constipation (FC)
At least 12 weeks, which need not be consecutive, in the preceding 12 months of two or more of; (1) Straining in more than 25% of defecations; (2) Lumpy or hard stools in more than 25% of defecations; (3) Sensation of incomplete evacuation in more than 25% of defecations; (4) Sensation of anorectal obstruction/blockade in more than 25% of defecations; (5) Manual manoeuvres to facilitate in more than 25% of defecations e.g. (digital evacuation, support of the pelvic floor) and/or (6) < 3 defecations /week Loose stools are not present and there are insufficient criteria for IBS

Diagnostic criteria for Pelvic Floor Dyssynergia (PFD)
(1) The patient must satisfy diagnostic criteria for Functional Constipation (above); (2) There must be manometric, EMG or radiological evidence for inappropriate contraction or failure to relax the pelvic floor muscles during repeated attempts to defecate; (3) There must be evidence of adequate propulsive forces during attempts to defecate; and; (4) There must be evidence of incomplete evacuation Loose stools are not present and there are insufficient criteria for IBS

1.3 Aetiology of constipation

The symptom of constipation has multiple aetiologies (Table 1). The colon is subject to both intrinsic and extrinsic factors that affect function. Dietary fibre deficiency is recognised as a common cause of mild to moderate constipation. Social factors, such ease of access to toileting facilities, should be considered. In the elderly, mobility issues that can inhibit evacuation should be considered. Endocrinological causes such as hypothyroidism must be considered although in young and middle aged women the prevalence of hypothyroidism appears to be low [14]. Furthermore, approximately 70% of patients with hypothyroidism actually defecate at least every other day [15].

Primary abnormalities of the central, autonomic and peripheral nervous system can produce constipation.

A distinction can made between constipation where a biochemical, endocrinological, structural or primary neurological cause can be found and constipation of an idiopathic origin. As stated in section 1.2 diagnostic criteria exist for the classification of idiopathic or functional constipation. This thesis concerns refractory idiopathic constipation.

Slow transit colonic constipation refers to a disorder of colonic motility characterised by reduced frequency, amplitude and duration of propulsive contractions in the large bowel. Pathophysiological differences in colonic function have been identified in patients with normal transit and slow transit. In slow transit constipation, the colon is hypersensitive to cholinergic stimulation [16], may have greater innervation by non-cholinergic inhibitory nerves [17] and in the postprandial state be characterised by increased secretion of proximal gut hormones [18].

Another aetiology is disordered defecation. This description, often used synonymously with outlet obstruction, obstructed defecation, disordered defecation, etc, can be due to weakness or impaired coordination of the pelvic floor muscles [19]. Paradoxical pelvic floor or sphincter contraction (or inadequate relaxation) during defecation may cause a functional or idiopathic outlet obstruction [20]. This problem has also been termed as anismus or pelvic floor dyssynergia [1,21].

In many cases the precise pathophysiological cause of disordered defecation may not be clear. Furthermore, slow colonic transit may coexist in patients with disordered

defecation. Abnormalities of colonic motility (evidenced by reduced amplitude of propagating pressure waves) can be demonstrated in patients with obstructed defecation [22].

Table 1: Aetiology of constipation

Dietary	Inadequate fibre		
Social factors	Immobility Environmental changes (hospitalisation) Ignoring call to stool Increasing age		
Endocrine and Metabolic	Hypothyroidism Hypercalcaemia Hypopituitarism	Hypokalaemia Pregnancy	Lead poisoning Porphyria
Central Nervous System Pathology	CVA	Multiple Sclerosis	
Autonomic Nervous System Pathology	Parkinson's disease Diabetes	Multiple Sclerosis	
Drugs	Iron Supplement Anti-depressants	Anticholinergics Calcium channel blockers	Opioids
Psychiatric	Depression	Psychoses	Anorexia nervosa
Gastrointestinal	Structural	Colonic stricture Neoplastic Intussusception Volvulus	
	Idiopathic	Constipation predominant IBS * Functional Constipation * Slow transit colonic constipation Normal transit colonic constipation	
	Other	Intestinal pseudo-obstruction Hirschsprung's Disease Mega colon / Mega rectum	
Disordered Defecation	Structural	Anal stenosis Anal fissure Rectocoele Enterocoele Pelvic floor weakness	
	Idiopathic	Anismus Outlet obstruction Pelvic Floor Dyssynergia *	

* Rome II criteria [10]

1.4 Prevalence and epidemiology of constipation

Constipation is a prevalent problem within the UK. In 2006 in England, more than 12 million prescriptions for laxatives were written by GP's [23]. The prevalence of constipation will vary depending on what definition is used. In the North American population prevalence of self reported constipation was 27.2%. However, when the Rome II criteria were applied prevalence was only 14.9% [24]. Geographical and cultural variation may also occur, with prevalence varying between countries. In a survey of European subjects Stanghellini et al found that in the UK, self reported prevalence was 6% whilst in Germany prevalence was 10% and in Italy 23% [4]. Age-related increases in the prevalence of constipation have been demonstrated in both men and women. Prevalence is also found to be greater in females compared to males [25]. In addition to age and sex, social class also affects prevalence, with constipation occurring more frequently in men and women from lower rather than higher social classes [26].

Increased prevalence has also been demonstrated in patients with concurrent psychiatric disorders (affective psychoses, schizophrenia and depression) [27]. The association with psychiatric morbidity is likely to be multi-factorial with direct action on GI tract physiology or the impact of medications contributing to constipation.

In addition to the above epidemiological observations, it has been suggested that constipation is more common in women who have undergone hysterectomy or abdominal-pelvic surgery [28,29]. It is hypothesised that such surgery (and even in childhood appendectomy) precipitates abnormalities of autonomic innovation [28]. Furthermore, it has been suggested that vaginal delivery and caesarean section during labour, have been associated pudendal nerve damage (possibly due to significant stretching of the pelvic floor tissue) and pelvic autonomic nerve dysfunction [30,31].

Childbirth has been associated with the development of rectocoele, a recognised cause of evacuatory difficulties and constipation. Dietz et al prospectively studied nulliparous pregnant females before delivery. Pre-delivery rectocoeles were not uncommon. Vaginal delivery increased the size of pre-existing rectocoeles but also led to new rectocoeles. However, only a small proportion of the rectocoeles post-delivery was associated with symptoms of constipation [32].

Prospective studies of the effect of childbirth on the prevalence and incidence of constipation (controlled against the background general population) are lacking. However, the importance of obtaining a history of pelvic-abdominal surgery and childbirth is stressed by authors [31,33]. Shytt et al have demonstrated that constipation was problematic for 20% of women after childbirth when assessed at two months after delivery [34]. In this study no comparison of prevalence in age matched non-pregnant females was made. Our own experience in the constipation clinic is that childbirth and pelvic-abdominal surgery (including caesarean section and hysterectomy) are triggers for the onset or deterioration of severe constipation in up to a third of patients.

1.5 Assessment of constipation

A patient centred approach is required. The exclusion of organic disease is necessary, particularly if patients are to be recruited into studies of idiopathic or functional constipation. The choice of investigation must reflect the fact that constipation is a heterogeneous condition that can be caused by multiple pathophysiologies.

Clinical examination

Assessment includes physical examination to detect evidence of systemic disease. Anorectal examination may reveal anal stricture, anal fissure, colorectal masses or rectal blood. During rectal examination, perianal descent during straining can be estimated. Anal sphincter tone at rest and squeeze can also be assessed. Rectocoele may be detected during this examination.

Relaxation of the external sphincter and perianal descent can be evaluated by simulated defection during *per rectum* examination. Abnormalities during this examination may suggest disordered defecation.

In those patients with a primary neurological diagnosis (such as multiple sclerosis or spinal cord injury) assessment may include examination of the relevant motor and sensory systems.

Assessment of symptom severity

Self-report of symptoms may be influenced by subjectivity on the part of the patient. Stool diaries can be prone to inaccuracy and may not correspond with recognised definitions of constipation [35]. The possibility of quantifying severity of constipation using scoring systems has been explored. The Cleveland Clinic score was developed by Agachen et al and assesses the duration of constipation and the severity of key symptoms [36]. The results from the questions can be expressed as a cumulative score, with a higher score representing more severe symptoms. Damon et al have previously found a moderate correlation between the cumulative Cleveland Clinic Score and QOL [37]. Knowles et al validated an 11 point system of different symptoms (Knowles Eccersley Scoring System, KESS) that could be used to score the severity of constipation[38]. However, this system has not been widely used in the literature.

Psychological profile

Psychiatric illness (such as depression, obsessive compulsive disorder and anorexia nervosa) has been recognised as a risk factor for constipation [39]. Mason et al have demonstrated that female patients with constipation have significantly increased psychological and social morbidity (expressed as anxiety, depression, and social dysfunction) compared to healthy women [40]. Recognising such factors is important and some authors have recommended psychological assessment for patients attending with refractory constipation [41]. Furthermore, psychological status may also influence response to treatment [42].

Quality of life

Considering the effect of constipation on quality of life (QOL) can be an important part of assessing the overall impact of the disorder on the patient. Overall QOL in idiopathic constipation has been shown to be lower than that of the normal population [42]. Increased reporting of fatigue, headaches and dizziness has been demonstrated in patients with Functional Constipation [43] and has been linked with absenteeism from work.

Biochemistry

A clinical index of suspicion will prompt laboratory blood testing that can be used to exclude organic causes of constipation.

Visualisation of the colon

The role of endoscopic visualisation of the colon in the assessment of constipation is controversial. The American Gastroenterology Association position statement recommends that structural evaluation of the colon is indicated [44]. In contrast, the American Society of Gastrointestinal Endoscopy document on indications for flexible sigmoidoscopy and colonoscopy does not include constipation as an indication [45].

Pepin et al evaluated the diagnostic yield of colonoscopy and flexible sigmoidoscopy in patients in whom the procedures were performed because of constipation. They suggested that chronic constipation alone was not an appropriate indication for lower endoscopy. The polyp and neoplasia pick up rate in subjects where the indication was constipation were comparable to that expected in asymptomatic subjects undergoing surveillance procedures [46]. The utility of barium enema examination has not been studied in detail. Patriquin et al used barium enema in a selected group of 62 patients with chronic constipation, however this modality did not demonstrate any unexpected organic lesions [47].

Whilst debate exists about the utility of visualising the colon in clinical practice, such investigation may form the basis of inclusion criteria for studies of functional or idiopathic constipation.

Proctography

A defecating proctogram can provide information about the anatomy of the pelvic floor. Proctography can be used to investigate disordered defecation. Proctographic parameters form part of the diagnostic criteria for Pelvic Floor Dyssynergia (PFD) in the Rome II criteria and for Dyssynergic Defecation in Rome III [1,11].

Defecating proctography can be used to diagnose rectocoele or enterocoele. The technique can provide data regarding the size and impact of a rectocoele on evacuation [48]. The reported prevalence of rectocoeles in idiopathic or functional constipation varies within the literature (between 9 and 71% [49-51]). Radiographic and scintigraphic proctography remain the mainstay of investigation of rectocoele, although techniques using Magnetic Resonance Imaging continue to evolve [52].

Colonic transit studies

Colonic transit time can be measured using two methods; ingestion of radio-opaque markers followed by plain abdominal X-rays or by using scintigraphy.

Radio-opaque marker studies are relatively inexpensive to perform (compared to other tests of gut motility) and are widely available. Comparison with norm referenced data allows arbitrary classifications to be made of what constitutes slow colonic transit in constipated patients [53]. It has been suggested that the distribution of markers can be used to identify different subtypes of constipation[11].

In scintigraphic transit studies, Indium-111 diethylenetriamine penta-acetic acid (DTPA) is ingested and the abdomen scanned using a gamma camera. Segmental and total transit can be calculated.

Physiological studies

Anorectal manometry provides an objective method of assessing physiology of the anorectal sphincter in evacuation. The presence of the rectal anal inhibitory reflex can be used to exclude Hirschsprung's disease. Balloon expulsion studies and pelvic floor and sphincter electromyography (EMG) studies may also be employed to assess the physiology of defecation [54].

However, controversy exists as to whether the results of physiological studies alter decision making or whether the tests have clinical utility [55,56]. Methodological differences exist between units, and reference values for normality and disease states are not universally agreed. In recognition of these issues, guidelines for anorectal physiology testing have been produced [57]. A further criticism is that anorectal physiology testing performed in the left lateral position in a laboratory does not reflect the true physiological state of the subject. This observation has led some authors to postulate that anismus is in fact over diagnosed [58,59]. Evolving techniques in the field of anorectal manometry include the use of ambulatory manometry and impedance planimetry [54,60].

Colonic manometry studies have increased knowledge regarding evacuation. Low amplitude non-propagating pressure waves and high amplitude propagating waves have been observed in the period prior to defecation using manometry catheters placed transnasally or at colonoscopy [61-63]. Abnormalities of colonic physiology have

been documented in constipated individuals; Dinning et al demonstrated that patients with obstructed defecation lacked the normal predefecatory augmentation in frequency and amplitude of propagating pressure waves [22]. They postulated that these abnormalities contributed to an inability to effectively expel stool.

Role of diagnostic test in constipation

Many of the above investigations are recommended in published guidelines for the evaluation of constipated patients [44]. They have a role in excluding organic causes and exploring physiology in idiopathic and functional cases of constipation. However, it is not clear whether these investigations provide data that predicts the severity of the patient's constipation as measured by their quality of life. This theme will be discussed further in section 2.

1.6 Management of constipation

The approach to management is currently divided into established treatments and evolving or novel therapies that had been developed within recent years. The evidence base behind many of the established treatments is limited. The following section provides a brief overview.

A review of the effectiveness of treatment is available from the BMJ Clinical Evidence resource [64]. The original search date was 2003 although the publication is continually updated. Table 2 summarises the key outcomes. The American College of Gastroenterology has also published a review of therapies that in addition to lifestyle and laxatives also considered Tegaserod [9].

The BMJ Clinical Evidence resource categorises the effects of treatments along a spectrum that includes beneficial treatments through to treatments likely to be ineffective or harmful. Categorisation is determined by the level of benefit (or harm) of an intervention, the level of evidence (RCT or observational data) and the level of certainty around the findings of the studies. Beneficial interventions are those where effectiveness has been demonstrated by clear evidence from well designed RCT. Regarding the evaluation of constipation treatments; only a minority of interventions fell into the beneficial category (Macrogols). The majority of interventions were categorised as being likely to be beneficial or of unknown effectiveness. Here the effectiveness is less well established (e.g. lacking in large well designed RCT evidence) or assessment of effectiveness is based on insufficient data or data of inadequate quality. The Evaluation undertaken by the BMJ Clinical Evidence resource illustrates that the evidence base behind many of the common therapies is not great. If the example of bisacodyl, a stimulant laxative, is considered; at the time of the evaluation no systematic reviews of the drug had been produced. Only one small RCT existed. This studied a small cohort of only 55 people (aged 19 to 89 years) with acute idiopathic constipation. The RCT compared 10 mg of bisacodyl once daily for three successive days versus placebo. The period of evaluation and follow up was very short (3 days only). Bisacodyl significantly increased stool frequency and stool consistency compared to placebo. The drug was well tolerated [65].

The application of these results for management of patients in the constipation clinic is difficult. Firstly, our cohort has chronic rather than acute symptoms, secondly the

patients require long term treatment and thirdly they generally already use a laxative and indeed often use multiple laxatives. Comparison of a therapy with placebo does not reflect the reality that our patients use multiple laxatives. Such deficiencies in the evidence base are being addressed (for example, Kienzele-Horn et al have compared bisacodyl and sodium picosulphate in subjects with chronic constipation [66]) however, evidence is still lacking to support the effectiveness of other interventions (such as lifestyle and dietary modification) in patients with severe chronic idiopathic constipation.

A therapeutic trial of fibre is often encouraged at the initial presentation of patients with idiopathic constipation (either as increased dietary fibre or prescribed fibre supplements). It is likely that fibre increases stool bulk and plasticity, so increasing colonic distension and increasing colonic transit through increased propulsive activity. However, side effects (bloating and flatulence) limit effectiveness. Many patients presenting to a specialist constipation clinic have already failed to improve with additional fibre and laxatives. Such failure often prompts further investigation of pelvic floor function and colonic transit.

Lifestyle may affect constipation and generally patients are advised to avoid ignoring the call to stool. Although large RCTs of the effect of exercise are lacking, it does appear that physically active subjects suffer less constipation then more sedentary subjects [67-69].

The findings of the BMJ Clinical Evidence review of laxative treatments are also shown in Table 2. Macrogols (polyethylene glycols) were found to be beneficial for treatment with evidence available demonstrating that macrogols improved symptoms compared to placebo. Macrogols also improved symptoms and global satisfaction when compared to other laxatives (ispaghula husk and lactulose)[64]. The tolerability of laxatives may limit effectiveness. In some patients' symptoms remain refractory even with multiple laxatives.

Treatment			Recommendation *
High fibre diet			Likely to be beneficial
Life style	Exercise		Likely to be beneficial
	Increase fluids		Unknown effectiveness
Laxatives	Bulking agents	Ispaghula husk (psylium)	Likely to be beneficial
	Stool softeners	Paraffin / arachis oil	Unknown effectiveness
	Osmotic laxative	Macrogols	Beneficial
		Lactulose	Likely to be beneficial
		Magnesium Salts	Unknown effectiveness
		Phosphate enema	Unknown effectiveness
	Stimulant laxatives	Bisacodyl	Unknown effectiveness
$5HT_4$ agonists		Tegaserod	Beneficial **
Biofeedback behavioural training			Unknown effectiveness

* BMJ Clinical Evidence 2007 [64] ** American College of Gastroenterology Chronic Constipation Task Force [9]

Table 2; Non invasive treatments for constipation.

Interest in serotonin agonists for the treatment of constipation has grown in recent years. Several placebo controlled studies of Tegaserod ($5HT_4$ agonist) have shown symptomatic benefit. Subjects receiving Tegaserod have increased rates of complete spontaneous bowel movement, improved self assessment of symptom severity, improved global assessment of bowel habit and improvement of IBS symptoms.

Through its action on $5HT_4$ receptors, Tegaserod stimulates the peristaltic reflex, increases colonic motility, decreases visceral hypersensitivity and facilitates secretion into the colon [70-72].

However, in March 2007 at the request of the FDA, the manufacturer of Tegaserod agreed to stop selling the drug [73]. 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 America 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.

Biofeedback behavioural training is a non-invasive technique that has been used to successfully manage disordered defecation / dyssynergic defecation [74]. The mechanism of action is poorly understood but improved extrinsic innervation to the gut is implicated [75,76]. Biofeedback may also improve colonic transit time and has also been used in slow transit constipation[75,77].

Chiarioni et al found that in patients with severe pelvic floor dyssynergia, biofeedback was more effective than macrogols. Biofeedback significantly improved symptoms, reduced the need for laxatives and frequency of abdominal pain. Furthermore, patients who reported major improvements demonstrated the ability to relax the pelvic floor and improved balloon defecation [78]. Improvements from biofeedback may also be due to beneficial effects arising from a close relationship between practitioner and patient.

Rectal irrigation

Rectal irrigation is a method of achieving a transanal retrograde washout of the distal colon. The technique can be used in selected patients with constipation and other defecatory disturbances. The procedure is performed with water, using equipment

similar to that for stoma irrigation. Irrigation can be performed in the patient's home. After irrigation, evacuation usually occurs within 15 minutes. The frequency of irrigation can be tailored to suit individual needs. A retrospective evaluation of effectiveness was performed by Crawshaw et al. They studied a heterogeneous group of 48 patients with idiopathic defecatory disturbances (including 15 with constipation). During a median follow up of 11 months, rectal irrigation provided symptomatic improvement. Christensen et al have studied the effectiveness in patients with spinal cord injury and neurogenic bowel dysfunction. In a prospective, controlled, multi-centre trial, 87 patients were randomized to receive transanal irrigation or conservative bowel management. Compared with conservative bowel management, transanal irrigation improved constipation, faecal incontinence, and symptom-related QOL [79].

Botulinum toxin

Botulinum toxin has been used to weaken the external anal sphincter muscle and puborectalis muscle in constipation. Experience is growing, suggesting a role for this technique in selected patients [80]. Maria et al studied 24 consecutive patients with chronic outlet obstruction constipation who demonstrated impaired relaxation of puborectalis. Botulinum toxin was injected into puborectalis muscle under ultrasonographic guidance. At 2 months, anorectal manometry demonstrated improvement during straining. Furthermore, symptoms of incomplete, prolonged and difficult evacuation were resolved [81]. However, these results have not been verified in clinical practice, and few units are offering this treatment.

Sacral nerve stimulation

Sacral nerve stimulation (SNS) has been used to treat urinary and faecal incontinence [82,83]. Subsequent studies suggested additional benefits, with increased stool frequency in patients with constipation [84-86]. A recent Cochrane review concluded that SNS can improve symptoms in selected patients with constipation[87]. Dinning et al studied eight patients with idiopathic slow-transit colonic constipation. Their findings give some insight into the mode of action of SNS. They evaluated the effect of stimulation on colonic pressure patterns using a manometry catheter positioned at colonoscopy. Electrical stimulation of the sacral nerve increased pan-colonic antegrade

propagating sequences. Six of the eight patients reported increased bowel frequency and reduced laxative use after a 3 week stimulation trial [88].

Surgery

Surgical treatment for constipation can be performed when specific abnormalities of the lower gastrointestinal tract are identified that directly precipitate constipation (for example, functionally significant rectocoele). Alternatively surgery is performed in idiopathic constipation in patients who have remained refractory to conservative treatments (for example in severe slow transit colonic transit). In these cases surgery represents an invasive approach associated with the inherent risks of general anaesthesia and possible short and long term complications. There has been an impetus to develop less invasive measures that can be used as an alternative to established surgical techniques such as colectomy.

Rectocoele repair

A rectocoele is an out-pouching of the anterior rectal and posterior vaginal wall into the lumen of the vagina. Many Rectocoeles are asymptomatic and prevalence is not accurately known in the general population. Between 20-80% of patients attending pelvic floor clinics have rectocoele [89]. Disordered defecation may arise. Surgical intervention is considered if the rectocoele is associated with significant retention of contrast after evacuation, size is greater than 3cm and there is a need for manual assistance for defecation. Criteria for selecting patients for surgery may vary between units. Rectocoele repair can be performed via anal, transvaginal, transperitoneal approaches or by a laparoscopic technique[90-92].

Antegrade Colonic Enema

Antegrade irrigation of the colon may be used as an alternative to colectomy and ileostomy in patients with refractory constipation. Malone reported on the archetypal procedure that allowed antegrade irrigation of the colon using the appendix and good results have been reported particularly in the paediatric population[93,94].

Colectomy

Subtotal colectomy with ileorectal anastomosis (STC-IRA) is recognised as a surgical approach in carefully selected patients with colonic slow transit [95,96]. Hassan et al found that 85% of their patients reported satisfaction with bowel function post

surgery. Furthermore, STC-IRA led to sustained improvement in symptoms and quality of life [97]. Post operative diarrhoea is a recognised complication of the procedure[98]. Recent developments have focussed on surgery that retains the ileocaecal valve; sub total colectomy with ceacorectal anastomosis (STC-CRA). Small case series have shown promising results for this procedure [99,100].

Summary

Constipation is a common disorder with multiple aetiologies. A structured approach is required for assessment and investigation. Idiopathic constipation may be associated with identifiable physiological changes affecting colonic transit or pelvic floor function (e.g. STCC and PFD). Management relies on the use of established measures that in some instances are not supported by a strong evidence base. Standard therapies, such as laxatives, may be ineffective and other non invasive interventions (such as biofeedback) may not work in all cases. In some instances definitive surgery is performed. Development of novel therapies and less invasive procedures (such as SNS) may allow patients to avoid major surgery.

2 QUALITY OF LIFE IN CONSTIPATION

2.1 Introduction

2.1.1 Defining Quality of Life

"Quality of life" (QOL) is a common place term used in everyday life by both lay people and clinicians. Most people in the western world are familiar with the expression and have an intuitive understanding of what it comprises. It has been suggested that QOL is a multidimensional construct influenced by several dimensions such as: physical functioning, physical symptoms, psychological symptoms, perceived distress and life satisfaction (to name but a few)[101]. It is impractical to assess all dimensions simultaneously. As a result instruments purporting to assess QOL may concentrate on specific dimensions at the expense of others. The terms Quality of life (QOL) and Health Related Quality of Life (HRQOL) are often used interchangeably and reflect the physical, social and emotional attitudes and behaviours of an individual as they relate to their prior and current health state [102].

2.1.2 Why measure Quality of Life in constipated patients?

In certain gastrointestinal disorders, the severity of the condition can be assessed using validated tools. For example, the Crohn's Disease Activity Index (CDAI) uses both qualitative and quantitative data to assess severity [103]. In constipation there are no similar measures of disease activity. Clinicians rely on a combination of methods to assess severity such as: symptom self-report by patients, a clinician record of symptoms or the results of objective tests (e.g. colonic transit study and anorectal physiology).

However, criticisms can be levelled at these approaches. Symptoms can be evaluated via a clinician led interview (during history taking), clinician led questionnaires or through patient self-report with diaries and questionnaires. These methods have potential for inaccuracy and bias. Studies of diseases, including GI disorders, show a general pattern of only weak to moderate agreement between the rating of symptoms by the patient and clinician [104-108]. The most common finding is for clinicians to underestimate the incidence of and severity of symptoms relative to patient

ratings[108]. Agreement on the presence and abscence of symptoms is generally better than agreement about symptom intensity[109].

Patient self-report and symptom diaries can be inacurate because of subjectivity and impaired recall. The respondent burden of diaries can be high and retrospective completion of entries has been reported [110]. Unfortunately, recall errors can be increased by such retrospective diary completion. Another problem with diaries is that subjects become conditioned and more tolerant of their symptoms during the diary exercise[111]. Consequently, the reporting of events diminishes during the diary period. Conversely, the problem of sensitisation is recognised. Here the awareness of symptoms heightens during the diary period, leading to increased reporting of symptoms or events [112].

Symptom questionnaires, either self administered or via clinician, require patients to remember symptom occurrence and intensity. Recall error can arise through omission or misplacing the occurrence of a symptom in time. Bias can occur particularly if the questionnaire is clinician administered. In this situation the subject alters answers to confirm with perceived behavioural or social norms (e.g. omitting to answer questions about potentially embarrassing issues such as digital manoeuvres to assist defecation). It is also important that the questionnaires used are well designed with robust psychometric properties and have been validated in the population for which they are intended for use in[112,113].

The role of objective tests for assessing severity has not been fully explored. Using symptoms as a measure of severity, some authors have found no correlation between the results of objective tests and symptom intensity (of course, the problems of symptom evaluation as outlined above must also be considered when interpreting this observation)[114].

Therefore, measuring QOL represents, at the very least, an adjunct to symptom assessment but may even provide a more complete and comprehensive way for clinicians to assess the severity and effect of constipation. This is certainly the case in other chronic diseases, where quality of life status gives a closer representation of the patient's well-being and disease impact then the results of laboratory investigations and measures of disease activity [115,116].

QOL can be used as an outcome measure in clinical trials of treatment in conjunction with other endpoints like symptom evaluation or the results of objective tests. In cluding QOL assessment is likely to give a more complete picture of the effect of treatment than using symptom evaluation or objective testing in isolation. The problems of symptom assessment already mentioned may introduce inaccuracy if this modality is used as the only endpoint. Traditionally, clinicians have aimed to treat and remove symptoms to cure or palliate a condition rather then considering the effect the disorder has on the global concept of QOL. Constipated patients themselves often express the opinion that overall QOL is more important to them then the treatment of an individual symptom. By using QOL as an endpoint in trials, treatments can be developed that address this issue.

QOL has also been shown to be a predictor of whether a patient will respond to treatment. For example, pre treatment QOL has been shown to predict the response to biofeedback therapy. Mason et al found that constipated subjects in whom pre treatment QOL was impaired by physical pain, emotional problems and low vitality were less likely to respond to therapy [42]. Measuring QOL may inform management decisions in clinical practice and represent a useful endpoint in clinical trials.

2.1.3 Measuring Quality of Life in constipation

There are a variety of instruments available for measuring QOL that include generic and disease-specific measures [113].

Generic quality of life instruments are designed to assess the overall health, well-being and functioning of an individual. They have no specific reference to any particular condition or disease and can also be used in healthy subjects. They can be applied to different patient groups and can be used to make comparisons of quality of life between diseases. They may detect unexpected or unusual effects of the disorder. Since these instruments are very general, small important changes, particularly those caused by the specific disorder, may not be detected. The Short Form-36 Health Survey (SF-36) is an example of a generic QOL measure that can be used to assess a subjects' QOL and perceived health status [117].

Disease-specific instruments are applied to patients with a specific condition (such as gastrointestinal disease or respiratory disease). These instruments are designed to identify relevant problems associated with the particular condition and are generally more sensitive to patient concerns and changes in health status [118]. However, a potential disadvantage is that unexpected effects that influence general health may be missed. The Patient Assessment of Constipation – Quality of Life questionnaire (PAC-QOL) is an example of a disease specific instrument[119].

Combining both generic and specific questionnaires allows the advantages of both to be incorporated into analyses. It has been suggested that generic and disease-specific measures of quality are complementary rather than interchangeable and the use of both types of measure in parallel is recommended [120].

2.1.4 Description of the Quality of Life instruments used in the thesis

Short Form-36 Health Survey (SF-36)

The Short form-36 was originally developed by the Rand Corporation for cost utility analyses in health insurance schemes [121]. It assesses generic health that is not specific to age, disease or treatment. Aspects of physical, social and emotional functioning are considered. The SF-36 contains 36 items categorised into eight domains: physical functioning, social functioning, physical limitation, mental role limitation, mental health, energy and vitality, bodily pain and general health perception. Scores for each domain are normalised to a reference population that was originally from the United States, however referenced norms are now available for a variety of disorders and populations from outside America. Two summary measures can be derived for physical health and mental health expressed as the Physical Component Score (PCS) and the Mental Component Score (MCS). The SF-36 can be completed in a short period of time (approximately 10 minutes). This represents an advantage for studies where several questionnaires are used together. Data regarding reliability and validity for this questionnaire in various populations and settings are widely published[122, 117]. Coons et al suggested that the SF-36 possessed the attributes of a "robust instrument having good validity, reliability" and having "extensive cultural and language adaptation and low administrative burden" [122]. When compared with other generic

measures, the SF-36 was found to have high scores for internal consistency, reliability and validity [123]. The SF-36 is commonly used in contemporary health services research [124].

The Patient Assessment of Constipation – Quality of Life (PAC-QOL)

The Patient Assessment of Constipation (PAC) was developed to address the need for "a disease-specific patient reported outcomes measure" that could be used to assess symptoms and QOL [119]. It consists of two separate questionnaires; PAC-SYM (evaluating constipation-specific symptoms) and PAC-QOL (evaluating constipation-specific QOL)[119,125]. The content was derived directly from individuals affected by constipation and from clinicians involved in the treatment of gastrointestinal disorders. Validation studies (conducted in North America, Europe and Australia) demonstrated an acceptable level of reliability, validity and responsiveness. PAC-QOL is a comprehensive but brief assessment of the burden of constipation on patients everyday functioning and well-being.

Both PAC-QOL and PAC-SYM are relatively new instruments in the field of constipation. They appear to be well-designed and conceived instruments. Item development was predominantly patient centred, rather than dictated by clinicians. Extensive patient led focus groups were used during the conception stage. It is believed that this approach has led to an instrument that truly reflects the patients' experience of constipation in terms of symptoms and QOL.

Currently there is no gold standard for measuring severity in constipation. Using a patient derived evaluation of symptoms and QOL may offer an alternative to relying on symptom evaluation by the clinician or the results of objective tests.

2.1.5 Quality of Life in constipation

Studies that have examined the burden of constipation with reference to QOL have involved observational studies and cross-sectional comparisons. Until recently, many authors relied on generic measures that assess overall QOL and health. Disorder-specific instruments for evaluating QOL across a range of gastrointestinal disorders (eg Gastro Intestinal QOL index, GIQLI[126]), that are not specific to constipation *per se*, have also been used to study QOL in constipation. It can be argued that using measures specifically designed for constipation is preferable for evaluating QOL in this disorder. Table 3 lists the instruments that have been employed in previous work. Studies of QOL in constipation have involved community dwelling patients and subjects from the general population with self reported constipation or subjects recruited from dedicated clinics dealing with constipation.

Generic measures of health status	
Short Form 36	SF-36
Measures of psychological well being	
Psychological General Well-Being index	PGWB
Hopkins Symptoms Check list	SCL-90-R
General Health Questionnaire	GHQ-28
Hospital Anxiety Depression scale	HADS
Disorder specific measures	
Gastrointestinal Symptom Rating scale	GSRS
Gastrointestinal Quality of Life Index	GIQLI
Disease (constipation) specific measures	
Patient Assessment of Constipation-Symptoms	PAC-SYM
Patient Assessment of Constipation-QOL	PAC-QOL

Table 3: Quality of Life Measures used in constipation.

2.1.6 Constipation and Quality of Life in the general population

Table 4 summarises the findings of studies in the general population. In a mail survey of Canadian subjects using SF-36, those with self-reported functional constipation (Rome II criteria) had a significantly lower QOL compared to general population norms. In these study participants, a factor predicting physician visits was impaired quality of life [127]. Constipation also affects QOL in community dwelling elderly subjects; manifest by psychological disability [128,129]. Donald et al demonstrated higher scores for psychological distress and depression in such patients compared to the non constipated or controls[130]. O'Keefe et al demonstrated lower SF-36 scores in independent subjects (age 60-80 years) who had constipation compared to controls[131].

2.1.7 Quality of Life in patients with severe constipation.

Table 5 summarises the finding of studies in patients referred to specialist clinics. Overall, it appears that QOL is impaired. Sailer et al demonstrated reduced quality of life in 14 constipated patients referred to a tertiary centre using GIQLI [132]. Scores in these patients were significantly less then those of age-matched controls or patients with benign anorectal disorders (faecal incontinence, anal fissure, perianal abscess, fistula in ano, haemorrhoids etc).

Using SF-36, Mason et al found that QOL was less then that of normal UK age matched subjects in a study of 22 patients [42]. Damon et al studied QOL in 78 patients with chronic constipation referred for anorectal physiological testing. Again, QOL was less in the constipated patients then that reported for healthy subjects and patients suffering from faecal incontinence[37].

Glia et al performed an observational study of symptoms and QOL in 84 patients with idiopathic constipation [133]. The Gastrointestinal Symptom Rating Scale (GSRS) and the Psychological General Well-being Index (PGWBI.) were used. The result suggested that emotional well-being, perceived health and overall well-being were reduced compared to the general population.

In patients where a rectocoele contributed to constipation, preoperative disease specific quality of life has been shown to be impaired [134].

These preceding studies support the concept that QOL in severe chronic constipation is reduced in comparison to healthy subjects and to patients suffering from other gastrointestinal diseases. However, they are limited by relatively small sample sizes. The choice of quality of life measures in some of the studies can be questioned. For example, GIQLI was designed to evaluate a wide variety of both upper and lower gastrointestinal disorders. The proportion of constipated patients from the 204 used to validate the initial GIQLI is not stated in the original paper. The instrument's responsiveness to change was assessed in patients undergoing laparoscopic cholecystectomy rather then in patients with constipation. A criticism can therefore be levelled at the use of GIQLI to evaluate constipation in that it is not specific to this disorder. Of the 36 items that make up this measure, only one refers directly to constipation. Similarly, neither GSRS nor PGWBI were specifically designed to evaluate constipation. Furthermore, the PGWBI essentially only assesses one dimension of QOL, i.e. psychological wellbeing. There is a need to evaluate QOL in this patient group using measures specifically designed for the index condition (constipation). In addition, the concurrent use of generic QOL measures is advocated. Generic QOL measures may detect changes in a wide range of aspects of health that might not register on more focused specific measures. Generic measures are more likely to detect non-specific effects caused by co morbidities. They may also detect unexpected general effects (either positive or negative) caused through interventions used to treat the index condition being studied. Thus, the use of generic and specific measures is complementary [120].

Table 4. Studies of QOL in community dwelling constipated subjects.
SCL-90-R: Hopkins symptoms check list, SF-36: Short Form-36, EBSQ: Elderly Persons Bowel Symptom Questionnaire.

Author	Study and participants	Number	Generic Instrument	Disorder specific instrument	Other parameters studied	outcome
Donald I et al 1985 [130]	Community dwelling elderly subjects (age >60yrs)	201	Wakefield Depression Rating Scale	-	-	Depression associated with constipation
Whitehead W et al 1989 [128]	Community dwelling elderly subjects (age >65yrs)	209	General Health Questionnaire	-	-	Psychological distress greater in constipated subjects
O'Keefe E et al 1992 [131]	Community dwelling elderly subjects (age >65yrs)	126	EBSQ SF-36	-	-	Lower SF-36 scores in constipated subjects
Merkel I et al 1993 [129]	Case control study of subjects aged >60yrs	18	SCL-90-R	-	-	Increased psychological distress in constipated subjects
Irvine E et al 2002 [127]	Self reported functional constipation from general population	162	SF-36	-	-	Lower SF-36 scores in constipated subjects compared to norms

Table 5. Studies of QOL in constipated subjects from dedicated clinics.
SCL-90-R: Hopkins symptoms check list, SF-36: Short Form-36, GIQLI: Gastrointestinal QOL Index, PGWB: Psychological General Well-Being index, GSRS: Gastrointestinal Symptom Rating scale, GHQ-28: General Health Questionnaire.

Author	Study and participants	Number	Generic instrument	Disorder specific instrument	Other parameters studied	outcome
Wald A et al 1989 [135]	Severe refractory idiopathic constipation	25	SCL-90-R	-	Transit time Anorectal physiology	Psychological distress in slow transit constipated patients
Grotz RL et al 1994 [2]	Chronic idiopathic constipation	184	SCL-90-R	-	Transit time Anorectal physiology Defecating proctogram	Increased depression scores in normal transit constipation
Sailer M et al 1999 [132]	Idiopathic constipation	14	-	GIQLI	-	Reduced GIQLI scores compared to normal controls
Glia A & Linberg G 1997 [133]	Idiopathic constipation referrals to a tertiary centre	84	PGWB	GSRS	Transit time Proctography EMG	Reduced PGWB scores compared to normal controls
Pigot F et al 2001 [134]	Prospective study of female patients with rectocoele	38	SF-36	PAC-QOL	-	Improvement of QOL after surgery
Charach G et al 2001 [136]	Prospective study Treatment in elderly patients	52	Not stated	-	-	Treatment improved mood
Mason J et al 2002 [42]	Patients receiving biofeedback for idiopathic constipation	22	SF-36 GHQ-28 HADS	-	-	QOL lower in constipated patients compared to normal controls
Damon H et al 2004 [37]	Consecutive patients referred for specialist investigation	78	-	GIQLI	Anorectal manometry Cleveland clinic symptom score	QOL lower in constipated patients compared to healthy subjects

2.1.8 Correlation between Quality of Life and symptoms, transit time and anorectal physiology.

A picture is emerging that suggests poor QOL in constipated patients referred to tertiary and secondary centres. The factors that dictate why QOL is impaired have not been fully studied. The relationship between disease specific factors (such as colonic transit time, symptoms intensity etc) remain unclear.

Damon et al studied QOL with GIQLI and symptoms with the Cleveland Clinic Symptom score [37]. A weak to moderate correlation was demonstrated between QOL and symptom intensity. Again, the choice of QOL instrument may have influenced this result. In contrast Glia et al found a strong correlation between symptoms and the psychological dimension of QOL (measured by PGWB) [133]. Symptoms were assessed by GSRS rather than a condition specific measure and this limitation must be kept in mind.

Four studies suggest worse psychological status in normal colonic transit constipation than in slow chronic transit constipation. Grotz [2] and Wald [135] used the SCL-90-R and an abbreviated SCL-90-R respectively to assess psychological status and transit time. Patients with normal transit time constipation reported greater psychological distress then those with slow transit constipation. Glia et al demonstrated worse psychological status (as measured by PGWB) in normal transit constipated patients compared to slow transit constipated patients [133]. Towers et al examined psychological parameters and transit time in older subjects; those with slow colonic transit constipation had less psychological distress then constipated subjects with more rapid transit [137]. Studies using constipation specific measures of QOL have not been performed to assess the effect of colonic transit. Again, these studies rely on QOL measures that are not specific to constipation.

Defecating proctography and a variety of anorectal physiological tests are often employed as investigations for constipation. Damon et al assessed QOL in relation to anal pressure (resting and squeeze) and rectal compliance but did not demonstrate a correlation between QOL scores and these parameters [37]. Several other studies have assessed anorectal physiology and defecating proctography however, results pertaining to any relationship between these tests and QOL were not specifically documented in the papers [2,133-135].

2.1.9 Studies of Quality of Life and treatment of constipation

Charach et al demonstrated increased stool frequency following a trial of laxative therapy in 52 patients over the age of sixty. In addition, mood improved and the authors suggested that treatment of constipation was associated with an improvement in QOL [136]. Nyam et al reported long term outcomes following surgery for chronic constipation. Overall QOL was "good or improved" in 90% of patients five years after surgery. The authors used a simple graded scale to obtain a global assessment of QOL rather then a recognised and validated generic measure [138]. This is a limitation of the study.

Mason et al studied the effects of biofeedback therapy in 22 patients with idiopathic constipation [42]. Symptoms improved following biofeedback. QOL (measured by SF-36) and psychological status (by General Health Questionnaire-28, GHQ-28 and Hospital Anxiety and Depression Scale, HADS) also improved after treatment. Furthermore, pre treatment QOL (SF-36 pain, vitality and emotional subscales) predicted response to treatment. Reduced QOL expressed by low scores in these domains was associated with a poor response to biofeedback.

2.2 Summary

Within the general population QOL is reduced in those who have constipation. There are fewer studies of QOL in patients with refractory constipation severe enough to warrant referral to a specialist clinic. In these studies, the choice of QOL instrument has been inconsistent. To improve our understanding of the impact of constipation on QOL, there is a need to perform studies using disease specific measures of QOL. Concurrent use of generic QOL instruments may also provide additional information about the burden of the disorder and the impact of interventions, including unexpected positive and negative effects of therapy. The relationships between QOL and parameters that are believed to have an impact on or predict the severity of the condition (such as symptoms, colonic transit and proctographic findings) have not been studied in depth.

Measures of QOL are becoming accepted as useful overall indicators of severity in many disease states because they may provide a more accurate representation of the complete experience of the individual than indices based only on symptoms, physiological tests or radiological imaging. The ability to identify factors associated

with poor QOL may help to appropriately target therapeutic interventions for those suffering the greatest burden of constipation. Review of the existing literature suggests that: normal colonic transit is associated with reduced QOL; functionally significant rectocoeles adversely affect QOL and; symptom intensity is weakly to moderately associated with QOL.

Our aim was to explore empirically the effect of these and other factors on disease specific QOL in a population of patients with idiopathic constipation severe enough to warrant referral to a specialist clinic.

3 AIMS OF THE STUDY OF QOL IN IDIOPATHIC CONSTIPATION

The primary aim of the study was;

To examine the factors that predict disease specific QOL in patients with refractory idiopathic constipation.

An important secondary aim and prerequisite of the primary aim, was;

To confirm the reliability and validity of the QOL instruments by evaluating their psychometric properties.

This was of interest because the original validation of the constipation-specific instruments had not been in a population of patients from a specialist clinic. This aim was addressed initially so that we could be confident of the results arising from the studies of the primary aim.

3.1 Design

This was a cross sectional, observational study of a sample of patients with idiopathic constipation recruited from a specialist clinic dedicated to the management of refractory constipation.

3.2 Ethical considerations

The study was conducted in accordance with the in the 2004 Declaration of Helsinki and approval was granted by the local research ethics committee (County Durham ethics committee). All participants gave written informed consent.

3.3 Sample size calculation

A convenience sample of all available patients with refractory idiopathic constipation was used. No specific power calculation was performed as it was felt that a population of approximately a hundred would be enough for the purpose of an exploratory analysis to address the aims of the project.

3.4 Inclusion criteria

Only patients with a diagnosis of idiopathic constipation were considered for inclusion. In such patients systemic, biochemical, pharmacological, primary

neurological, structural abnormalities of the colon or endocrinological explanations for symptoms of constipation had been excluded by appropriate investigation.

The diagnosis of constipation required at least a 12 week history (which need not be consecutive) of 2 of the following in patients who had not responded to previous interventions (e.g. refractory constipation) and who had been referred to the dedicated clinic at University Hospital of North Durham;

(a) Fewer than 3 defecations /week;

(b) Straining in more than 25% of defecations;

(c) Lumpy or hard stools in more than 25% of defecations;

(d) Sensation of incomplete evacuation in more than 25% of defecations;

(e) Sensation of anorectal obstruction/blockade in more than 25% of defecations;

(f) Manual manoeuvres to facilitate in more than 25% of defecations
e.g. (digital evacuation, support of the pelvic floor)

Male and female patients over the age of 18 were included. Details regarding inclusion criteria were obtained at a clinician led face to face interview.

The inclusion criteria were designed to allow recruitment of patients with idiopathic constipation rather than the more specific categories enshrined in the Rome II criteria (i.e. Functional Constipation and constipation predominant Irritable Bowel Syndrome, IBS-C). As previously stated (section 1.2), and in keeping with our past experience, it can be difficult to differentiate between these two categories and overlap may exist.

3.5 Exclusion criteria

The presence of any of the criteria disqualified the patient for inclusion.

a) Age less than 18 years

b) Severe psychiatric disease

c) Known pregnancy, suspected pregnancy or patient trying to conceive.

d) Incapacity of higher mental function such that informed consent could not be achieved

e) Evidence of diarrhoea predominant Irritable Bowel Syndrome (IBS-D) according to Rome II criteria.

3.6 Subject recruitment

Subjects were recruited from the specialist constipation clinic at the University Hospital of North Durham. The clinic receives referrals from primary care (general practitioners) and secondary care. Referrals from secondary care originate from within the North Eastern region and also from outside the region. The referrals are generally from consultant clinicians (predominately gastroenterologists and general surgeons). A referral bias exists since the patients represent an extreme of the constipation spectrum. These patients have chronic symptoms that have not responded to prior therapies[7]. It is therefore recognised that the clinic population is not representative of the general population of constipated patients but only those with sufficient problems to warrant referral to a specialist clinic.

3.7 Subject disposition

One hundred and forty eight patients were identified in the constipation clinic as potential participants. Informed consent was obtained from 122 patients who were then included in the study (Figure 2). The remaining 26 subjects declined the invitation to be included. There were no important differences between the 26 non participants and the 122 participants. Comparisons of the demographics between these two groups are presented in section 4.5.

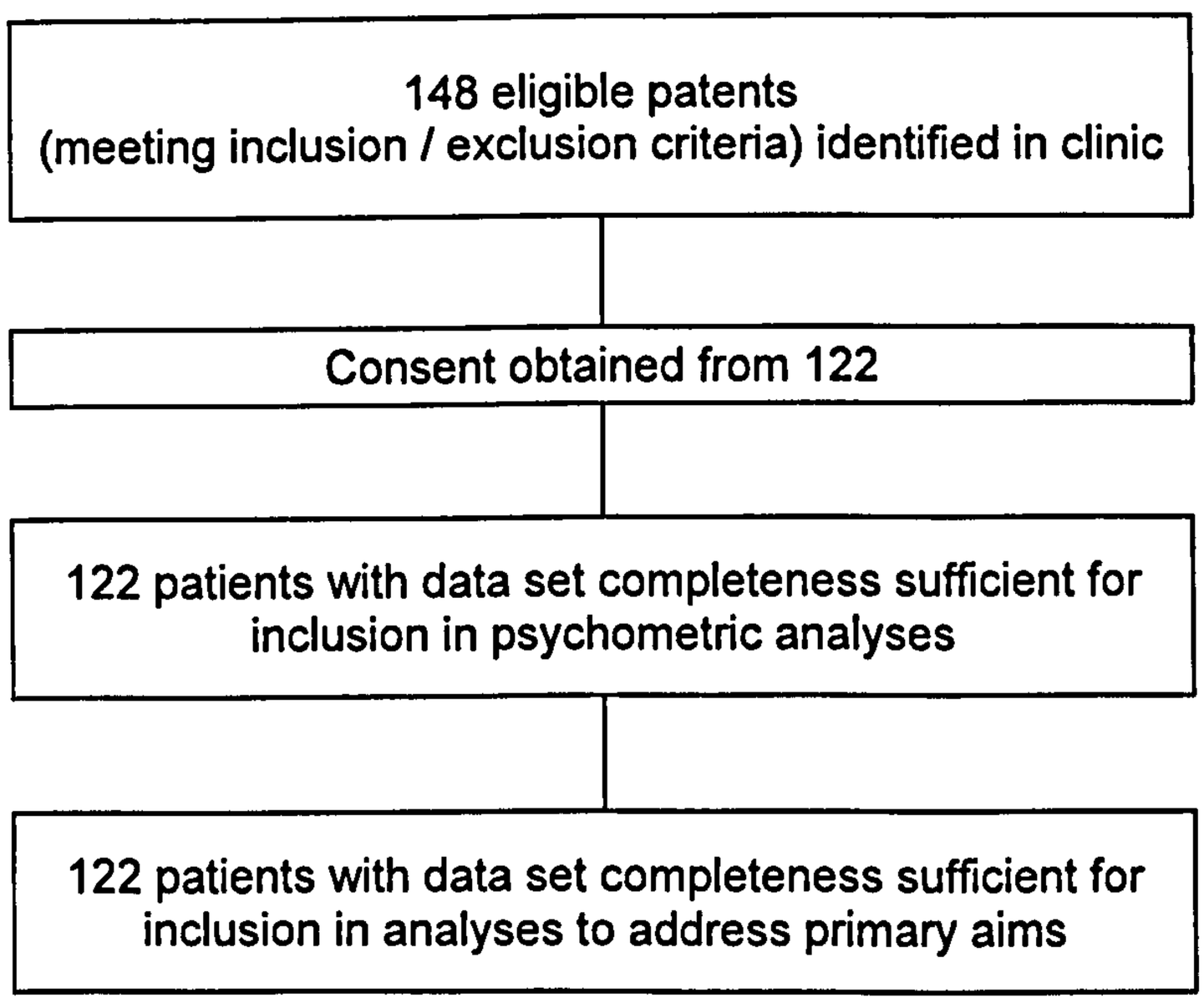

Figure 2. Subject disposition

3.8 Study protocol

Patient characteristics

Data regarding demographics (age, sex etc) were obtained at face to face clinician led interview (SC or YY). Other features of the history that have previously been held to be important in patients with constipation (section 1.4) were explored (past medical history, surgical history, prior psychiatric history, exposure to child birth). Regarding the characteristics of constipation; age of onset and duration of symptoms were also assessed.

During the consultation with subjects, symptoms were assessed by the clinician (SC or YY). On the same day, patient self assessment of symptoms, disease specific QOL and generic QOL and were undertaken by a single administration of the appropriate questionnaires (in the following order; PAC-SYM, PAC-QOL and SF-36). Radiological assessments with transit study and proctography were also undertaken (below). Detailed descriptions of these procedures are outlined in section 7.5.3 and section 7.5.4.

Assessment of symptoms and chacteristics

The clinician performed an evaluation of symptoms using a question based proforma that scored individual symptoms on Likert scales. The questions assesseds symptom including bowel frequency, pain at evacuation, sensation of incomplete evacuation, abdominal pain, abdominal bloating, time spent at toilet, requirement for digital manoeuvres to facilitate defecation and unsuccessful attempts. Coding details for the symptoms and characteristics assessed in the proforma questions are included in Appendix B, table 2. Symptoms were also self-assessed by the patient by completing the PAC-SYM measure [125].

QOL assessment

QOL was evaluated using PAC-QOL and SF-36 [117,119]. These measures were self-administered by the patients.

Colonic transit

Colonic transit time was determined using radio-opaque marker studies. In this multiple bolus, single abdominal X-ray technique, a known number of markers are

ingested on days 1, 2 and 3 followed by a single plain abdominal X-ray on day 4 [53]. One advantage of this method is that subjects need only refrain from laxatives for three days. This is of relevance since many patients are dependent on daily laxatives because of the intensity of symptoms. A second advantage is that in contrast to multiple bolus, multiple X-ray methods the current technique minimises radiation exposure.

Radionuclide Defecating Proctography

Radioisotope defecating proctography was used to give a dynamic assessment of defecation. This technique involves the use of a radioisotope neo-stool inserted *per rectum* that is visualised using a gamma camera during different stages of evacuation. The technique can provide quantative, qualitative and morphological data regarding defecation in constipated patients. It is an alternative to barium defecating proctography (a method that utilises barium paste visualised by fluoroscopy). Radioisotope proctography is associated with less radiation exposure than barium proctography [139]. This is an important issue since many patients with idiopathic constipation are women of child bearing age.

4 EVALUATION OF THE PSYCHOMETRIC PROPERTIES OF PAC-QOL

4.1 Abstract

Introduction The psychometric properties of the Patient Assessment of Constipation –QOL (PAC-QOL) have been examined in American patients. The aim of the evaluation reported here was to confirm the reliability and validity of the measure for use in the main study of idiopathic constipation patients recruited from a dedicated UK clinic.

Methods A single self-administration of PAC-QOL was undertaken by 122 patients. Item-total correlations and Cronbach's α coefficient were calculated to test reliability (internal consistency). Construct validity was assessed by comparison with the Short Form 36 Health Survey (SF-36).

Results Cronbach's α coefficients were high. Moderate item-total correlations were demonstrated. There were moderate inverse correlations between SF-36 and PAC-QOL domains that shared construct similarities. There were weak inverse correlations between SF-36 and PAC-QOL domains that did not share construct similarities. Only 4% of the study population had no abdominal pain. Adequate evaluation of known group validity was not possible.

Conclusions The psychometric evaluations suggest that PAC-QOL is reliable and valid for assessing QOL in patients with idiopathic constipation. The use of the measure for analysing data in the main study is supported.

Preliminary validation of the PAC-QOL questionnaire for chronic idiopathic constipation.
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Data collection	SRC, YY
Data entry	SRC
Data Analysis	SRC (advice from EM)
Data interpretation	SRC, EM

4.2 Introduction

The PAC-QOL is a relatively new instrument designed to evaluate a patient's perceived quality of life specifically related to constipation. The measure was developed by Marquis and colleagues to address the lack of a constipation-specific measure for assessing patient experience of constipation and for use in treatment trials of constipation[119]. It was designed to complement the Patient Assessment of Constipation – Symptoms (PAC-SYM). The two instruments can be used separately or in combination.

In order to select material for the PAC-QOL questions (items), the developers reviewed the literature and performed semi-structured interviews with patients suffering from constipation. At interview, groups of patients were asked open ended questions addressing the impact of constipation and its treatment on social functioning, psychological functioning, physical functioning, perceived wellbeing and level of impairment. The patient comments were used to identify relevant QOL issues and to generate PAC-QOL items.

To confirm the initial interview findings and to further evaluate effects on QOL, the patients also completed a structured survey that explored the impact of constipation on activities of daily living, social interaction, emotional status and general well-being. The survey findings were reviewed by the developers and an international panel of clinical gastroenterologists and a concept model of important QOL issues was created. This model was used by interviewers as a guide in subsequent patient focus groups. These focus groups were conducted in the UK to further explore QOL issues and generate items for the measure. Using verbatim quotes from the initial interviews and from the focus groups, a provisional 35 item questionnaire was developed. This was administered to 260 patients in the US and UK. Item reduction was undertaken to produce the final 28 item version of the PAC-QOL. This measure assesses QOL from the preceding 2 weeks (2 week recall) with response options scored with a five-point (0-4) Likert scale. The questionnaire is made up of 4 domains including constipation related worries and concerns (11 items), physical discomfort (4 items), psychosocial discomfort (8 items) and satisfaction (5 items).

Validation of the PAC-QOL has been performed in a group of 223 American patients with chronic idiopathic constipation (minimum duration of three months) [119]. The patients were recruited either through physician clinics or via advertisement. The patients were observed over a 6 week period. In the first 2 weeks, patients maintained their usual regime of management for constipation. In the following 4 weeks, patients were treated with a standardised regime (Magnesium tablets and bisacodyl). Patients completed the PAC-QOL at baseline, two weeks and 6 weeks. The results of psychometric analyses suggested that measure was valid, internally consistent and responsive to change over time.

However, it is recommended that the validity and reliability of a measure is restablished when applying the measure in a different population [113]. In order to use the questionnaire with confidence in our patients various psychometric characteristics of PAC-QOL were assessed and the results compared with those from previous studies. Where possible, the methods used in previous studies were used in these analyses.

Reliability and validity were tested by evaluating internal consistency and construct validity. Reliability is the ability to produce consistent results from items within the instrument purporting to measure the same trait or concept. Validity refers to the ability of an instrument to accurately measure the trait that it was designed to measure. Construct validity refers to the establishment of quantitative relationships (based on theory or previous empirical evidence), between scores on the instrument under examination and those on other instruments measuring similar constructs, and to relationships with demographic and clinical variables ("known groups" validity).

4.3 Aim

To evaluate the psychometric properties of PAC-QOL for use in our own population.

4.4 Patients and method

4.4.1 Subjects

One hundred and forty-eight patients with idiopathic constipation were identified as potential participants and 122 provided informed consent and completed the questionnaire (section 3.6)

4.4.2 Psychometric analysis

Missing data

Total scores and domain scores from a measure cannot be confidently estimated if the number of missing items is high. A high level of missing data is also suggestive that the items in the questionnaire are unacceptable to respondents and / or poorly understood. The number and percentage of patients with missing PAC-QOL items was computed for the total sample. Overall and domain scores can still be accurately calculated even if some items are missing, unless a critical number of items are absent. In these situations a "missing data handling rule" is invoked that invalidates the measure.

Scores

PAC-QOL is made up of 4 domains including; worries and concerns (11 items), physical discomfort (4 items), psychosocial discomfort (8 items) and satisfaction (5 items). Items are scored on a five-point (0-4) Likert scale. High scores are indicative of a worse QOL.

Sub-scale scores (constipation related worries and concerns; physical discomfort; psychosocial discomfort; satisfaction) and PAC-QOL total scores were calculated according to the developers' instructions, by summing scores across all non-missing items in the sub-scale (or total instrument) and dividing by the number of non-missing items in that sub-scale (or in the instrument as a whole). The PAC-QOL questionnaire, domain summaries, scoring algorithm and data handling rule (for

calculating overall and subscale scores in the presence of missing data) are displayed in Appendix A, Table 1; Appendix A, Table 2 and Appendix A, Table 3.

Floor and ceiling effects

The PAC-QOL domain scores were assessed for ceiling and floor effects. Ceiling effect refers to the percentage of patients achieving the highest possible score; floor effect refers to the percentage of patients achieving the lowest possible score.

In PAC-QOL, high scores are indicative of a worse QOL. Therefore, if there are marked ceiling effects at baseline in an intervention study or a longitudinal observation study, the potential to detect deterioration over time is compromised. Likewise, marked floor effects at baseline diminish the ability to detect improvement over time. It has been suggested that when more than 20% of respondents score at either extreme, the instrument may be considered to have marked ceiling and/or floor effects [140]. The distribution of responses for each PAC-QOL domain was examined using frequency histograms.

Internal consistency

The internal consistency of the PAC-QOL domains was assessed using Cronbach's α coefficient. A commonly accepted minimum standard of reliability is a coefficient of >0.70 for comparisons at group level [141].

Item-total correlation

A further measure of internal consistency is corrected item-total correlation. This approach is also referred to as item-domain correlation. This is the correlation between the item and the domain (sub-scale) total but omitting that item. It allows us to determine whether an item is related to its own domain (e.g. the extent to which item 1 of PAC-QOL: "felt bloated to the point of bursting" correlates with the physical discomfort domain of PAC-QOL). An item-total correlation coefficient of 0.40 or higher suggests adequate internal consistency. Item-total correlation less than 0.2 suggests that an item does not fit well with the other items in the domain or sub-scale[142].

Construct validity

Validity can be expressed by evaluating agreement between domains from different measures. For example, domain scores from PAC-QOL can be compared with domain scores from SF-36 and the strength of association studied. Construct validity tests the proposition that SF-36 domains that share similarities in construct and assess similar concepts as PAC-QOL domains will be related, i.e. that correlations will be moderate to high. Conversely, the association between domains that measure different concepts will be weaker (eg where the SF-36 and PAC-QOL domains do not share similarities of construct).

In this study, inverse correlations are expected between SF-36 and PAC-QOL because a low PAC-QOL score indicates better QOL, whereas high SF-36 scores are indicate better QOL. The strength of the expected relationships was informed using the definitions proposed by McHorney et al for interpreting correlation coefficients: strong association ($r \leq -0.70$), moderate association ($r = -0.69$ to -0.31), weak association ($r \geq -0.3$) [143].

It was hypothesised that the PAC-QOL domain of physical discomfort would have moderate associations with the SF-36 domains of bodily pain, vitality, social functioning and mental health.

Weak associations only were predicted between PAC-QOL physical discomfort and SF-36 role-physical, general health, role-emotional and physical functioning domains. Stronger associations were not proposed because the content of these SF-items address different concepts to those measured in the physical discomfort domain of PAC-QOL. For example, in SF-36, role-physical and physical functioning items refer to physical activity (lifting, carrying, shopping, bathing and dressing etc) or limitation of physical activity. In contrast, the PAC-QOL physical discomfort items focus on abdominal symptoms (feeling heavy or bloated) rather than physical activity.

It was postulated that PAC-QOL psychosocial discomfort would be moderately associated with the SF-36 domains of social functioning, general health, role emotional and mental health. The association between SF-36 physical functioning, role-physical, vitality and bodily pain with PAC-QOL psychosocial discomfort was expected to be weak.

The association between PAC-QOL worries and concerns and the SF-36 domain of mental health, was expected to be at least moderate. A stronger association was not postulated because the concepts addressed in this PAC-QOL domain are slightly different to those addressed in the SF-36 mental health domain. In the former, feelings of "irritability", "stress", "obsession", "upset" and "self-confidence" are evaluated. In the SF-36, items in the mental health domain assess more specific depressive symptoms. It is likely that the feelings evaluated in PAC-QOL will be influenced to a certain extent by depressive symptoms. Consequently, a moderate association is predicted between these domains.

Moderate associations were hypothesised for the relationship between PAC-QOL worries and concerns and the SF-36 domains of general health, bodily pain, vitality, social functioning, physical functioning, role physical and role emotional. It was postulated that the association between worries and concerns and bodily pain would be weak.

Regarding PAC-QOL satisfaction, association with SF-36 physical function, role physical, bodily pain, social functioning, role emotional, vitality and mental health was expected to be weak. The association with SF-36 general health was expected to be moderate.

Known group validity

A feature of a psychometrically valid measure is the ability to discriminate between patients where a known or recognised difference in a parameter (eg QOL) has been previously shown.

Marquis et al studied 223 patients with idiopathic constipation and found that 26% suffered no abdominal pain[119]. A comparison of mean PAC–QOL scores demonstrated significant difference between subjects with abdominal pain and patients without abdominal pain. Overall PAC-QOL was lower, with a mean of 1.37, in patients without pain compared to a mean of 2.17 in patients with pain ($p=0.001$).

This observation suggested that we could evaluate the "known group validity" of PAC-QOL in the current study population by comparing PAC-QOL scores of those subjects reporting abdominal pain with the scores of those subjects who suffer no abdominal pain. It was hypothesised that QOL would be worse in patients who have abdominal pain compared to those without. A statistically significant difference in scores was expected.

SPSS® version 12 for Windows (SPSS, Chicago, Illinois, USA) was used to analyse data. A value $p < 0.05$ was considered statistically significant.

4.5 Results

One hundred and forty eight patients were identified in the constipation clinic as potential participants. Informed consent was obtained from 122 patients who were then included in the study. Mean age of the total group was 43 years (sd 14.0). The mean duration of constipation was 17.7 years (sd 15.5). There were 118 females (97%) with a mean age of 42.5 years (sd 13.9) and 4 males (3%) with a mean age of 57.3 years (sd 5.3).

Patients who decided not to participate were not significantly different from the responders in terms of age, sex or duration of constipation (Table 6).

	Study participants	Non-participants	p value
Mean age (years)	43 (sd 14.0)	44 (sd 15.1)	0.73
Sex distribution	Female = 118 Male = 4	Female = 23 Male = 3	0.10*
Duration of constipation (years)	17.6 (sd 15.5)	19.8 (sd 14.5)	0.37

Table 6: Comparison of participants and non-participants.
*** Fisher's Exact test.**

4.5.1 Missing data

Completion of the instrument was high with 105 subjects (86% of subjects) responding to all items. Of the 17 patients who did not complete every item, 13 left a single item blank and 4 left two items blank.

Fifteen patients did not enter a value in response to item 28. The missing value rate for this item was therefore 12.3%. Item 28 forms part of the satisfaction domain (during the past two weeks, to what extent or intensity have you been satisfied with your treatment?). The missing value rate for the other uncompleted items (items 12, 13, 16, 17, 19, 20, 24, 26, 27) was low; 0.8%.

4.5.2 PAC-QOL scores

The mean overall PAC-QOL score was 2.4 (sd 0.73). Regarding the specific domains: worries and concerns mean score was 2.5 (sd 0.88), physical discomfort 2.7 (sd 0.77), psychosocial discomfort 1.8 (sd 0.95) and satisfaction 3.3 (sd 0.72).

Table 7 shows a comparison of the mean scores from the current study and scores from 223 patients studied by Marquis et al[119]. The current study scores are higher in all domains except satisfaction. This suggests a worse QOL in the current study population. Marquis et al found the mean satisfaction score in idiopathic constipation to be 3.49, reflecting "substantial dissatisfaction with the frequency and regularity of bowel movements, overall bowel function and treatment". In the current study the satisfaction score is 3.3.

	Current study Idiopathic constipation		Marquis et al[119] Idiopathic constipation	
Domains	n=122		n=223	
	Mean	sd	Mean	sd
Overall PAC-QOL	2.4	0.73	1.85	0.93
Worries and concerns	2.5	0.88	1.69	0.90
Physical symptoms	2.7	0.77	2.09	0.87
Psychosocial discomfort	1.8	0.95	0.93	0.80
Satisfaction	3.3	0.72	3.49	0.60

Table 7. Mean PAC- QOL domain scores.

4.5.3 Floor and ceiling effects for PAC-QOL

Only one patient PAC-QOL recorded the minimum score (in the psychosocial discomfort domain) suggesting no meaningful floor effect. The ceiling effect (the percentage of patients achieving the highest score) was encountered in the in the psychosocial discomfort domain; 18% of patients scored the maximum score of 4 (Table 8). This value was therefore close to the threshold of 20% indicative of a marked ceiling effect.

The distributions of responses for each domain are displayed in frequency histograms (Figure 4, Figure 5, Figure 6 and Figure 6). Distribution of scores was uni-modal and for the domains of worries and concerns, physical discomfort, psychosocial discomfort appeared to show a normal distribution. The satisfaction domain, however, showed a negatively skewed distribution.

	Number of patients with the minimum possible domain score (%)	Number of patients with the maximum possible domain score (%)
Overall PAC-QOL score	0 (0)	1 (0.8)
satisfaction score	0 (0)	22 (18)
physical symptoms score	0 (0)	4 (3.3)
psychosocial discomfort score	1 (0.8)	2 (1.6)
worries and concerns score	0 (0)	6 (4.9)

Table 8 . Ceiling and floor effects for PAC-QOL.
The minimum possible score for PAC-QOL is 0 and the maximum possible score is 4.

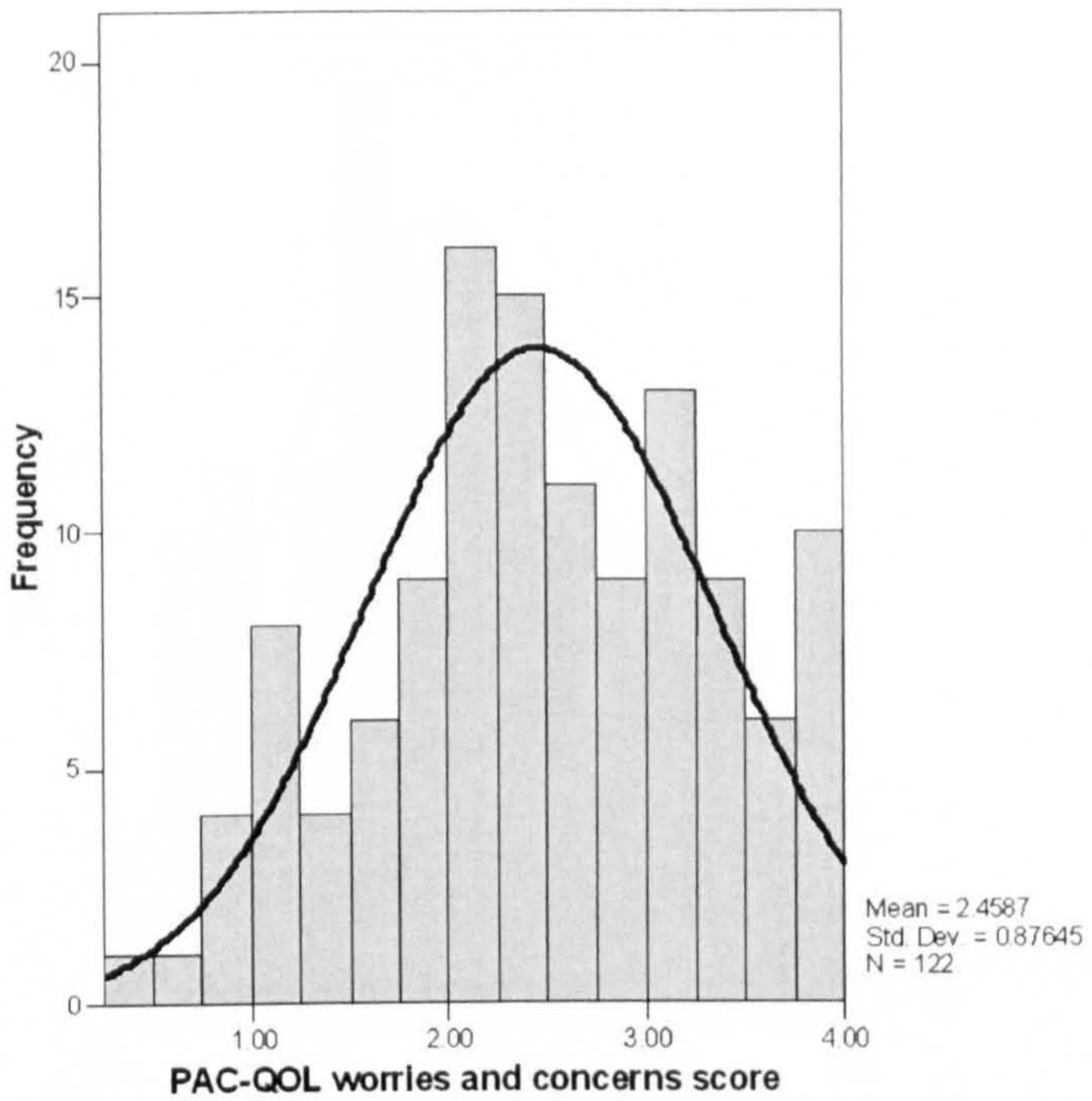


Figure 3. Histogram of responses for worries and concerns domain of PAC-QOL

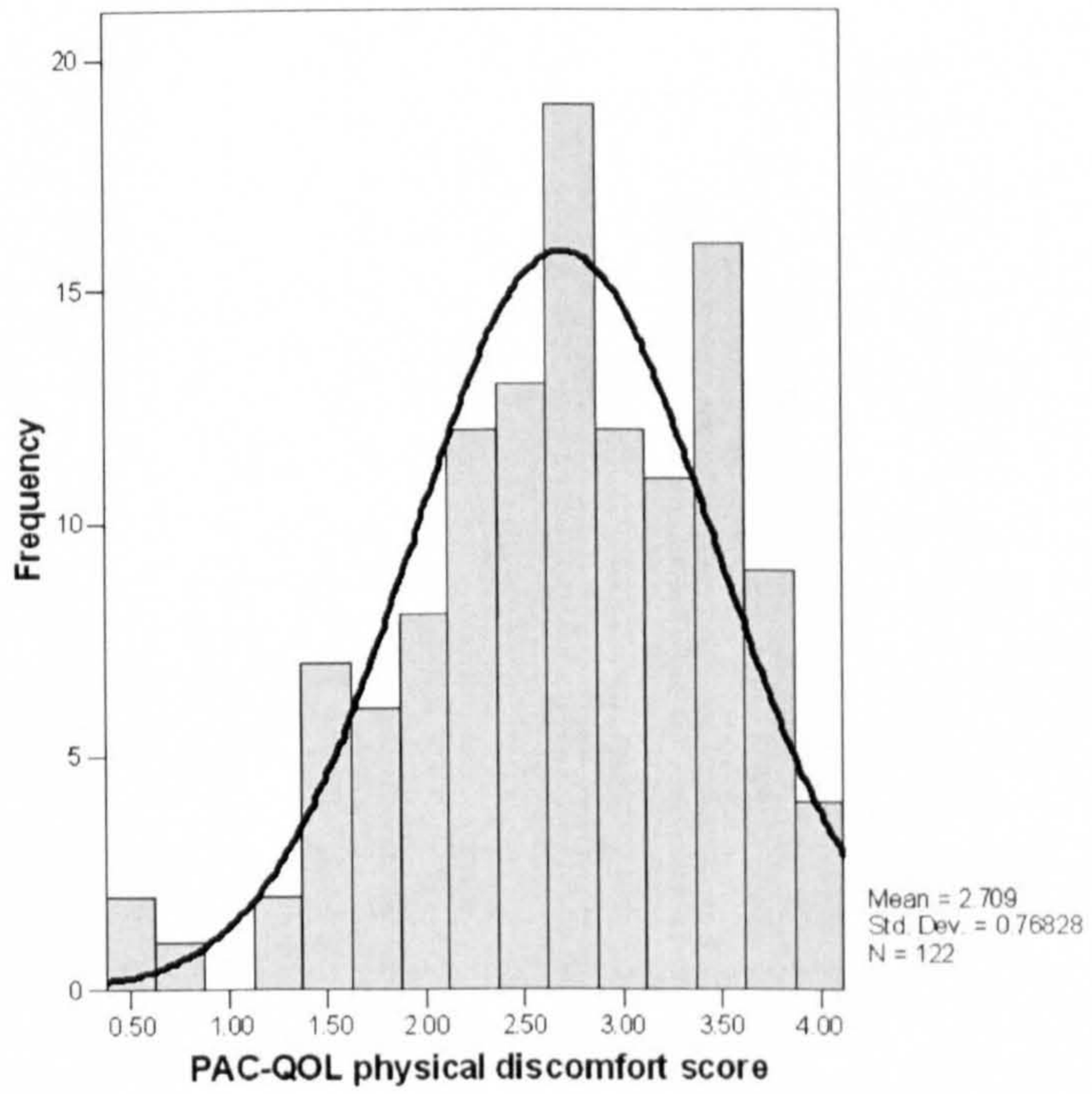


Figure 4. Histogram of responses for physical discomfort domain of PAC-QOL

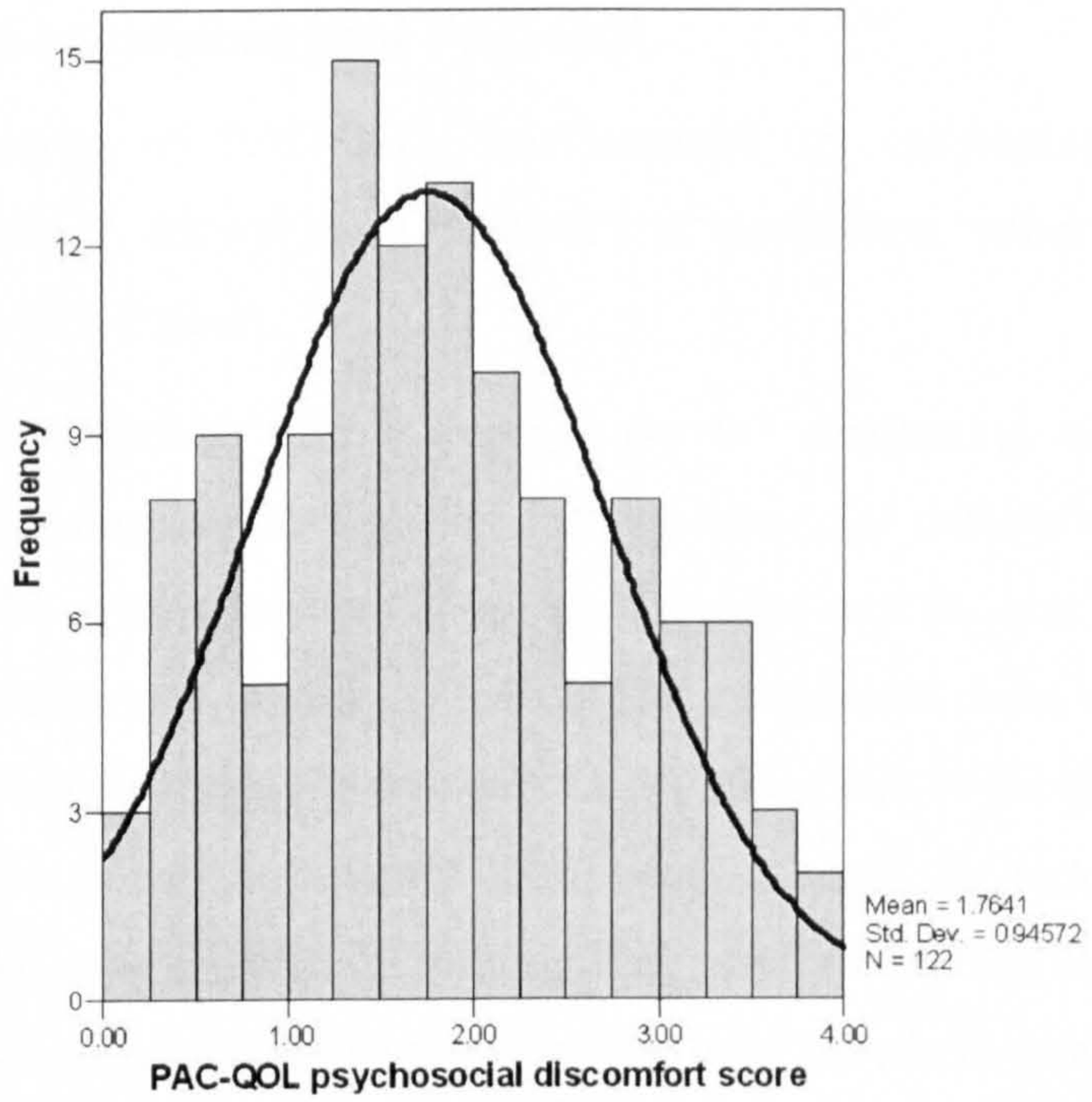


Figure 5. Histogram of responses for psychosocial discomfort domain of PAC-QOL

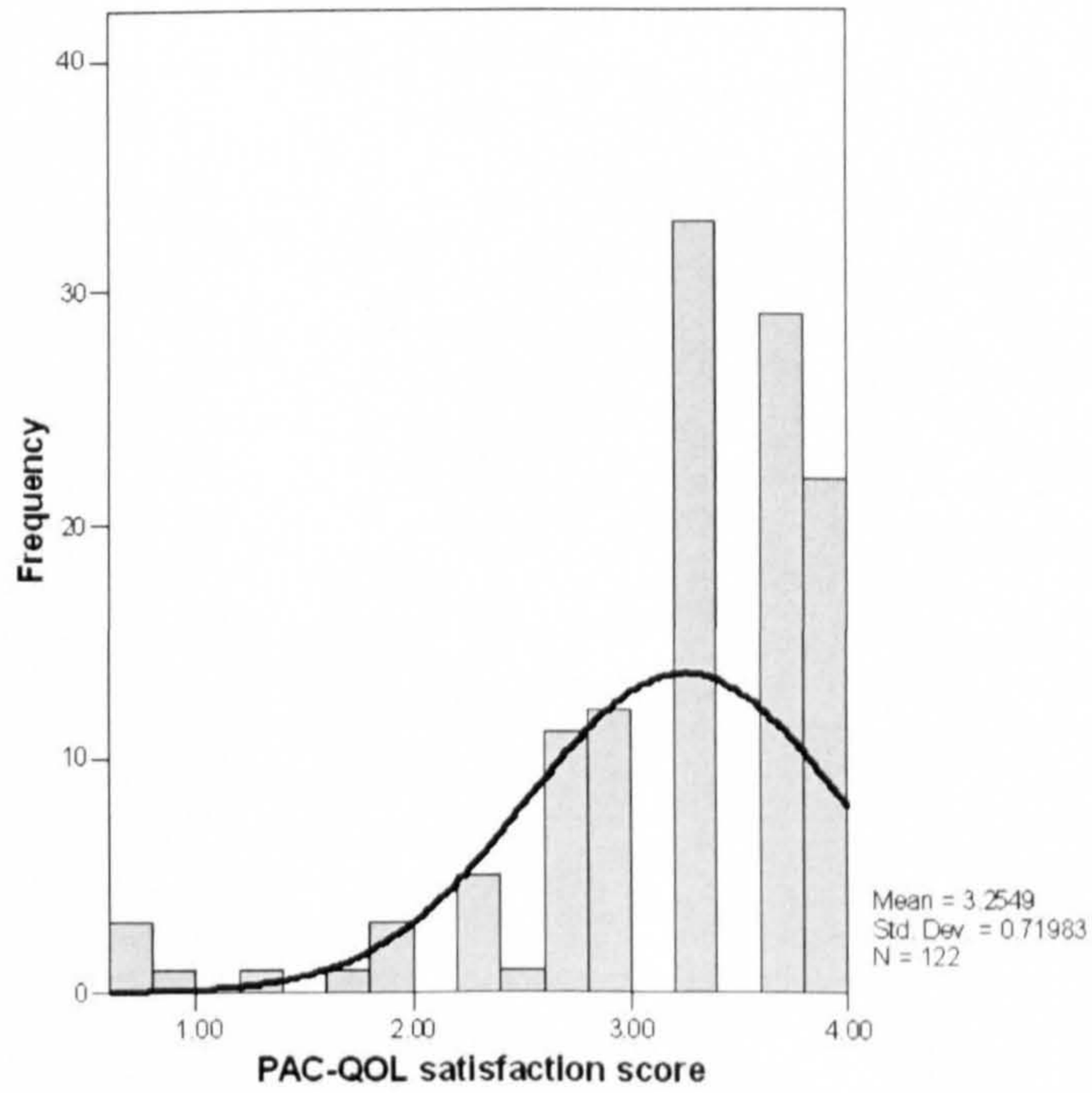


Figure 6. Histogram of responses for satisfaction domain of PAC-QOL

4.5.4 Internal consistency for PAC-QOL

Internal consistency of PAC-QOL was assessed by calculating Cronbach's α coefficient. Table 9 shows the Cronbach's α coefficient values and item-total correlations for each domain.

Cronbach's α coefficient values were above 0.7 suggesting adequate internal consistency. The range of coefficients for the item-total correlations was 0.28 to 0.81. In all but two cases the items from each domain met the criteria for item-total correlation with their own domain (>0.40). The exceptional cases were items 4 and 28. Regarding item 4 (during the past two weeks how much of the time have you felt the need to have a bowel movement but not been able to?) the item-total correlation was 0.37. In the case of item 28 (during the past two weeks, to what extent or intensity have you been satisfied with your treatment?) the item-total correlation was 0.28.

Table 10 compares Cronbach's α coefficients obtained by Marquis et al in the validation study of patients with idiopathic constipation with the results from our study.

	Cronbach's α	Item-total correlations
Physical symptoms domain	0.72	0.37-0.64 *
Psychosocial discomfort domain	0.84	0.50-0.67
Worries and concerns domain	0.91	0.41-0.81
Satisfaction domain	0.76	0.28-0.71 **

Table 9. Cronbach's α values and Item-total correlations for each domain of PAC-QOL. * Item 4 fell below the 0.4 value at 0.37. ** Item 28 fell below the 0.4 value at 0.28.

	Cronbach's α Marquis et al [119]	Cronbach's α Current study
Physical symptoms domain	0.86	0.72
Psychosocial discomfort domain	0.91	0.84
Worries and concerns domain	0.83	0.91
Satisfaction domain	0.81	0.76

Table 10. Comparison of Cronbach's α values for PAC-QOL from current and previous studies.

4.5.5 Construct validity for PAC-QOL

The definitions proposed by McHorney et al were used as the basis for interpreting the strength of the correlation coefficients (strong association; $r \leq -0.70$, moderate association; r = -0.69 to -0.31, weak association; $r \geq -0.3$)[143].

Moderate strength associations were demonstrated between SF-36 domains and PAC-QOL domains that had been postulated to share construct similarities (range - 0.49 to -0.32). The Pearson correlation coefficients are displayed in Table 11. The strength of association was weaker between domains hypothesised not to share construct similarities (range - 0.3 to -0.03).

In several instances the actual strength of association was different to that hypothesised (Table 12). For example, weak associations were predicted between the following; PAC-QOL satisfaction and SF-36 bodily pain, physical discomfort and general health, physical discomfort and role emotional, PAC-QOL psychosocial discomfort and SF-36 role physical. However, in these instances a moderate strength of association was found, although the coefficients (r= -0.33, -0.34, -0.32, -0.34 respectively) were at the lower limit of accepted definitions for moderate association (r = -0.69 to -0.30).

In two cases, completely unexpected results were demonstrated. Strength of association between PAC-QOL psychosocial discomfort and SF-36 bodily pain was weak; r -0.27 (a moderate correlation had been predicted). A weak association was postulated to exist between PAC-QOL worries and concerns and SF-36 bodily pain but a moderate association was present; r - 0.40).

	PAC-QOL domain			
SF-36 domain	Satisfaction	Physical discomfort	Psychosocial discomfort	Worries & concerns
Physical functioning	-0.03	-0.13	-0.26	-0.20
Role physical	-0.17	-0.29	-0.34	-0.31
Bodily pain	-0.33	-0.34	-0.27	-0.40
General health	-0.26	-0.32	-0.37	-0.39
Vitality	-0.26	-0.36	-0.30	-0.35
Social functioning	-0.23	-0.44	-0.47	-0.49
Role emotional	-0.19	-0.34	-0.38	-0.37
Mental health	-0.18	-0.41	-0.41	-0.44

Table 11. Pearson correlation coefficients between PAC-QOL domain scores and SF-36 domain scores.

SF-36 domain	PAC-QOL domain							
	Satisfaction		Physical discomfort		Psychosocial discomfort		Worries & concerns	
	Association		Association		Association		Association	
	Expected	Actual	Expected	Actual	Expected	Actual	Expected	Actual
Physical functioning	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Weak
Role physical	Weak	Weak	Weak	Weak	**Weak**	**Moderate** [d]	Weak	Weak
Bodily pain	**Weak**	**Moderate** [a]	Moderate	Moderate	**Moderate**	**Weak** [e]	**Weak**	**Moderate** [f]
General health	Weak	Weak	**Weak**	**Moderate** [b]	Moderate	Moderate	Moderate	Moderate
Vitality	Weak	Weak	Moderate	Moderate	Weak	Weak	Moderate	Moderate
Social functioning	Weak	Weak	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Role emotional	Weak	Weak	**Weak**	**Moderate** [c]	Moderate	Moderate	Moderate	Moderate
Mental health	Weak	Weak	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

Table 12. Expected and actual associations between PAC-QOL and SF-36 domains.

Shaded regions indicate where the strength of the actual association was different to expected. In certain cases weak associations were postulated but moderate associations were demonstrated ([a,b,c,d]). In these instances, the demonstrated moderate association was actually at the lower limit of the accepted definition for a moderate inverse association (as described by Mchorney et al, r= -0.69 to -0.31 [143]). These instances included; [a] -0.33, [b] -0.34, [c] -0.32 and [d] -0.34.

An unexpected weak association was found between psychosocial discomfort and Bodily pain; [e] r - 0.27. An unexpected moderate association was found between worries & concerns and Bodily pain; [f] r -0.40.

4.5.5.1 Known group validity for PAC-QOL

Only 5 (4%) patients reported no abdominal pain. This result is in contrast to that reported by Marquis et al, where approximately a quarter of subjects reported no abdominal pain[119]. No significant differences were demonstrated in the overall or specific domain scores for PAC-QOL between groups defined by the presence of pain (Table 13).

Domains	With abdominal pain n=5	sd	Without abdominal pain n=117	sd	p value
Overall score	2 .1	1.2	2.4	0.7	0.37
Physical discomfort	2.6	1.1	2.7	0.76	0.75
Psychosocial discomfort	1.8	1.1	1.8	0.95	0.93
Worries and concerns	2.3	0.72	2.4	0.89	0.16
Satisfaction	3.4	0.58	3.3	0.73	0.69

Table 13. PAC-QOL results for known groups
Mean scores for "known groups"; with abdominal pain and without abdominal pain.

4.6 Discussion

The study results provide preliminary evidence that suggests PAC-QOL is a reliable and valid measure of QOL in patients with chronic idiopathic constipation. Satisfactory internal consistency, item total correlation and construct validity have been demonstrated.

The total PAC-QOL scores are higher than those reported by Marquis et al [119]. It is likely that the current study population is different to that previously evaluated. This possibility illustrates the importance of confirming validity and reliability of PAC-QOL with regard to evaluation of our own population.

It would appear that the current study population suffer more severe constipation and greater impairment of QOL compared to the subjects in Marquis' paper (as evidenced by higher PAC-QOL scores). The patients were recruited from a clinic population that deals with the extreme end of the spectrum of constipation sufferers. They have severe intractable constipation with chronic symptoms unresponsive to conservative therapies implemented in primary and secondary care[7]. In comparison, the subjects studied by Marquis et al were not recruited from such a clinic but were recruited from primary care and from the general population through advertising. Although Marquis' subjects had chronic constipation, it appears that the burden and severity was less extreme. This observation is supported by the fact that more than two thirds responded to a simple regime of dietary fibre, magnesium supplement and as required low dose bisacodyl. In contrast, the majority of patients seen in the constipation clinic in Durham have already failed similar simple regimes and require multiple laxatives taken daily at high doses[7].

Confirmations of psychometric properties pertaining to a single administration were evaluated in this chapter. Other recognised psychometric evaluations (test-retest reliability) require administration of the instrument on more than one occasion. Assessment of predictive validity, responsiveness and sensitivity to change (eg following treatment) also require the measure to be administered on multiple occasions and were not examined.

Factor analysis is a technique that has also been employed for evaluating internal consistency[140]. However, it is generally accepted that larger sample sizes are required

for such analyses than were available for the current study. For example, a rule of thumb is that 10 responses per item are required so that factor analysis for PAC-QOL would require a minimum sample of 280.

The values for Cronbach's α coefficient in the current study were, for the most part, lower than those demonstrated by Marquis et al. However, the requirements for confirming adequate internal consistency for PAC-QOL in group comparisons are met. The item-total correlations also support the reliability of the measure. In only two instances did an individual item not appear to correlate at the expected level with the other items in its own domain. Item 4 of the physical discomfort score refers to how often the subject felt the need to have a bowel movement but been unable to. Unlike items 1, 2 and 3, item 4 does not directly refer to abdominal discomfort. Consequently, it is perhaps unsurprising that the item-total correlation was lower than for the other items in the subscale. A similar situation exists in the case of item 28 of the satisfaction domain where item-total correlation was only 0.28. The other items in this domain (items 24-27) specifically explore the patient's sense of satisfaction with the frequency and regularity of bowel movements. These concepts appear to be different to those evaluated in item 28 which concerns satisfaction with *treatment* rather than satisfaction with frequency of bowel movements. Again, it is perhaps unsurprising that item-total correlation is lower for this item. Unfortunately, reference data regarding item-total correlations for PAC-QOL are not quoted in the literature.

Overall, the construct validity of the instrument was confirmed. Items in PAC-QOL and SF-36 that measured similar concepts shared similarities in construct and their scores were correlated. The strength of these associations were moderate rather than strong. This was to be expected, because generic QOL measures (eg SF-36) assess slightly different concepts to those assessed by a disease specific measure (eg PAC-QOL). However, if the study had involved the administration of two generic quality of life measures we might have expected stronger associations.

In four instances weak associations were hypothesised between domains but the actual results showed moderate associations. In these cases, the coefficients only just qualified as moderate associations. The results did not differ dramatically from the original hypotheses of weak relationships. For all intents and purposes, the results

can be considered as being supportive of the original hypotheses and thus construct validity.

Completeness of data was high with 86% of subjects responding to all items. This suggests that PAQ-QOL contains items that were readily understood and acceptable to patients and could be self administrated with minimal respondent burden. However, another factor contributing to high completeness is that the study group was motivated to complete the measure and be involved in the study.

No significant floor effects were demonstrated. Ceiling effects were encountered in the psychosocial discomfort domain where 18% of patients recorded the highest score possible. The percentage almost reached the threshold value of 20% for significant ceiling effects[140]. The fact that 18% of patients perceived their QOL in this domain to be at the worst possible level is relevant if an intervention or longitudinal study were to be performed in this patient sample. If the intervention actually worsened the existing psychosocial discomfort then this effect would not be picked up by changes in their psychosocial discomfort scores. Marquis et al did not specifically provide values for ceiling and floor effects in their validation study.

PAC-QOL was not fully completed by 17 subjects. In each of these cases the degree of incompleteness did not invalidate their PAC-QOL scores because the missing data handling rule was not violated. As a result all 122 questionnaires could be analysed.

Item 28 of the satisfaction domain had the highest missing value rate of 12.3%. It is recognised that items that are difficult to understand, unclear or present a large respondent burden (eg require a lot of cognition to answer) might be omitted by respondents. Marquis et al did not report similar problems with missing values for item 28 and in fact found high rates of completion.

It is difficult to believe that this specific item was confusing or ambiguous because almost universally the other questions in this domain were completed. The poor response to item 28 may be related to some quality that has specific relevance to the patients recruited for this study. These subjects may not have responded on the grounds that, expressing dissatisfaction with their treatment would be construed as a criticism of the clinician who referred them. Therefore, instead of entering a response that they feared would be misinterpreted they decided not to answer at all. This explanation is of course conjecture.

The possibility of performing known group analyses was entertained because of the observation made by Marquis et al that patients who did not complain of abdominal pain had better QOL. For our study it was hypothesised that QOL would be significantly worse in patients with abdominal pain compared to those without. No statistically significant differences were detected between the groups. However, the limitations of this comparison must be considered when interpreting these results. The number of subjects in the no pain group is extremely small (only 4% of the whole cohort had no abdominal pain). With such small numbers it is difficult to undertake meaningful known group analyses with regard to the presence of pain.

In our study patients with idiopathic constipation were recruited. Our experience is that it can be difficult to classify further into Functional Constipation (FC) or Constipation predominant Irritable Bowel Syndrome (IBS-C). This observation has been made by other authors also [9,13].

The description of Functional Constipation, as defined in Rome II, refers to two or more symptom sets (present in a defined time period) including straining, lumpy or hard stools, sensations of incomplete evacuation, sensation of anorectal obstruction, manual manoeuvres to facilitate defection and less than three defecations per week. Insufficient criteria for constipation predominant IBS must be present to qualify for Functional Constipation. A cardinal feature for classifying as IBS is the presence of abdominal pain or discomfort that may be relieved by defecation (in addition to other descriptor symptoms). Abdominal pain and discomfort was clearly common in our cohort (as evidenced by the PAC-QOL subscale scores). However, it can be difficult for patients and clinicians to clarify the relationship between abdominal pain and constipation. It is not always any easy task to separate constipation related pain that is relived by defecation from constipation pain that is also present but not relieved by defecation. It becomes a matter of judgement to decide whether a patient can be confidently classified as having exclusively Functional Constipation (FC) and not constipation predominant Irritable Bowel Syndrome (IBS-C) when the issue of abdominal pain and discomfort is considered.

4.7 Conclusion

The results of the psychometric analyses confirm the reliability and validity of PAC-QOL for evaluating QOL in the current population of constipated patients. These results support the findings of the previous validation study of the measure[119].

5 EVALUATION OF THE PSYCHOMETRIC PROPERTIES OF PAC-SYM

5.1 Abstract

Introduction The psychometric properties of the Patient Assessment of Constipation – Symptoms (PAC-SYM) have been examined in American patients and patients with opioid induced constipation. The aim of the current study was to confirm the reliability and validity of the measure for use in the main study of idiopathic constipation patients recruited from a dedicated UK clinic.

Methods A single self-administration of PAC-SYM was undertaken by 122 patients. Item-total correlations and Cronbach's α coefficient were calculated to test reliability (internal consistency). Construct validity was assessed by comparison with the Short Form 36 Health Survey (SF-36).

Results Cronbach's α coefficients were high. Moderate to high item-total correlations were demonstrated. There were moderate inverse correlations between SF-36 and PAC-SYM domains that shared construct similarities. There were weak inverse correlations between SF-36 and PAC-SYM domains that did not share construct similarities.

Conclusions The psychometric evaluations suggest that PAC-SYM is reliable and valid for assessing symptoms in patients with idiopathic constipation. The use of the measure for analysing data from the main study is supported.

Data collection	SRC, YY
Data entry	SRC
Data Analysis	SRC (advice from EM)
Data interpretation	SRC, EM

5.2 Introduction

The PAC-SYM is a relatively new instrument designed to evaluate a patient's perception of symptoms of constipation. The measure was developed by Frank and colleagues to address the lack of a constipation-specific measure for assessing patient experience of constipation and for use in treatment trials for constipation[125]. It was designed to complement the Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL); the two instruments can be used separately or in combination.

Item content for the PAC-SYM was identified through a review of the literature and through focus groups with a range of patients with constipation. The group provided the range of symptoms important to patients and provided insight into the language used by patients to describe constipation. Two broad symptom classes emerged from the focus group work; constipation specific symptoms (i.e. pain with bowel movement, frequent small bowel movements, incomplete evacuation) and systemic symptoms that were associated with constipation by some patients (i.e. nausea and fatigue).

In an attempt to maximise the relevance of the PAC-SYM assessment for patients, the symptom description and language used by patients in the focus groups was used to construct the items in the questionnaire. A recall of two weeks was chosen. This allowed a period long enough for sufficient occurrences of infrequent bowel movements to take place and also reduced recall burden for subjects. Five pilot subjects completed the initial questionnaire to evaluate comprehensiveness and ease of understanding.

The initial version of PAC-SYM comprised 44 items, including both constipation-specific symptoms (e.g. pain on defecation) and systemic symptoms that patients associated with constipation (e.g. nausea). Each item had a 5-point Likert scale response format; 23 of these items assessed symptom frequency and 21 assessed symptom severity. Item reduction, (based on the initial US validation sample of 216 patients with a history of chronic idiopathic constipation) led to the deletion of all the frequency items, the reduction of the symptom items to twelve and to the removal of the items relating to systemic symptoms.

PAC-SYM is thus made up of 12 items, covering three domains: abdominal symptoms (4 items); rectal symptoms (3 items) and stool symptoms (5 items). The items are scored on a five-point (0-4) Likert scale (absent, mild, moderate, severe, very severe). High subscale and total scores are indicative of worsening severity of symptoms. Sub-scale and total scores are computed by taking the average of item scores across the non-missing items in that sub-scale (domain) or across all non-missing items in the instrument. The PAC-SYM questionnaire and data handling rule are displayed in Appendix A, Table 4 and Appendix A, Table 5.

Validation of the PAC-SYM has been performed in two previous studies examining different groups of patients; chronic idiopathic constipation and opioid induced constipation [125,144].

In chronic idiopathic constipation, Frank et al studied 216 American patients from multiple sites who participated in a 6-week psychometric evaluation of PAC-SYM. Subjects were male and female, aged 18 – 70 years. All had a history of idiopathic constipation in the preceding 3 months. Two thirds were recruited from medical practices whilst the remainder were recruited through advertising. Subjects were assessed over a 6 week period; for two weeks they controlled their symptoms with their existing treatments. In the subsequent 4 weeks they received a regime of fibre supplements and magnesium tablets. For those in whom there was no improvement bisacodyl was added. PAC-SYM was completed at week zero, 2 and 6. The psychometric proprieties of the PAC-SYM were confirmed and the measure was found to be internally consistent, reproducible, valid and responsive to change[125].

In the study of opioid induced constipation, in addition to evaluating psychometric properties, Slappendel et al tested for differences in opioid-induced constipation between a transdermal opioid and an oral sustained-release opioid in patients with chronic low back pain. Six hundred and eighty male and female patients were randomised to receive either transdermal (n=338) or oral opioid analgesia (n=342) in a 13-month, open-label, parallel-group study. Assessments were made at baseline, after 29 days and at 13 months. PAC-SYM was completed at these assessments. Laxative therapy was used by the patients as required. The authors concluded that PAC-SYM was a reliable, valid and responsive measure of the presence and severity of opioid-induced constipation.

To assess whether the PAC-SYM was appropriate for use in our patients, various psychometric characteristics of PAC-SYM (in particular internal consistency reliability and construct validity) were assessed and the results compared with those from previous studies [125,144]. In as far as possible, the methods used in the previous studies were used in these analyses.

Reliability and validity were tested by evaluating internal consistency and construct validity respectively. Internal consistency refers to the coherence or consistency of items purporting to measure the same trait or concept. Validity refers to the ability of an instrument to measure accurately the trait that it was designed to measure. Construct validity refers to the establishment of quantitative relationships, based on theory or previous empirical evidence, between scores on the instrument under examination and those on other instruments measuring similar constructs, and to relationships with demographic and clinical variables.

5.3 Aims

To evaluate the psychometric properties of PAC-SYM so that the use of the measure could be legitimised in the main study.

5.4 Patients and method

5.4.1 Subjects

148 patients with idiopathic constipation were identified as potential participants, 122 gave consent and completed the questionnaires (section 3.6)

5.4.2 Psychometric analysis

Missing data

The number and percentage of patients with missing PAC-SYM items was computed for the total sample. Where more than half of the items in a particular sub-scale are missing, the developers of the PAC-SYM recommend that the sub-scale score should be treated as missing (Appendix A, Table 5).

Scores

Sub-scale scores (bowel symptoms; abdominal symptoms; rectal symptoms) and PAC-SYM total scores were calculated according to the developers' instructions, by summing scores across all non-missing items in the sub-scale (or total instrument) and dividing by the number of non-missing items in that sub-scale (or in the instrument as a whole). Data handling rules are described in Appendix A, Table 5.

The mean PAC-SYM scores from our study were compared to those from the validation study (Frank et al[125]) using independent sample t-tests.

Two comparisons were made. The first comparison was with the mean scores of all patients studied by Frank et al. The second comparison was with the mean scores of a subset of patients who failed to respond to laxative treatment. Comparison with these patients was performed because they were deemed to share similarities with our cohort in terms of severity (i.e. severe refractory constipation resistant to therapy). The non-responder group in the Frank et al[125] study comprised 36 patients unresponsive to four weeks with either dietary fibre and magnesium or dietary fibre with magnesium plus bisacodyl. The group contained patients in whom symptoms remained static with these treatments (n = 28) and patients in whom symptoms worsened (n = 6) with treatment.

Ceiling and floor effects

Ceiling and floor effects for PAC-SYM domain scores were evaluated using the techniques described in section 4.4.2.

Internal consistency

Reliability of the PAC-SYM domains was assessed using Cronbach's α coefficient (a coefficient of >0.70 was used to define a minimum standard of internal consistency for group comparisons [141]). A further measure of internal consistency was provided by corrected item-total correlations (section 4.4.2).

Construct validity

Construct validity in this study was assessed by examining the pattern of correlations between PAC-SYM and SF-36 scores, reflecting the analyses conducted by Slappendel and colleagues[144]. More specifically, we tested the proposition that PAC-SYM and SF-36 scores that share similarities in construct (e.g. pain) would be correlated with one another. Conversely, the association between domains that measure different concepts should be weaker (i.e. where the SF-36 and PAC-SYM domains do not share similarities of construct). Hypotheses regarding the pattern of correlations expected were based on findings from the previous validation study in patients with opioid induced constipation [144]. Since high scores on the SF-36 are indicative of better quality of life, while high scores on the PAC-SYM denote more severe symptoms, we expected correlates to be negative, though low to moderate.

SPSS® version 12 for Windows (SPSS, Chicago, Illinois, USA) was used to analyse data. A value $p < 0.05$ was considered statistically significant.

5.5 Results

Of the 148 patients identified as potential participants, informed consent was obtained from 122. The mean age of this group was 43 years (sd 14.0). There were 119 females (97%) with a mean age of 42.5 years (sd 13.9) and 4 males (3%) with a mean age of 57.3 years (sd 5.3). The mean duration of constipation was 17.7 years (sd 15.5).

There was no significant difference between those patients who agreed to participate in the study and those who did not give consent for inclusion in the study in terms of age, sex or duration of constipation (Table 6).

5.5.1 Missing data

Data completeness was high. The number of patients who fully completed PAC-SYM was 112 (92%). Of the 10 patients who did not complete every item, 7 left a single item blank and 3 left two items blank. Missing item rates were uniformly low; 0.8% for items 3, 9, 11 and 12, item 5 (1.6%), item 4 (2.5%) and item 12 (3.3%).

5.5.2 PAC-SYM scores

The mean overall PAC-SYM score was 2.13 (sd 0.68). Mean scores for each of the three domains were: stool symptoms 2.35 (sd 0.89); abdominal symptoms 2.39 (sd 0.89); rectal symptoms 1.40 (0.97). The mean scores for stool and abdominal symptoms thus correspond to a rating between 'moderate' and 'severe', while that for rectal symptoms corresponds to a rating between 'mild' and 'moderate'.

Table 14 compares the PAC-SYM scores from our study with those from 157 patients with idiopathic constipation studied by Frank et al [125]. Overall PAC-SYM score was significantly higher in our study than in the Frank et al study ($p < 0.001$).

Table 15 makes the comparison with the subset of patients studied by Frank et al who had refractory constipation despite laxative treatment. Overall PAC-SYM score was significantly higher ($p < 0.001$) in our sample, as were domain scores for abdominal and stool symptoms ($p = 0.002$ and $p < 0.001$ respectively). Mean scores

for rectal symptoms were slightly higher in Frank et al's study but the difference was not statistically significant (p = 0.195).

	Current study		Frank et al				
	Idiopathic constipation		Idiopathic constipation		t-test		
	n=122		n=157*				
Domains	Mean	sd	Mean	sd	95% CI for mean difference	t	p
Overall PAC-SYM	2.13	0.68	1.61	0.69	0.36, 0.68	6.28	<0.001
Abdominal symptoms	2.39	0.89	2.05	0.89	0.13, 0.55	3.17	0.002
Rectal symptoms	1.40	0.97	1.54	0.83	0.35,0.07	-1.30	0.195
Stool symptoms	2.35	0.89	0.98	0.86	1.16,1.59	12.94	<0.001

Table 14: Comparison of mean PAC-SYM scores

	Current study		Frank et al[125]				
	Idiopathic constipation		Refractory idiopathic constipation		t-test		
	n=122		n=36*				
Domains	Mean	sd	Mean	sd	95% CI for mean difference	t	p
Overall PAC-SYM	2.13	0.68	1.44	0.66	0.44, 0.94	5.38	<0.001
Abdominal symptoms	2.39	0.89	1.68	0.90	0.37, 1.04	4.20	<0.001
Rectal symptoms	1.40	0.97	0.73	0.66	0.33,1.01	3.88	<0.001
Stool symptoms	2.35	0.89	1.68	0.80	0.34, 0.99	4.06	<0.001

* Subgroup of 36 patients from the initial 157 patients (see table 12) who were unresponsive to laxatives

Table 15: Comparison of PAC-SYM scores in refractory constipation

5.6 Floor and ceiling effects for PAC-SYM

The number of patients that recorded the maximum score of 4 in each domain was low; no appreciable ceiling effects were demonstrated. These results are displayed in Table 16. Just fewer than 10% of patients had the lowest possible score of 0 for rectal symptoms. This value did not reach the threshold of 20% indicative of marked floor effects.

	Number of patients with the minimum possible domain score (%)	Number of patients with the maximum possible domain score (%)
Overall PAC-SYM	0 (0)	0 (0)
Abdominal symptoms	2(1.6)	4 (3.3)
Rectal symptoms	12 (9.8)	1 (0.8)
Stool symptoms	1 (0.8)	5 (4.1)

Table 16. Ceiling and floor effects for PAC-SYM.

The distributions of responses for each domain are displayed in frequency histograms (Figure 7, Figure 8, Figure 9). Distributions of responses were uni-modal. For the rectal domain there was a positively skewed distribution. Normal distributions were observed for abdominal and stool domains.

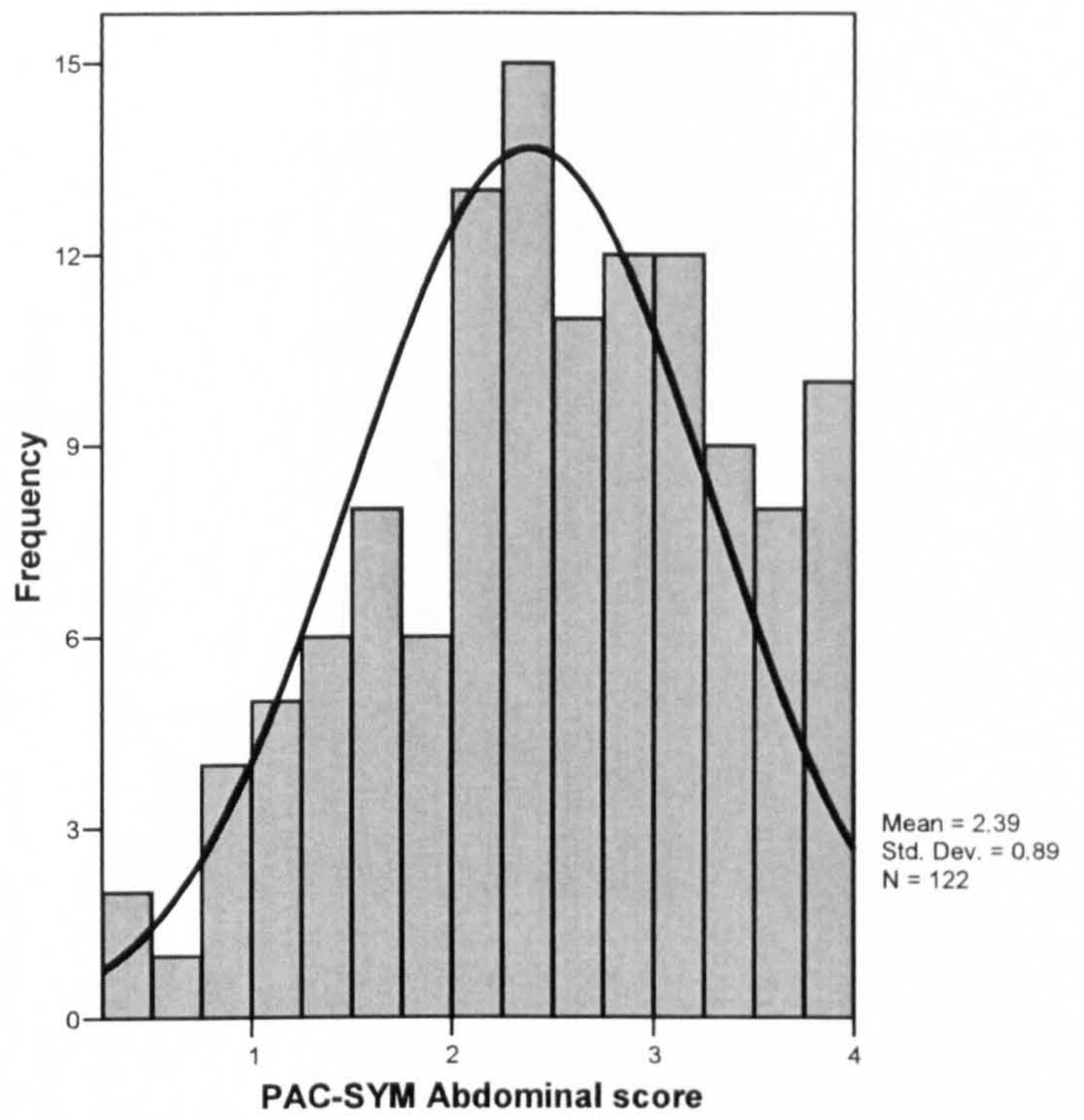


Figure 7. Histogram of responses for abdominal symptoms score of PAC-SYM.

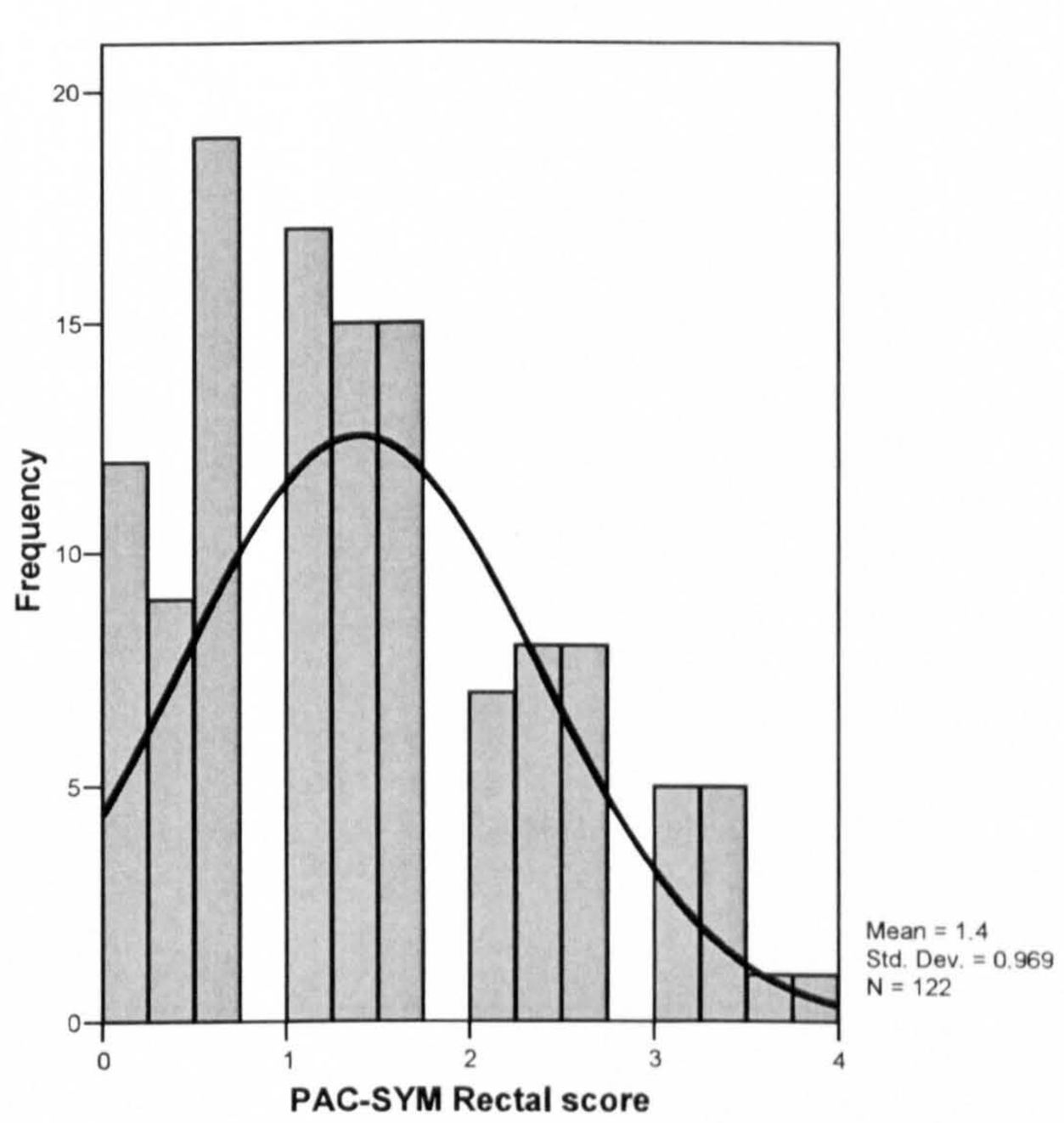


Figure 8. Histogram of responses for rectal symptoms score of PAC-SYM.

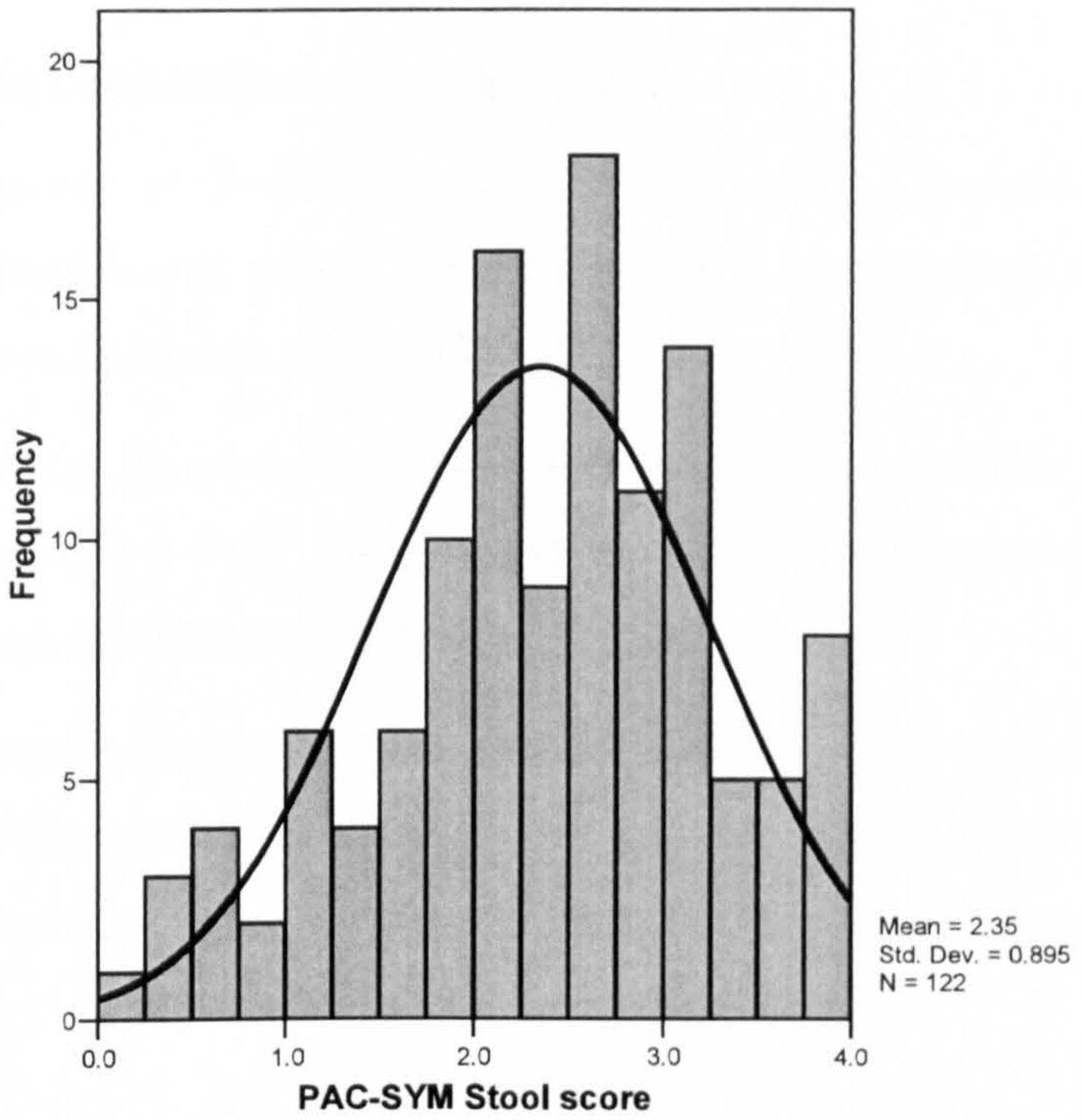


Figure 9. Histogram of responses for stool symptoms score of PAC-SYM.

5.6.1 Internal consistency for PAC-SYM

Internal consistency of PAC-QOL was assessed using Cronbach's α coefficient. Cronbach's α coefficient values were all above 0.7 suggesting adequate internal consistency for each domain (Table 17).

The coefficients for item-total correlations are also shown in Table 17. The range of correlations was 0.48 to 0.79. All items met the criteria for item-total correlation with their own domain (coefficient > 0.4).

Table 18 compares Cronbach's α coefficients from our study with those obtained by Frank et al and Slappendel et al. Our values for stool and abdominal symptoms were similar to those from the two previous studies, but our values for the rectal subscale were lower.

	Cronbach's α	Item-total correlations
Total score	0.93	0.67- 0.19
Abdominal symptom domain	0.85	0.69-0.79
Rectal symptom domain	0.77	0.57-0.68
Stool symptom domain	0.78	0.48-0.62

Table 17. Cronbach's α values and item-total correlations for each domain of PAC-SYM.

	Cronbach's α Frank et al [125]	Cronbach's α Slappendal et al [144]	Cronbach's α Current study
Total score	0.89	0.91	0.93
Abdominal symptom domain	0.80	0.83	0.85
Rectal symptom domain	0.87	0.90	0.77
Stool symptom domain	0.80	0.78	0.78

Table 18. Comparison of Cronbach's α values for PAC-SYM from current and previous studies.

5.6.2 Construct validity of PAC-SYM

The correlation coefficients are shown in Table 19 and the expected and actual associations displayed in Table 20. As expected, there was a moderate negative association between PAC-SYM abdominal symptoms and the bodily pain domain of SF-36 (r = -0.40). As hypothesised, weak negative associations existed between PAC-SYM scores and SF-36 physical functioning, role physical, general health, vitality, social functioning, role emotional and mental health (r -0.39 to -0.04).

	PAC-SYM domain		
SF-36 domain	Abdominal	Rectal	Stool
Physical functioning	-0.04	-0.15	-0.19
Role physical	-0.18	-0.12	-0.15
Bodily pain	-0.40	-0.11	-0.08
General health	-0.22	-0.17	-0.17
Vitality	-0.27	-0.15	-0.20
Social functioning	-0.29	-0.06	-0.23
Role emotional	-0.19	-0.15	-0.19
Mental health	-0.28	-0.09	-0.24

Table 19. Pearson correlation coefficients between PAC-SYM domains and SF-36 domain scores.

SF-36 domain	PAC-SYM domain					
	Abdominal		Rectal		Stool	
	Association		Association		Association	
	Expected	**Actual**	**Expected**	**Actual**	**Expected**	**Actual**
Physical functioning	Weak	Weak	Weak	Weak	Weak	Weak
Role physical	Weak	Weak	Weak	Weak	Weak	Weak
Bodily pain	Moderate	Moderate	Weak	Weak	Weak	Weak
General health	Weak	Weak	Weak	Weak	Weak	Weak
Vitality	Weak	Weak	Weak	Weak	Weak	Weak
Social functioning	Weak	Weak	Weak	Weak	Weak	Weak
Role emotional	Weak	Weak	Weak	Weak	Weak	Weak
Mental health	Weak	Weak	Weak	Weak	Weak	Weak

Table 20. Expected and actual associations between PAC-SYM and SF-36 domains. No unexpected associations were demonstrated.

5.7 Discussion

The results provide preliminary evidence of the reliability and validity of the PAC-SYM as a measure of symptom severity in patients with chronic idiopathic constipation. Satisfactory internal consistency has been demonstrated and the pattern of correlations between PAC-SYM and SF-36 scores provides evidence of construct validity.

Completeness of data was high with 92% of subjects responding to all items. This reflects the fact that PAC-SYM was constructed for ease of self-administration, with minimal respondent burden and contains items that were readily understood and acceptable to patients. The fact that the study group was highly motivated to take part may have also contributed to the high response rate.

The overall PAC-SYM scores are higher then those reported by Frank et al. This suggests severity of constipation in the current study is greater then that previously evaluated by other authors[125].

In our study no significant ceiling effects were demonstrated. Furthermore, marked floor effects were not found. Although 9.8% of patients recorded the lowest score on the rectal sub-scale score (suggesting mild rectal symptoms), this percentage did not reach the threshold value of 20% that is widely used to define a significant floor effect [113]. The observation that 9.8% of patients scored at the best possible level on this single administration is nonetheless worth noting particularily if an intervention study was to be performed in this patient population. On the assumption that the intervention would improve symptoms, post intervention PAC-SYM scores would be expected to fall. However, patients with floor effects at baseline in the rectal domain would not be able to score any "better" than their pre-intervention PAC-SYM.

The floor and ceiling effects observed in our study were less marked than in the validation study in patients with opioid induced constipation[144]. For example, in patients requiring opiate analgesics, the percentage reporting the lowest scores (floor effect) were 30%, 25% and 50% for the abdominal, stool and rectal sub-scales respectively. In comparison, in our study, floor effects in the abdominal, stool and rectal sub-scales were lower; 1.6%, 9.8% and 0.8% respectively. Patients with opioid induced constipation represent a different etiological group to those with idiopathic

constipation and this may explain differences in perception of symptom severity and lead to a different pattern of floor effect.

The Cronbach's α coefficients in the current study were slightly lower than those demonstrated by Frank et al in the original validation study. However, the requirements for confirming adequate internal consistency are met. Item-total correlations also support the reliability of the measure.

The strength and direction of associations demonstrated between PAC-SYM and SF-36 domains were all as hypothesised. This supports the construct validity of PAC-SYM. These findings are in keeping with those reported by Slappendel et al who also assessed the psychometric properties of the measure and confirmed validity[144].

PAC-SYM was administered once in the main study. Therefore, only those psychometric properties pertaining to a single administration were evaluated. Evaluation of test-retest reliability and responsiveness to change in this patient population remains to be established.

Known group analysis was not undertaken. This analysis would have involved comparing the PAC-SYM scores from two groups where symptom severity in one group was known to be significantly different to that in the other group. Frank et al showed that PAC-SYM scores were significantly higher in constipated patients who did not respond to fibre and laxatives. The design of the current study did not involve assessment of response to a treatment regime. Consequently, known groups that are similar to those described by Frank et al are not available to replicate the analyses previously performed. Furthermore, we did not analyse validity with respect to patient and/or clinician rating of severity of condition. Further study of test-retest reliability could be performed in this cohort of patients in the future.

5.8 Conclusion

The results of the psychometric analyses provide preliminary evidence of the reliability and validity of PAC-SYM for evaluating symptoms in the current population of constipated patients. These results support the findings of the previous validation study in idiopathic and opioid induced constipation[125,144].

6 EVALUATION OF THE PSYCHOMETRIC PROPERTIES OF SF-36

6.1 Abstract

Introduction The psychometric properties of the Short Form Medical Outcomes Survey (SF-36) have previously been evaluated in the general population and in a variety of disease states. Psychometric analyses were performed on data obtained from the current study population to confirm reliability and validity in patients with idiopathic constipation.

Methods A single self-administration of SF-36 was undertaken by 122 patients. Item-total correlations and Cronbach's α coefficient were calculated to test reliability and internal consistency.

Results Cronbach's α coefficients and item-total correlations were high.

Conclusions The psychometric evaluations suggest that SF-36 is reliable and valid generic measure of QOL in patients with idiopathic constipation. The use of the measure for analysing data from the main study is supported.

Data collection	SRC, YY
Data entry	SRC
Data Analysis	SRC (advice from EM)
Data interpretation	SRC, EM

6.2 Introduction

The Short Form Medical Outcomes measure (SF-36) is an established measure of generic quality of life. In the studies described in the preceding sections, SF-36 has been used as a standard to compare PAC-SYM and PAC-QOL against so that their psychometric properties can be evaluated. This approach has been adopted by other authors who have validated condition-specific measures [125,144]. An assumption here is that SF-36 itself has robust psychometric properties. This assumption is supported by the results of validation studies in the general population and in diverse disease states (hypertension, congestive heart failure, type II diabetes etc)[145]. SF-36 has also previously been employed in studies of constipated patients although data regarding the psychometric properties of the measure are not reported [146]. The purpose of the following study was not to undertake an exhaustive revalidation of the measure in patients with chronic constipation. Rather, it was to assess some key psychometric properties using the available data so that the use of SF-36 in the main study could be supported.

6.3 Aims

To evaluate psychometric properties pertaining to SF-36 using data from the current population of constipated patients.

6.4 Patients and methods

6.4.1 Subjects

One hundred and forty-eight patients with idiopathic constipation were identified as potential participants and 122 provided consent and completed the questionnaires (section 3.6).

6.4.2 Psychometric analysis

Missing data

As previously stated, the accuracy of a measure depends on the completeness of responses. If a patient does not answer a SF item, no response code can be entered for that item. The response is therefore treated as "missing". If all items have missing responses, no domain scores can be calculated for that patient.

QualityMetric provide an online scoring system that employs scoring algorithm software. These algorithms can still score many records if only some item responses are missing. The algorithm substitutes a patient specific estimate for missing items when the subject has answered at least half of the items in any domain. The average score across completed items in the same domain for that patient is used as the substitute response. This approach is considered to be a psychometrically sound way of estimating the substitutions[121]. The QualityMetric online scoring system also provides a missing data estimator (MDE) that can be employed to maximise the data available for analysis. This makes it possible to calculate domain scores for many respondents who do not answer every survey item but for whom scores would be missing if only the substitution method described above was used.

Ceiling and floor effects

The techniques described in section 4.4.2 were used to assess ceiling and floor effects.

Internal consistency and Item-total correlation

Cronbach's α coefficient and corrected correlations between the SF items and domain totals were calculated, as described in section 4.4.2.

Known-group validity

Brazier et al measured QOL in 1980 general practice patients of different ages via a postal survey. The patients were selected at random from the lists of practices in South Yorkshire. In the physical functioning domain there were statistically significant differences in SF-36 scores were found between young and old patients. Patients in the 16-24 years age category reported a better QOL in these domains than

those in the 65-74 age groups. Furthermore, males scored significantly higher than females in all domains except general health[147].

These observations allowed us to evaluate known group validity of SF-36 in the current study population. It was hypothesised that significant differences in SF scores will be demonstrated in patients of different sex and age. Student's t Test (and Mann Whitney Test for non-normally distributed data) were used to compare domain scores between known groups defined by age and sex.

Ideally, known group analyses in our study would have been informed by observations reported from previous studies of constipated patients that used SF-36. Unfortunately, studies that report clear differences in SF-36 scores between groups defined by sex and age in populations similar to our own are lacking.

SPSS® version 12 for Windows (SPSS, Chicago, Illinois, USA) was used to analyse data. A value $p < 0.05$ was considered statistically significant.

6.5 Results

There was no significant difference between those patients who agreed to participate in the study and those who did not give consent for inclusion in the study in terms of age, sex distribution or duration of constipation (Table 6).

6.5.1 SF-36 scores

The mean SF-36 domain scores are displayed in Table 21. Figure 10 shows the norm based domain scores. In norm based scoring each of scale or domain is scored to have the same general population mean (50) and the same standard deviation (10 points).

Domain		Mean	sd
Physical functioning	PF	71.3	26.8
Role physical	RP	61.1	32.4
Bodily pain	BP	40.6	21.2
General health	GH	48.4	22.8
Vitality	VT	35.3	22.6
Social functioning	SF	53.9	31.8
Role emotional	RE	62.1	32.6
Mental Health	MH	53.6	24.6

Table 21. Mean SF-36 domain scores.

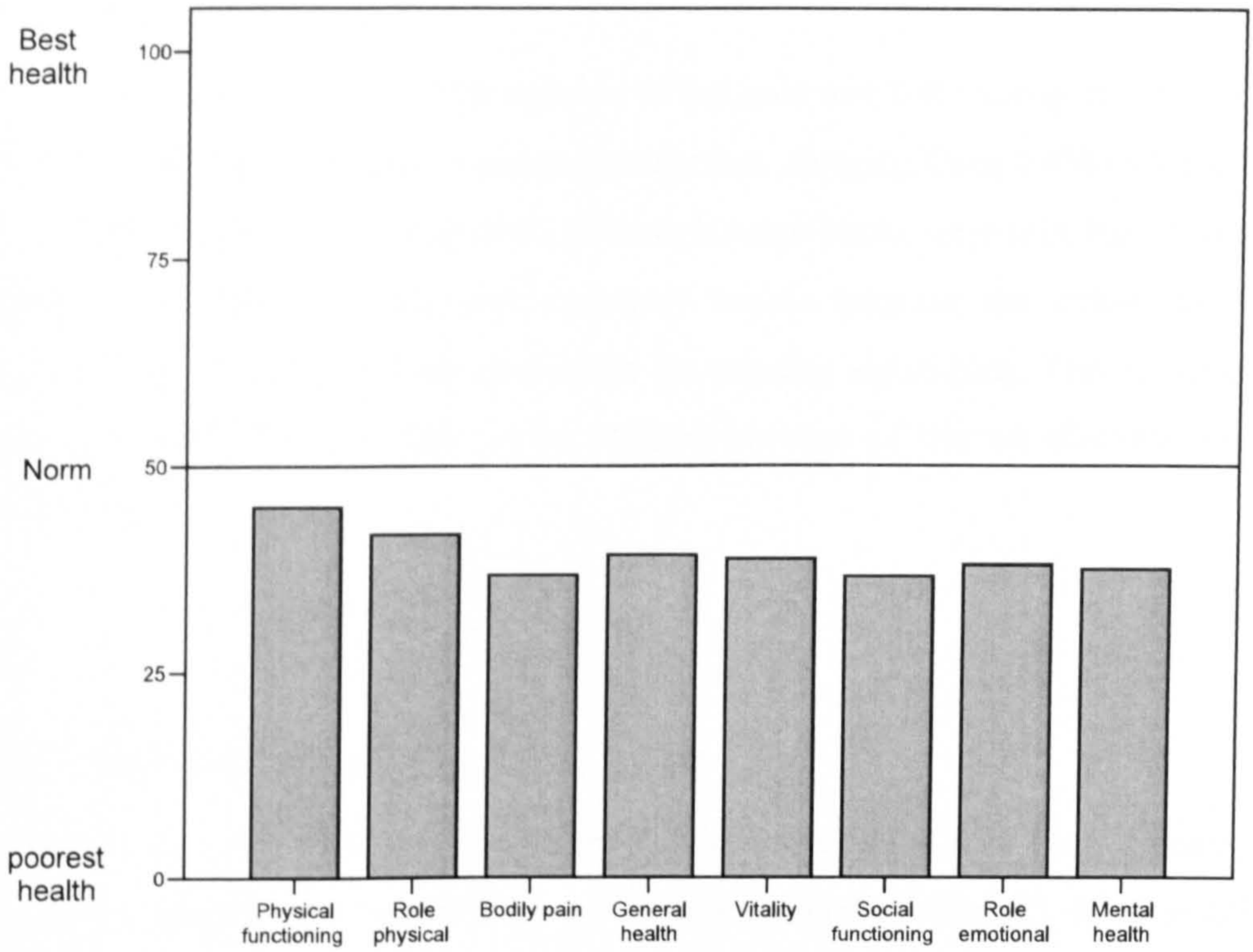


Figure 10. Norm based scores for SF-36 domains.
In norm based scoring each domain is scored to have the same general population mean (50) and the same standard deviation (10 points). Therefore, a domain score below 50 represents health status that is below average for the general population.

6.5.2 SF-36 completion

Data completeness was high. The number of patients that fully completed SF-36 was 104 (85%). Missing item rates were uniformly low; ranging from 0.8% to 4.1% (item GH03 of the general health domain). Although some items were missing, it was still possible to calculate domain and summary scores because the extent to which responses were missing did not invalidate the scoring algorithms. The missing data estimator (MDE) did not have to be utilised because of the satisfactory level of completeness.

6.5.3 Floor and ceiling effects for SF-36

The number of patients that recorded the minimum score of 0 in each domain was low and no appreciable floor effects were demonstrated (Table 22). Modest ceiling effects were seen for the physical functioning (18%), role physical (21.3%), social functioning (14.8%) and role emotional (27.9%) domains. There was no appreciable ceiling effect in the other domains. Table 23 shows a comparison of the floor and ceiling effects of the current study with the findings reported by Ware et al [148].

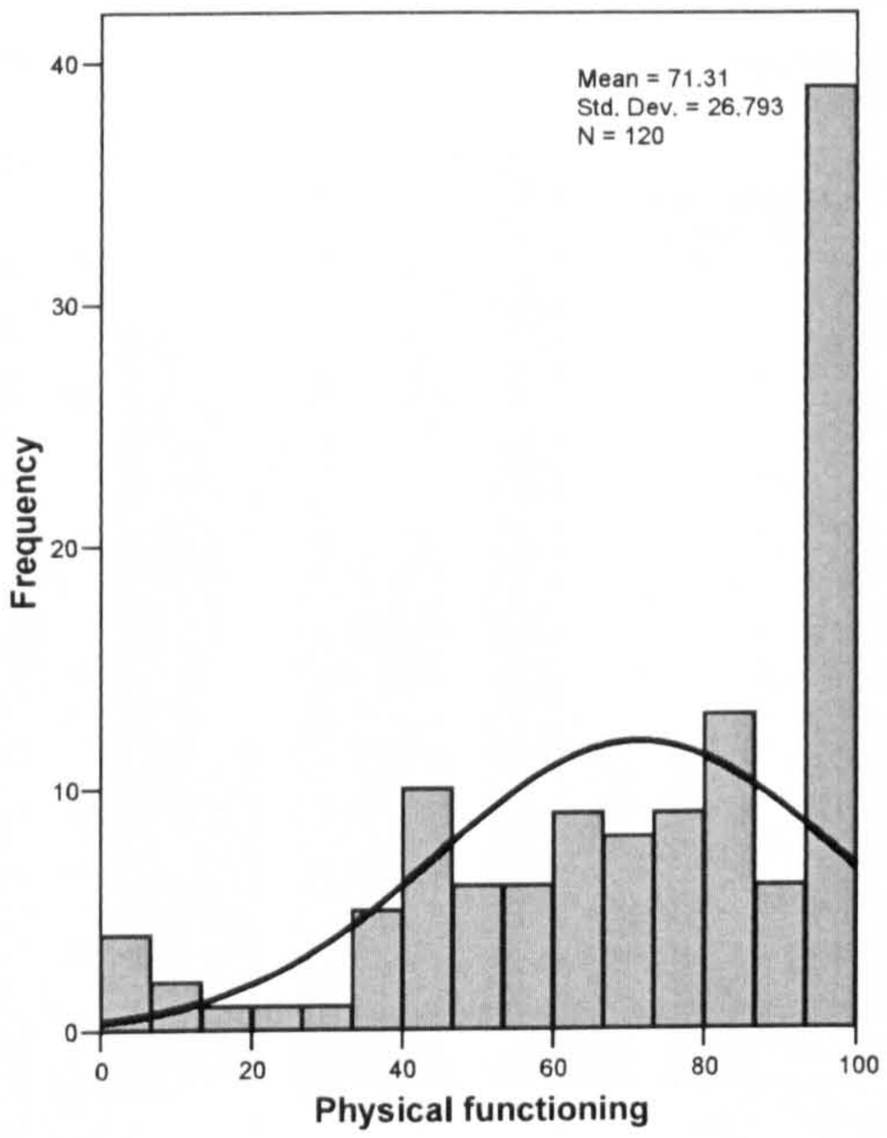
The distributions of responses for each domain are shown by frequency density histograms (Figure 11 and Figure 12). Distributions of responses were uni-modal. For the physical functioning domain there was a negatively skewed distribution. Normal distributions were observed in the other domains.

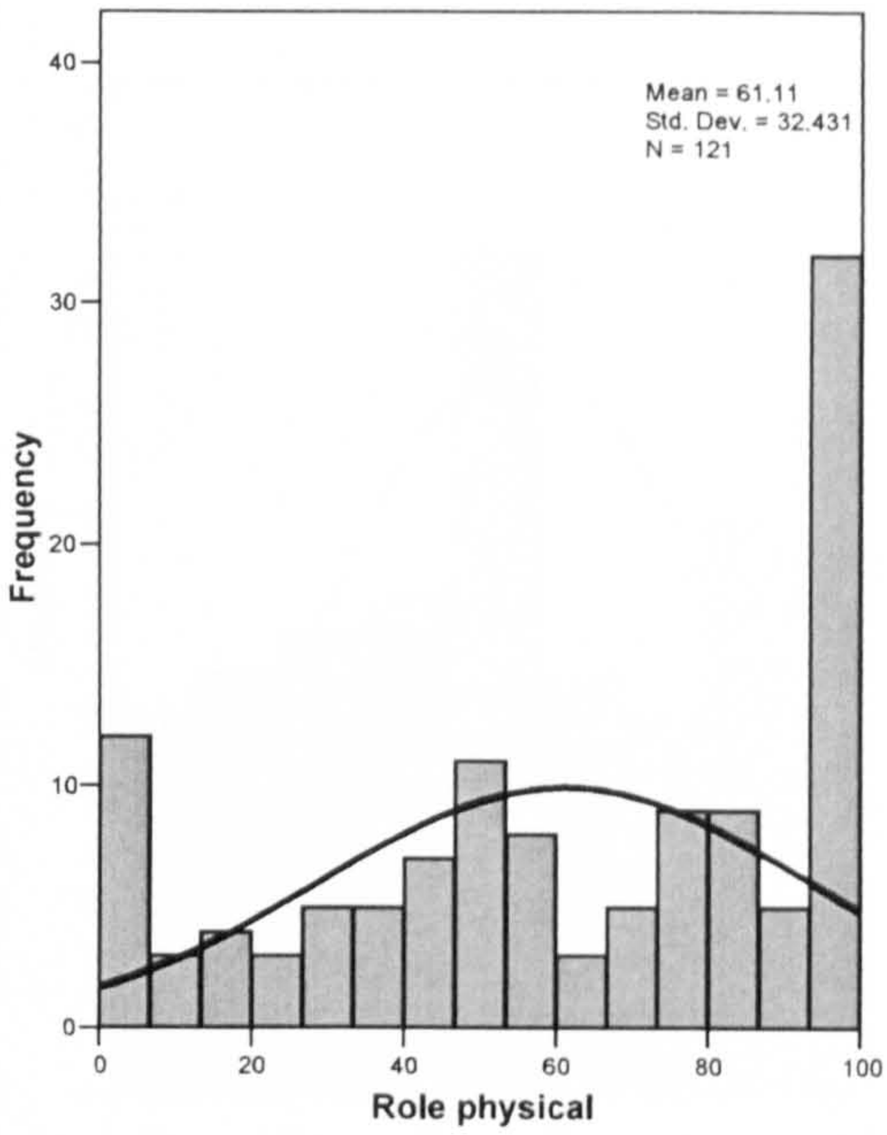
		Number of patients with the minimum possible domain score (%)	Number of patients with the maximum possible domain score (%)
Physical functioning	PF	3 (2.5)	22 (18)
Role physical	RP	8 (6.6)	26 (21.3)
Bodily pain	BP	5 (4.1)	3 (2.5)
General health	GH	3 (2.5)	1 (0.8)
Vitality	VT	11 (9.0)	0 (0.0)
Social functioning	SF	10 (8.2)	18 (14.8)
Role emotional	RE	10 (8.2)	34 (27.9)
Mental health	MH	1 (0.8)	3 (2.5)

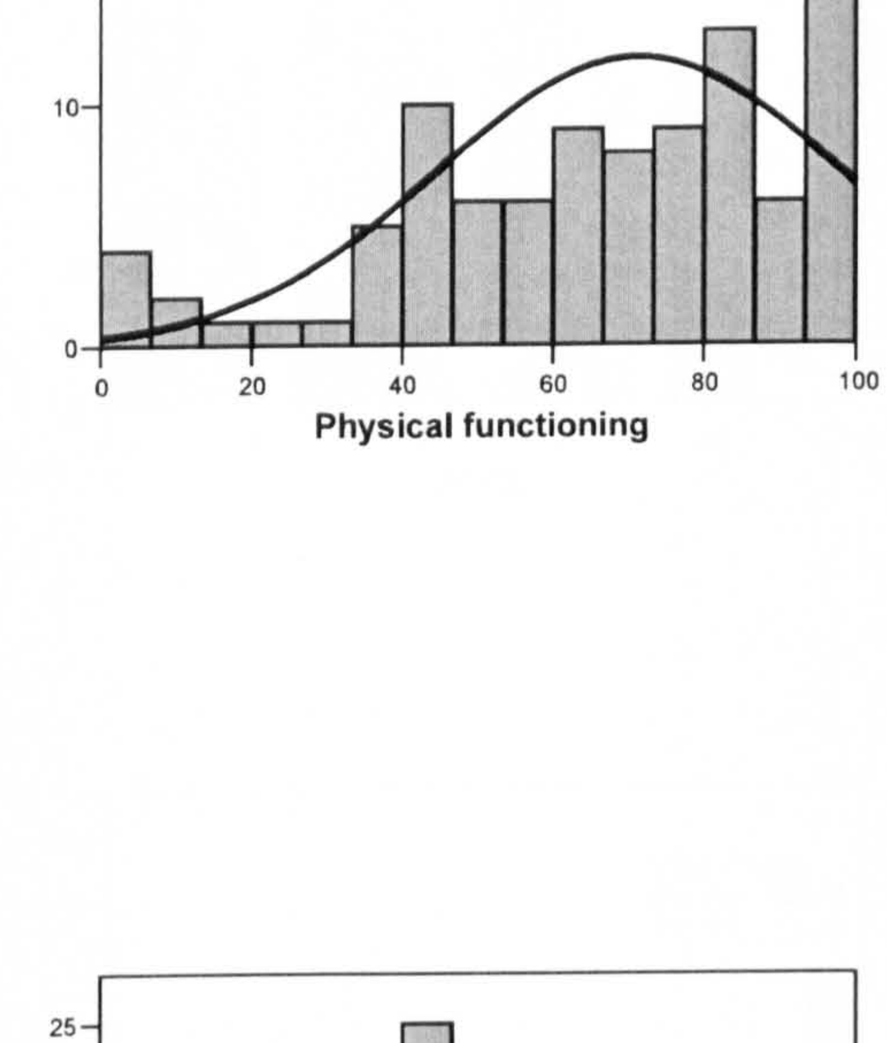
Table 22. Ceiling and floor effects for SF-36.
The minimum possible score for SF-36 domains (not using norm based scoring) is 0 and the maximum possible score is 100.

		Floor effect (%)		Ceiling effect (%)	
		Current study	Ware et al[148]	Current study	Ware et al[148]
Physical functioning	PF	32.5	1.0	18.0	25.6
Role physical	RP	6.6	2.1	21.3	47.4
Bodily pain	BP	4.1	1.0	2.5	22.0
General health	GH	2.5	0.0	0.8	6.0
Vitality	VT	9.0	1.1	0.0	2.1
Social functioning	SF	8.2	1.0	14.8	55.7
Role emotional	RE	8.2	1.0	27.9	60.2
Mental health	MH	0.8	0.1	2.5	5.1

Table 23. Comparison of ceiling and floor effects from the current study with previous studies.







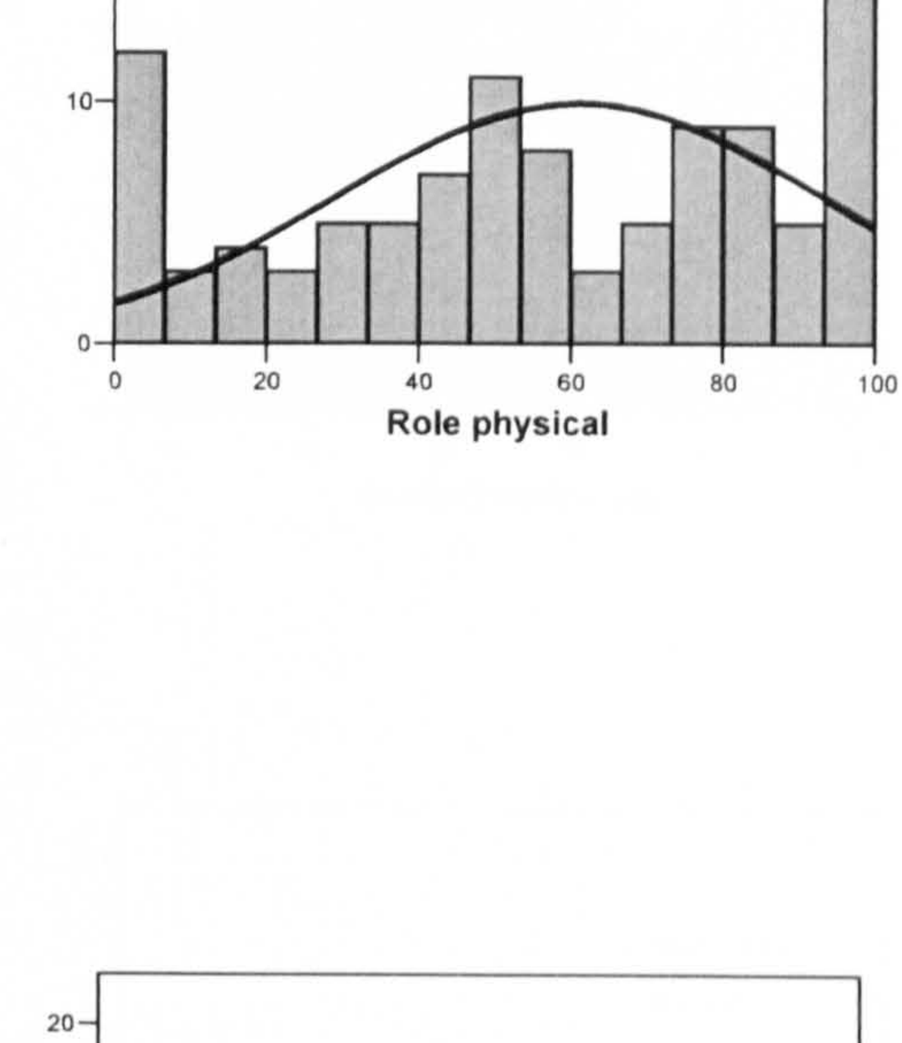
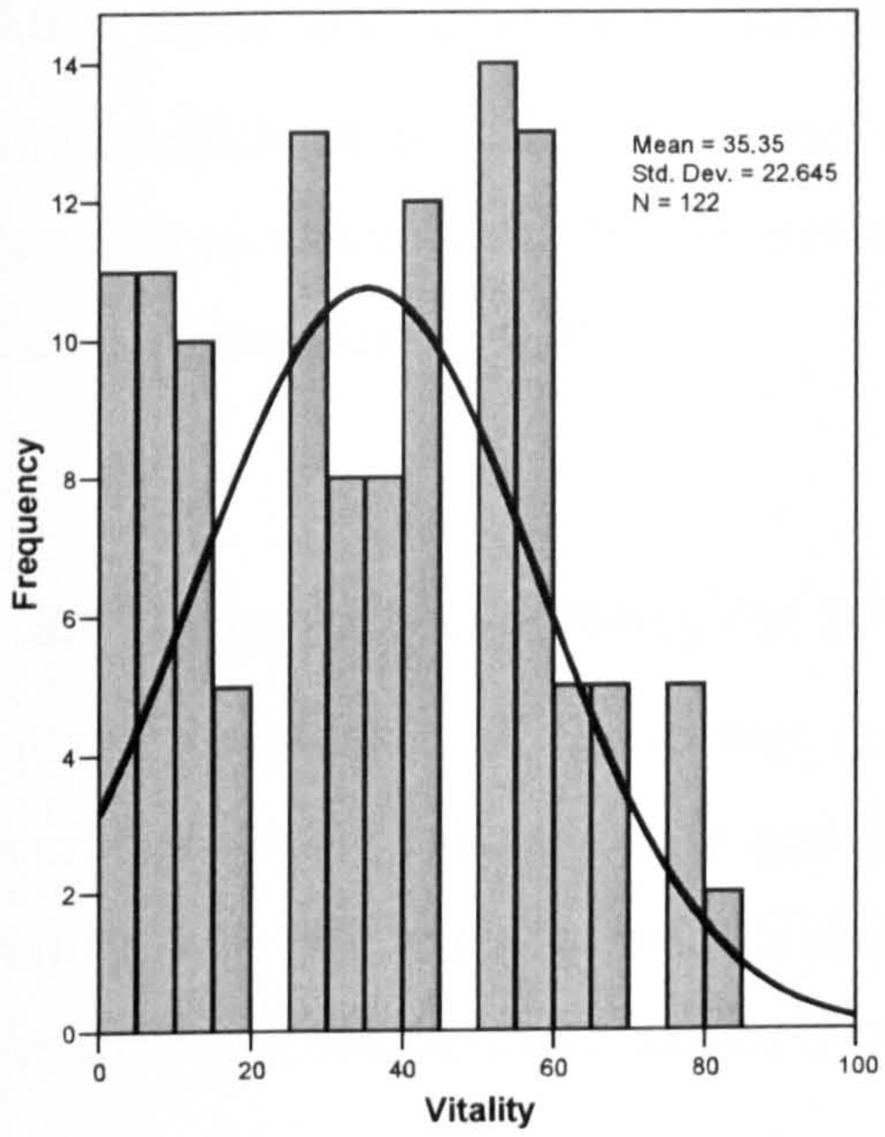
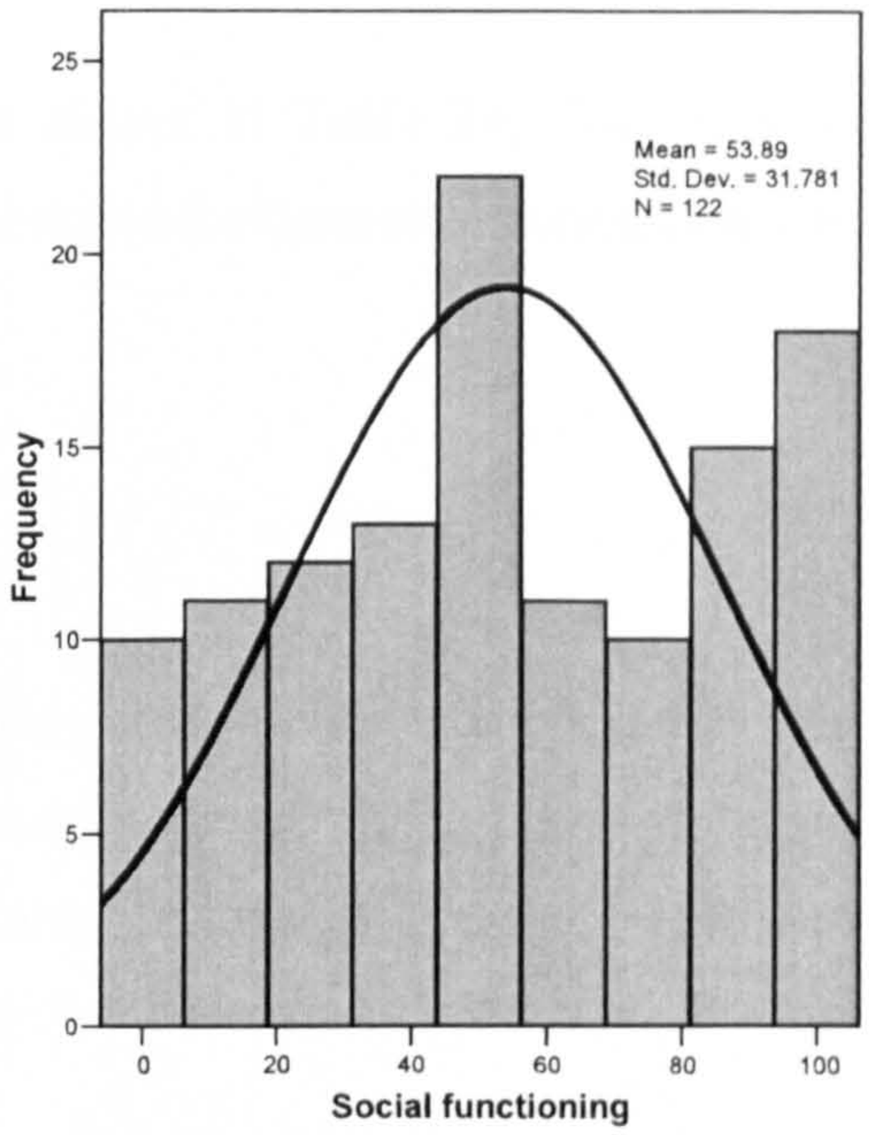
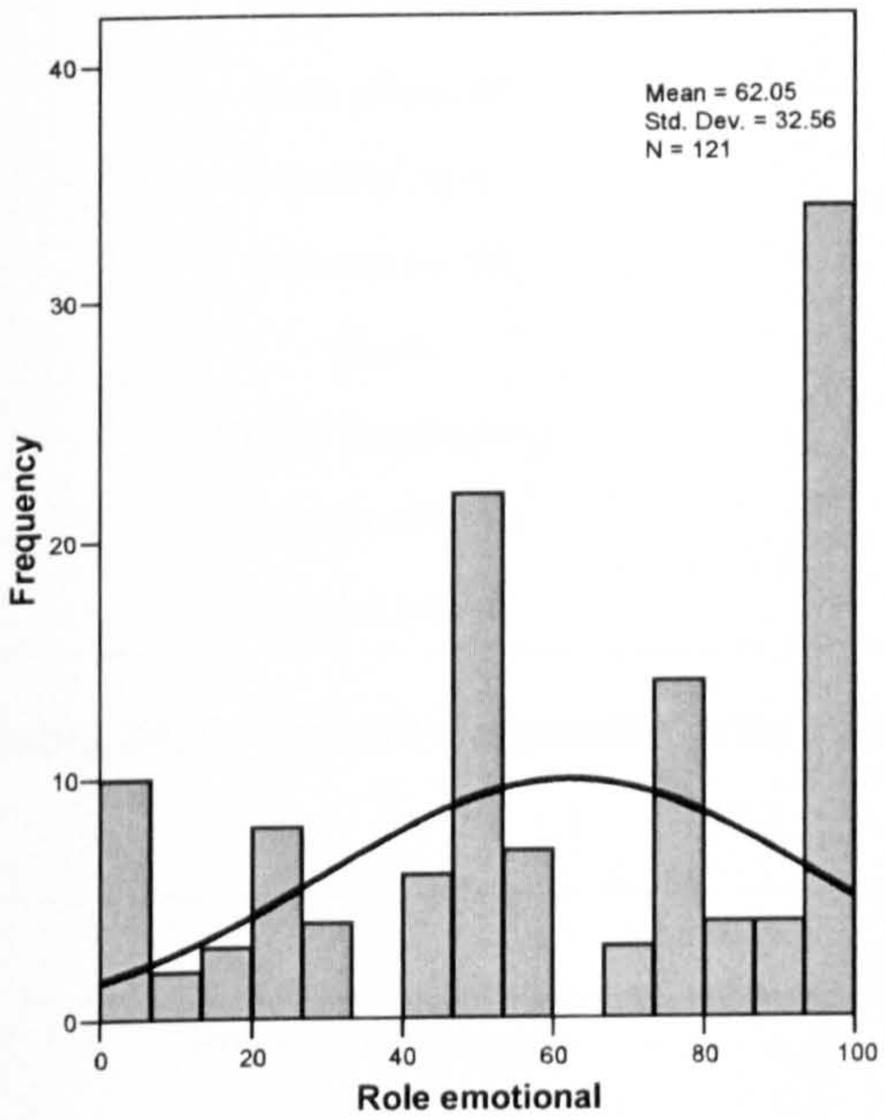


Figure 11.Histogram of responses for physical functioning, role physical, bodily pain and general health domains of SF-36.







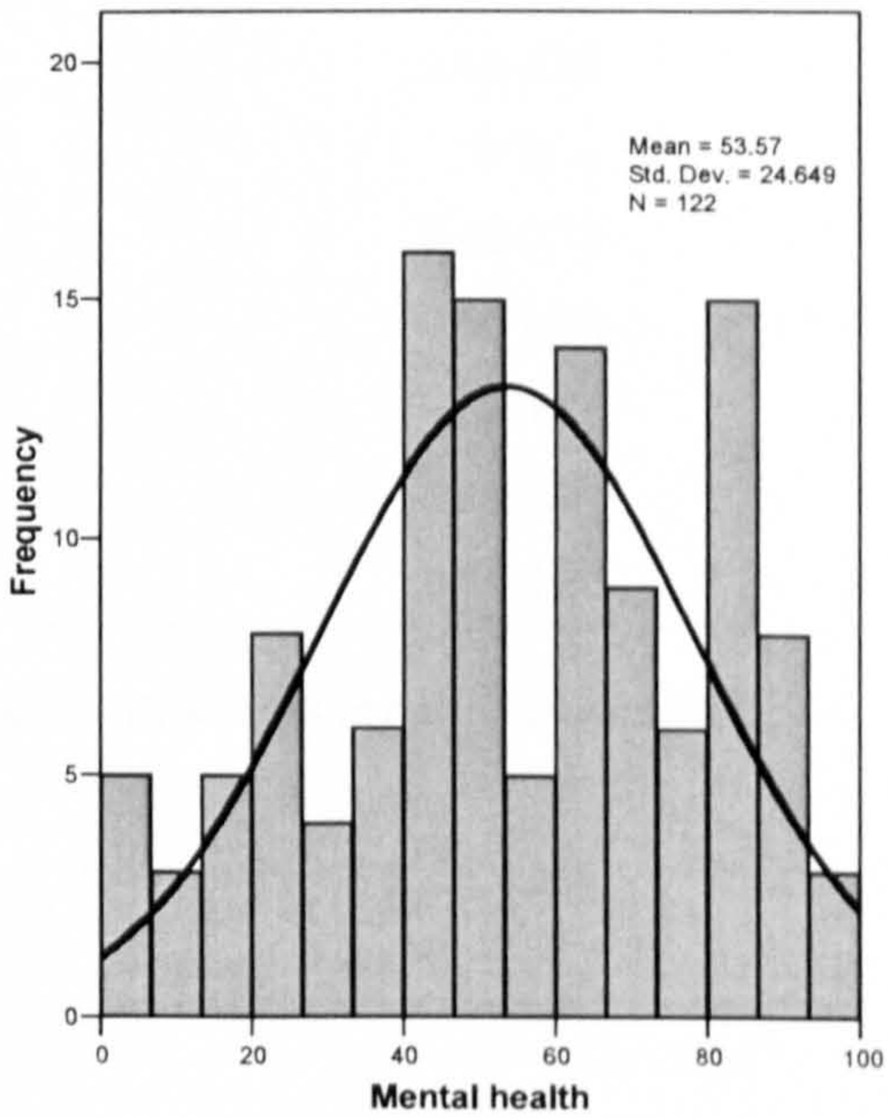


Figure 12. Histogram of responses for vitality, social functioning, role emotional and mental health domains of SF-36.

6.5.4 Item-total correlation for SF-36

The coefficients for item-total correlations are shown in Table 24. The range of correlations was 0.42 to 0.93. All items met the criteria for item-total correlation with their own domain ($r > 0.4$).

6.5.5 Internal consistency for SF-36

Internal consistency of SF-36 was assessed using Cronbach's α coefficient. The coefficients were above 0.7 suggesting adequate internal consistency for group comparisons for each domain (Table 24). Table 25 shows a comparison with Cronbach's α coefficients obtained by Ware et al[148].

	Cronbach's α	Item-total correlations
Physical functioning	0.94	0.60-0.80
Role physical	0.96	0.89-0.93
Bodily pain	0.74	0.58
General health	0.83	0.42-0.70
Vitality	0.80	0.54-0.72
Social functioning	0.86	0.76
Role emotional	0.95	0.86-0.91
Mental health	0.88	0.64-0.80

Table 24. Cronbach's α coefficients and item-total correlations for SF-36 domains.

	Cronbach's α current study	Cronbach's α Ware JE et al [148]
Physical functioning	0.94	0.94
Role physical	0.96	0.95
Bodily pain	0.74	0.85
General health	0.83	0.83
Vitality	0.80	0.85
Social functioning	0.86	0.88
Role emotional	0.95	0.93
Mental health	0.88	0.85

Table 25. Comparison of Cronbach's α coefficients for SF-36 from current and previous studies.

6.5.6 Known-groups analysis

The results of the known group analyses are summarised in Table 26 and Table 27. There were 12 patients in the age category 16-24 years and 14 patients in the 65-74 age category. No significant differences were demonstrated in the domain scores between the two age groups except in the PF domain. Here, the physical functioning score was significantly lower in the 65-74 age category (p=0.02).

Female patients accounted for 97% of the study population. In male patients, scores were significantly higher in the physical functioning and bodily pain domains (Table 27).

	Age category				
	16-24 years		**65-74 years**		
	n = 12		**n = 14**		
	Mean score	sd	Mean score	sd	p value
Physical functioning	84.1	17.8	60.2	28.1	0.02 *
Role physical	60.4	37.5	58.57	30.6	0.89
Bodily pain	36.3	24.4	36.0	22.1	0.98
General health	41.2	18.9	49.1	19.6	0.35
Vitality	32.2	21.3	40.8	22.1	0.33
Social functioning	51.3	36.7	52.9	32.9	0.98
Role emotional	62.5	39.1	61.9	35.1	0.92 *
Mental Health	51.7	22.7	56.5	23.9	0.60

* Mann Whitney test

Table 26. Mean differences in SF-36 domain scores between age categories.

	Mean domain scores				
	Female		**Male**		p value
	n = 119		**n = 4**		
		sd		sd	
Physical functioning	70.7	26.9	90.0	7.1	0.003
Role physical	60.8	32.8	85.9	16.4	0.120
Bodily pain	39.7	20.8	67.8	11.2	0.009
General health	48.0	22.9	62.0	15.8	0.227
Vitality	35.0	22.7	46.9	19.4	0.303
Social functioning	53.0	31.8	81.3	16.1	0.080
Role emotional	61.3	32.7	83.3	20.4	0.185
Mental health	52.1	24.9	68.8	8.6	0.212

Table 27. SF-36 domain scores for male and female patients.

6.6 Discussion

The results suggest that SF-36 is a reliable and valid measure of QOL in patients with chronic idiopathic constipation. Satisfactory internal consistency, item total correlation and construct validity have been demonstrated.

The detrimental impact of constipation on QOL is demonstrated by the norm based scores; in all domains scores are less than 50. This suggests that QOL is lower than in the normal general population.

Although completeness of data was high (85% of subjects responding to all items), this was less than for PAC-SYM and PAC-QOL. SF-36 contains more items than these other measures. Completing it fully may have been a greater burden for respondents leading to lower completeness. Another issue relating to the reduced completeness compared to PAC-SYM and PAC-QOL is patient perception of the relevance of the SF-36 items. Since the PAC items were specific to constipation (the reason that the subjects had been referred to the clinic) the patients may have had a greater motivation to answer these fully compared to the SF-36 items that appear less relevant to their primary complaint.

No significant floor effects were demonstrated. Modest ceiling effects were seen for the physical functioning, role physical, social functioning and role emotional domains. This suggests that despite suffering constipation, a proportion of patients are still able to perform with maximum ability in these domains. As a result of this ceiling effect it would be difficult to detect "improvement" post intervention in these domains if a treatment study was performed. These subjects would unable to score any "better" than their pre-intervention domain score. The ceiling effects reported by Ware et al were greater than demonstrated in the current study. Ware et al evaluated SF-responses from the US normal general population where we would expect higher proportions of subjects displaying maximal QOL in any given domain (and therefore greater ceiling effect) [148,149].

The Cronbach's α coefficients in the current study were comparable to those previously reported except in the bodily pain domain (0.74) [148]. However, adequate internal consistency was achieved in this and all other domains. Item-total correlations also suggest reliability.

The known group analyses were based on the observation made by Brazier et al who found that QOL measured by SF-36 was higher in males than females and higher in young patients than older patients[147]. In the current study there were only 4 male patients. Consequently, the results of known group validity analyses regarding the effect of sex must be interpreted with this in mind. It was possible to reproduce the analyses undertaken by Brazier with regard to age categories. In their study no difference was found in QOL between the young an old, except in the physical functioning domain. A similar pattern emerged in our study with young patients reporting a better QOL for physical functioning compared to the older patients. No other differences were found in the domains with regard to age. Although these findings support the known group validity of SF-36, the fact that the known groups contained relatively small numbers and a female preponderance must be born in mind as a limitation of these particular analyses.

6.7 Conclusion

The results of the psychometric analyses confirm the reliability and validity of SF-36 for evaluating symptoms in the current population of constipated patients.

7 PREDICTORS OF QUALITY OF LIFE IN REFRACTORY IDIOPATHIC CONSTIPATION.

7.1 Abstract

Introduction Determining predictors of disease specific QOL in refractory constipation could enable clinicians to identify patients in whom the impact and severity of constipation is greatest. Predictors could be used to target therapies to those with greatest need. The aim was to establish whether disease specific QOL depends on: demographics, symptoms assessed by clinician, symptoms assessed by the patient, results of objective tests, and / or the patient's perception of health.

Methods 122 patients were evaluated by; clinician led assessment of demographics and symptoms; self-administration of PAC-SYM, PAC-QOL and SF-36; colonic transit study and defecating proctography. Multiple linear regression analyses were used to identify predictors of disease specific QOL (PAC-QOL).

Results Symptom severity (expressed through PAC-SYM) and patient perception of mental health were the main explanatory variables for disease specific QOL. Mental health scores (indicating psychological morbidity) were lower compared to those in the general population. There was little association between demographics, symptom intensity assessed by clinician, colonic transit or proctography and disease specific QOL.

Conclusions Therapeutic strategies that reduce abdominal and stool symptoms and address problems with psychological wellbeing may offer a way of improving QOL in refractory idiopathic constipation.

Data collection	SRC, YY
Data entry	SRC
Data Analysis	SRC (advice from TH)
Data interpretation	SRC, TH, YY

7.2 Introduction

Idiopathic constipation can be a severe chronic refractory illness that has a significant impact on a patient's life. Measuring the impact of this condition has traditionally been undertaken by clinicians assessing symptom severity (through history taking at consultation) or by performing objective investigations. As previously stated, there may be inaccuracy and bias inherent in the use of symptom evaluation by clinician as the main measure of severity (section 2.1.2). Furthermore, the role of objective tests for assessing severity in constipation is not fully explored.

As with other chronic diseases it is possible that measuring quality of life (QOL) provides a more meaningful insight into the complete experience of the affected individual.

Identifying factors associated with poor QOL may help anticipate the problems faced by patients and allow effective targeting of therapy to those with the greatest need.

The objective of this element of the research study was to explore empirically the relationship between potential predictor variables and constipation specific QOL.

7.3 Aims

The aim was to explore the relationship between disease specific quality of life and several key factors including: demographics, symptoms assessed by clinician, constipation related variables evaluated by objective tests, symptoms assessed by patient and the patient's perceived health status. The objective was to identify predictors of disease specific quality of life.

The findings of previous studies were used to guide the selection of variables for inclusion in regression analysis to identify predictors of QOL. For example, Damon et al have previously shown a relationship with QOL (measured by GIQLI) and symptom intensity expressed as a cumulative score (Cleveland Constipation score) and, Grotz and Wald have shown greater psychological distress in subjects with normal transit constipation compared to slow transit constipation. [2,37,135]. These variables were included in the regression analyses. For other variables, the literature does not suggest extensive study of their relationship with disease specific QOL. However, there is a held belief that these factors are important for assessing

constipation (section 1.5 and section 2.1.8). Therefore, variables such as the presence of coexisting medical conditions, psychiatric illness, history of child birth, surgery and proctographic parameters were also included in the regression analysis based on pragmatic grounds and our desire to investigate their relationship with QOL.

In our study no *a priori* assumptions were made regarding the relationships between the variables. Consequently, no specific hypotheses were tested regarding determinants of disease specific QOL.

7.4 Materials and methods

7.4.1 Study design

This was a cross-sectional observational study of individuals attending a district general hospital in the North East of England. Appropriate ethical approval was obtained (section 7.7). Subjects were recruited from the constipation clinic at University Hospital North Durham. Data were collected by patient self-administration of questionnaires and by clinician led interview. Data obtained from the results of objective tests were also analysed (proctography and colonic transit study).

7.4.2 Patients

Patients with idiopathic constipation were identified at the constipation clinic at the University Hospital of North Durham. The criteria used to define constipation are summarised in Figure 13. All subjects were clinically assessed in a consultant led clinic and had undergone investigation to exclude organic causes for their constipation. Inclusion and exclusion criteria are summarised in section 3.4.

At least 12 weeks, which need not be consecutive, in the preceding 12 months of two or more of;

(1) Fewer than 3 defecations /week

(2) Straining in more than 25% of defecations;

(3) Lumpy or hard stools in more than 25% of defecations;

(4) Sensation of incomplete evacuation in more than 25% of defecations;

(5) Sensation of anorectal obstruction/blockade in more than 25% of defecations;

(6) Manual manoeuvres to facilitate in more than 25% of defecations e.g. (digital evacuation, support of the pelvic floor)

Figure 13. Diagnostic criteria for constipation used in the study.

7.5 Data collection

Information regarding several essential themes was gathered:

Patient demographics;

The results of an evaluation by the clinician of salient symptoms and characteristics of constipation;

The results of a patient self-assessment of symptoms;

The results of a patient self-assessment of perceived health status;

The results of a patient self-assessment of disease specific QOL.

7.5.1 Patient demographics, characteristics and salient symptoms

Data were gathered at face to face interview with the clinician including age, sex and duration of constipation for each subject. Standardised questions regarding salient symptoms and characteristics were asked during the clinician led interview from a questionnaire format. A two week period of recall was used to answer the questions. The content of the questions was based on the Cleveland Clinic Score [36].

The 11 questions evaluated bowel frequency, frequency of laxative use, frequency of unsuccessful defecatory attempts, time spent attempting to defecate, straining during defecation, defecatory pain, sensation of incomplete evacuation, digital manoeuvres to assist defecation, vaginal manoeuvres to assist defecation, abdominal pain and abdominal bloating. Likert scales were used with higher scores indicating a greater intensity or severity of the symptom or characteristic assessed by the question. In keeping with the Cleveland Clinic Score, the scores for each individual question were combined to calculate a cumulative constipation score. Higher scores indicated a greater intensity or severity of constipation. The range of possible scores in the cumulative constipation score is from 0 to a maximum of 44.

In addition, data were obtained regarding the duration of constipation and the age at onset. Details regarding a subject's exposure to childbirth, exposure to abdominal / pelvic surgery, presence of coexisting medical conditions and psychiatric history were gathered. Details of the variables that were evaluated at the clinician led interview are summarised in Appendix A, Table 6.

Data regarding the patients' perception of their constipation specific symptoms were gathered using the PAC-SYM questionnaire (section 2.1.3 and section 5) [125]. PAC-SYM assesses 3 domains (stool symptoms, rectal symptoms and abdominal symptoms). Individual domain and totals are scored from 0 to 4, with a high score indicating increasing severity of symptoms. The psychometric properties have been confirmed in our own population (section 5) and by other authors [125].

7.5.2 Quality of life assessment

Disease-specific and generic measures of quality of life were included. PAC-QOL was used to evaluate disease specific quality of life. It comprises 4 domains (constipation related worries and concerns, physical discomfort, psychosocial discomfort and satisfaction). Individual domain and totals are scored from 0 to 4. High domain or overall PAC-QOL scores indicate poor quality of life. The psychometric properties of the measure have been evaluated in our population (section 4) and by other authors studying patients with constipation [119,144].

The SF-36 is a generic measure of general health status [117] and as such should capture the impact on functioning and well-being of co existing conditions in addition to the effect of the index condition (constipation). The SF-36 domains include; physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain and general health perception. Scores in the eight domains can be combined to produce standardised norm referenced summary scores: physical and mental component summary scores (PCS and MCS). High component summary scores indicate better health and QOL.

7.5.3 Colonic transit

Total and segmental colonic transit time was determined using radio-opaque marker studies based on a method described by that Metcalf et al [53]. The protocol involves the ingestion of capsules containing 24 radio-opaque markers (Konsyl, Easton, USA) on each of days 1, 2 and 3 with a plain abdominal x-ray taken on day 4. Subjects are instructed to discontinue laxative therapy or treatments that could interfere with intestinal motility for the duration of the investigation.

The method is a multiple bolus single x-ray model. To determine the colonic transit time (CTT) time in a given segment the following equation is applied;

$$CTT_i = n_i (\Delta T / N)$$

CTT_i represents the colonic transit within segment $_i$ and n_i is the number of markers seen on the x-ray in segment $_i$. N is the number of markers ingested each day (24 in this current study) and ΔT is the time interval between ingestion of markers (24 hours in the present study) [53,150].

This technique works under the assumptions that marker transit has achieved a steady state on the day of the abdominal x-ray and that the patient has not deviated from the study protocol or taken their radio-opaque markers incorrectly [151]. Subjects who have been unable to discontinue their laxative therapy, who are taking agents that affect motility or who have diarrhoeal states may have colonic segments with few or no markers on the day of the abdominal x-ray [150].

To validate the technique, Metcalf et al studied normal non-constipated individuals. They demonstrated mean total colonic transit times in men of 30.7 hours (sd 3.0) and 38.8 hours (sd 2.9) in women [53]. In the absence of normal controls obtained from a cohort in the North East of England, these results can be used as a guide for arbitrary definitions of slow colonic transit.

7.5.4 Proctographic assessments

The technique for radioisotope defecating proctography was based on that developed by Papachrysostomou et al [139].

The radiopharmaceutical used was ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP). This was mixed with re-hydrated porridge oats to form a thick paste that could be inserted into the rectum to simulate stool. The volume of the porridge/radioisotope mixture inserted was determined by a balloon inflation study in the rectum to determine rectal capacity. The radiopharmaceutical was prepared by adding approximately 200MBq of ^{99m}Tc-MDP to a volume of warm water determined by the results of the rectal capacity study for each individual patient. The dehydrated porridge mixture was slowly added and stirred constantly to produce a smooth thick paste. A foley catheter filled with approximately 20 MBq ^{99m}Tc-MDP was positioned to act as a marker of the anal canal.

If necessary the rectum was cleared using phosphate enema (Forest Laboratories, Kent, UK) prior to the study. To introduce the radiopharmaceutical, a tube (E-Z-EM, NY, USA) was positioned in the distal bowel 10cm from the anal verge. The paste was injected into the rectum using a 50ml syringe. During this procedure the patient was positioned in the left lateral position.

The patient was then sat upright on a screened commode with a collection pan. Dynamic acquisition of data with 2 second images was performed during the study. Images were acquired during the patient's attempt to defecate. The images were recorded using a small field Starcam 300 A/M Gamma Camera (General Electric Medical Systems, Chalfont, UK). Data and images were processed using Xeleris ™ workstation software (General Electric Medical Systems, Chalfont, UK). At the termination of the study, if evacuation was incomplete, the residual paste was evacuated by administration of a phosphate enema (Forest Laboratories, Kent, UK).

An advantage of this technique over barium defecating proctography is a reduced radiation exposure. Exposure is limited and the effective dose equivalent (EDE) is low (EDE <0.3mSv/min) irrespective of the duration of the study. Furthermore, absorption of radioactive material from the rectum is minimal [152]. EDE for

fluoroscopy in the left lateral position (as used in video barium defecating proctography is significantly greater (1mSv/min) [153].

Radioisotope defecting proctography allows quantitative data (such as rectocoele size, evacuation time, % evacuation, evacuation rate) and qualitative data regarding the patient's evacuatory efforts during defecation to be gathered. By convention, a rectocoele that retains 25% or more of the radioisotope is described as being radiologically significant. Hutchinson et al have undertaken radioisotope isotope proctography in normal subjects [152]. In the absence of normal controls obtained from a cohort in the North East of England, their results can be used as reference data for constipated individuals.

7.6 Statistical analysis

Normality of data was assessed by the Kolmogorov-Smirnov test. For comparisons between groups defined by salient characteristics (e.g. colonic transit time), normally distributed data were analysed with Student's *t* test for unpaired samples and non-normally distributed data were analysed with the Mann-Whitney *U* test. Categorical data were compared using Fisher's exact test.

To evaluate the relationships between the dependent variable of disease specific QOL (overall PAC-QOL score) and the independent (predictor) variables, bivariate analysis was initially performed. To further examine the relationship between predictors and the dependent variable, Multiple Linear Regression was used. Although it is possible to pre-select variables for regression modelling by using bivariate analyses (to identify variables that show a statistically significant association) this approach was not used because it has been suggested that pre selection can exclude variables that otherwise would contribute to the regression model in unforeseen ways [154]. Furthermore, we were interested in analysing the relationships between all the variables that we had chosen as potentially important explanatory variables.

Multiple Linear Regression is an extension of the simple linear regression model that allows researchers to investigate more than one variable at a time. In essence, the

aim is to construct a hierarchy of predictive values for variables remaining in the model at the end of the exercise.

There were five core areas that we were interested in investigating as to possible relationships with the primary outcome (overall PAC-QOL). These comprised: 1) demographic factors 2) patient characteristics, 3) constipation related variables evaluated by objective tests, 4) symptoms assessed by patient (PAC-SYM) and 5) the patient's perceived health status (SF-36).

To measure perceived health status, SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were chosen rather than the individual domains scores of SF-36. The reason for this was to reduce error caused by multiple comparisons.

In multiple regression several assumptions exist: that for each value of the independent (predictor) variable, the distribution of the response or dependent variable is normal and that the relationship between the independent and dependent variables should be linear. It is also assumed that the effects of each variable are independent, i.e. the effect of one variable is the same regardless of the values of other variables. This latter assumption might not be satisfied with regard to some variables that share a common theme and maybe interrelated (i.e. where there is multicollinearity). This is a recognised limitation of the technique.

The initial regression model used was the forward selection method. This strategy starts with an empty model and attempts to determine the best combination of variables by starting with a single variable and increasing the number of variables used, step by step. The independent variable that has the highest correlation with the dependent variable is entered first. Each subsequent step adds the variable that has the highest correlation in the presence of the predictors already in the equation. The procedure stops when there are no variables that meet the entry criterion.

Stepwise regression was used to confirm the findings of the forward selection strategy. Stepwise regression is similar to forward selection except that independent variables can be removed from the model if they become non-significant as other independent variables are added. The method terminates when no more variables are eligible for inclusion or removal.

Additional confirmation was undertaken by performing a backwards elimination regression strategy. In this method, all variables are entered into the equation and then sequentially removed. The variable with the smallest partial correlation with the dependent variable is considered first for removal. After the first variable is removed, the next variable remaining in the equation with the smallest partial correlation is considered. The procedure stops when there are no variables in the equation that satisfy the removal criteria.

Data were analysed using the SPSS® version 12 for Windows (SPSS, Chicago, Illinois, USA). A value $p < 0.05$ was considered statistically significant.

7.7 Ethical considerations

The study was carried out in accordance with the 2004 Declaration of Helsinki and approval was granted by the local research ethics committee. All participants gave written informed consent.

7.8 Results

7.8.1 Group characteristics

One hundred and forty eight patients were identified in the constipation clinic as potential participants. Informed consent was obtained from 122 patients. There were 118 females (97%) and 4 males (3%). In view of the female preponderance it was decided that the male patients would be removed from the analyses.

The patients who decided not to participate were not significantly different from the responders in terms of age, sex distribution or duration of constipation (Table 28).

The mean age of the 118 females was 42.5 years (sd 13.9). The mean duration of constipation was 17.7 years (sd 15.5). The characteristics of the female subjects are shown in Table 29. Of these, 81 (68.6%) have been exposed to childbirth. Forty two subjects (35.6%) had a history of exposure to pelvic-abdominal surgery. All subjects had a history of laxative use prior to attendance in the constipation clinic. At the point of assessment, 96.6% were using laxative therapy. Common reasons for not taking laxatives were that they were ineffective or that side effects had limited their use. A history of a psychiatric disorder was found in 14 subjects (11.9%). None of these subjects were receiving active input from psychiatric services because of persistent psychiatric symptoms. Forty five subjects (38.1%) had coexisting medical conditions. These conditions are displayed in Table 30.

The results of the evaluation of the intensity of salient symptoms and characteristics, performed by the clinician at interview, are shown in Table 31. The cumulative constipation score is the sum of the scores for each individual evaluation of symptom or characteristic. Higher scores indicate greater severity of constipation. There was no missing data for the individual questions or the cumulative constipation score. The high degree of data completeness was possible because the questions were administered by the clinician (SC or YY).

	Study participants	Non-participants	p value
Mean age (years)	43 (sd 14.0)	44 (sd 15.1)	0.73
Sex distribution	Female = 118 Male = 4	Female = 23 Male = 3	0.10§
Duration of constipation (years)	17.6 (sd 15.5)	19.8 (sd 14.5)	0.37

Table 28. Comparison of participants and non-participants.
§ Fisher's Exact test.

	Number of subjects	Percentage
Exposed to childbirth	81	68.6
Exposed to pelvic-abdominal surgery	42	35.6
Co-existing medical conditions	45	38.1
History of psychiatric disorder	14	11.9
Currently using laxatives	114	96.6

Table 29. Characteristics of the study population.
(118 female subjects)

Co-existing medical history	Number of subjects
Nil	74
Osteoarthritis	4
Asthma	2
Hypertension	4
Rheumatoid arthritis	1
Chronic Renal Failure	1
Hypothyroidism (treated)	7
Angina	3
Epilepsy	5
Endometriosis	1
Primary Biliary Cirrhosis	1
Non Ulcer Dyspepsia	4
Chronic back pain	2
Diabetes	4
Migraine	1
Oesophagitis	1
GORD	1
Dysmenorrhoea	2

**Table 30. Co-existing medical conditions in the study population.
(118 female subjects)**

Symptom / characteristic	Range of possible scores[§]	Mean	sd
Days between defecations with laxative	0-5	2.18	1.46
Laxative use	0-3	2.20	0.81
Unsuccessful defecatory attempts	0-4	2.35	1.20
Time spent attempting to defecating	0-4	1.62	0.98
Straining during defecation	0-4	3.25	0.81
Painful defecation	0-4	1.96	1.17
Sensation of incomplete evacuation	0-4	2.16	1.21
Digitation to assist defecation	0-4	0.97	1.28
Vaginal pressure to assist defecation	0-4	0.52	1.12
Abdominal bloating	0-4	3.03	0.74
Abdominal pain	0-4	2.52	0.98
Cumulative constipation score	**0-44**	**22.78**	**4.94**

Table 31. Cumulative constipation score obtained from clinician evaluation of symptoms and characteristics.
[§] High scores indicate greater intensity of symptoms. The cumulative constipation score is the sum of scores for each item and was studied as a predictor variable in the Multiple Regression Analyses.

All 118 of the female patients had radio-opaque marker transit studies. Inspection of the transit studies revealed five subjects who had unexpected aberrant results. Subjects 29, 39, 76, 97 and 107 all had total colonic transit times of 9 hours or less (Table 32). Appendix B, Table 1 shows data from the transit studies of all 118 subjects (aberrant results highlighted). The most likely explanation for these aberrant results is that either the subjects did not discontinue their laxatives or mistimed the ingestion of their radio-opaque markers.

Subject identification	Colonic transit (hours)			
	Right	Left	Rectosigmoid	Total
29	6	3	0	9
39	0	4	0	4
76	2	0	0	2
97	7	1	0	8
107	3	0	5	8

Table 32. Aberrant colonic transit study results.

These subjects were removed form further analyses pertaining to colonic transit. Therefore, the mean total colonic transit time for the remaining group of 113 subjects group was 59.4 (sd 13.8) hours (Table 33). Using a cut off value of $\geq$ 40 hours to classify patients as slow transit constipation (STC); one hundred and two patients (90 %) had slow transit constipation according to this definition (Table 34).

There was no difference between patients with NTC and STC (cut off $\geq$ 40 hours) with respect to age, sex, duration of constipation, exposure to childbirth, exposure to surgery, presence of co-existing medical conditions or psychiatric history (Table 35). These findings are comparable to those of Grotz et al and Wald et al who likewise found no differences with respect to age or duration of constipation between STC and NTC constipated patients [2,135]. Comparison of mean PAC-QOL scores between NTC and STC showed no differences (Figure 14 and Table 36).

Colonic transit (hours)	Mean	sd
Right colon	21.13	15.45
Left colon	25.33	13.21
Rectosigmoid colon	12.97	11.50
Total colonic	59.43	13.84

Table 33. Total and segmental colonic transit time.
(113 female subjects)

Colonic transit		Number of subjects
Normal	< 40 hours	11
Slow	≥ 40hrs	102

Table 34. Subjects with normal and slow transit constipation
(113 female subjects)

Parameter		NTC 16 subjects	STC 102 subjects	p value
Mean age	years (sd)	42.5 (15.9)	42.5 (14.0)	0.86 §
Duration of constipation	years (sd)	14.0 (12.8)	18.2 (15.6)	0.43 §
Exposure to childbirth	number of subjects exposed	8	71	1.00 §§
Exposure to pelvic abdominal surgery	number of subjects exposed	5	36	0.52 §§
Coexisting medical conditions	number of subjects	3	41	0.52 §§
History of psychiatric illness	number of subjects	1	13	1.00 §§

Table 35. Characteristics of normal and slow transit constipation subjects.
NTC: Normal Transit Constipation, STC: Slow Transit Constipation. §Student's T test.
§§ Fisher's Exact Test.

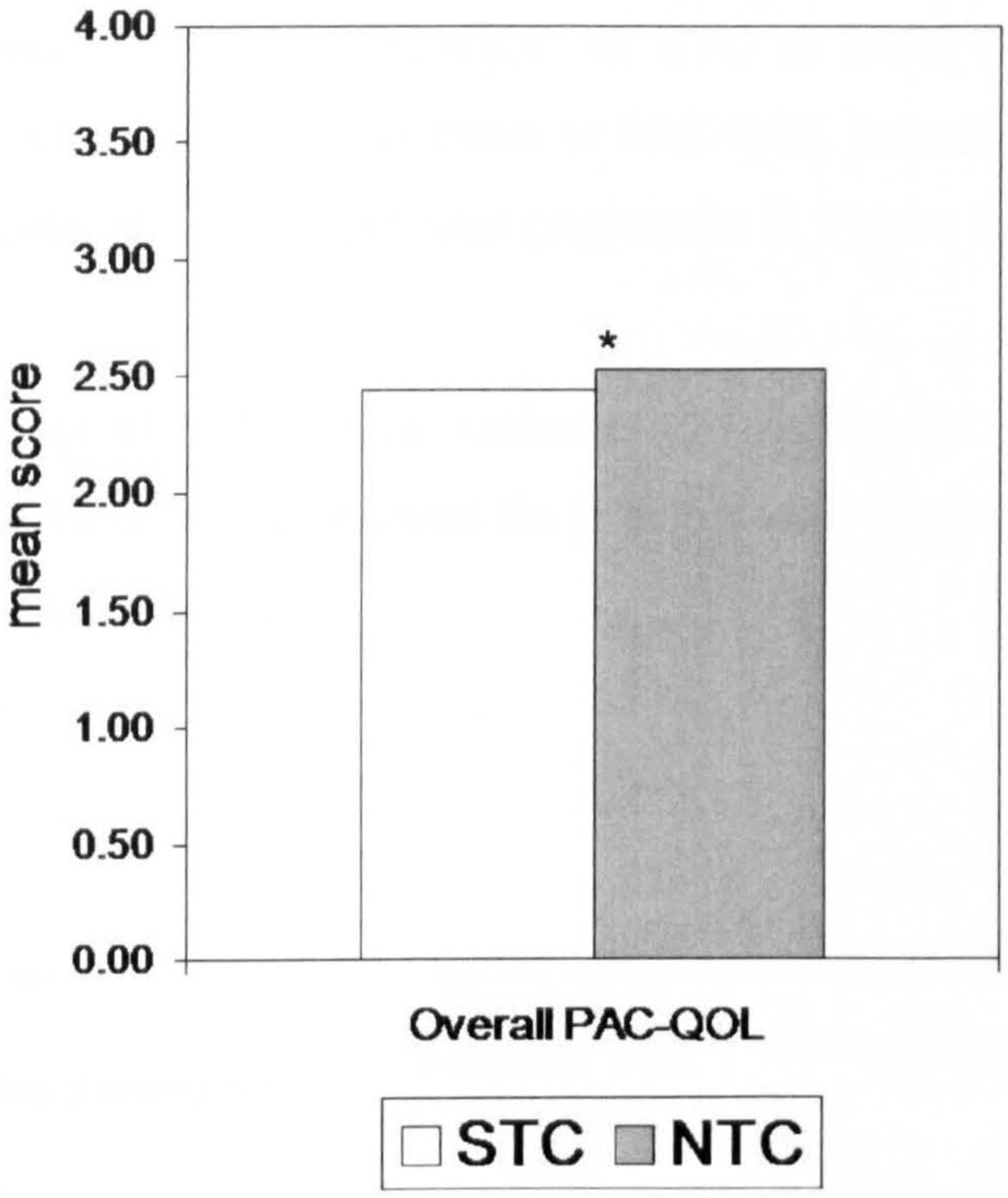


Figure 14. Overall PAC-QOL in slow and normal transit constipation.
*** p 0.71**

	Slow transit constipation n=102		**Normal transit constipation** n=11		p value
	mean	sd	Mean	sd	
Overall PAC-QOL score	2.45	0.74	2.53	0.62	0.71

Table 36. PAC-QOL in slow and normal transit constipation.
Cut off for slow transit ≥ 40hrs

Additional analyses, at a cut off of ≥ 50 hours to define STC, did not show a difference between overall PAC-QOL in STC or NTC (Appendix B, Table 2). Furthermore, there were no differences in PAC-QOL between patient groups defined by different categories of transit time (Appendix B, Figure 1 and Appendix B, Table 3).

From the group of 118 female subjects, 114 underwent radioisotope defecating proctography. Table 37 summarises the proctographic results and includes reference values for normal subjects [152].

Proctographic parameter		Number of subjects with complete data	Study results		Normal reference	
			Mean	sd	Mean	sd
% Evacuation	(%)	113	68.3	20.9	67	15.0
Evacuation time	(sec)	107	70.6	87.8	31	14.0
Evacuation Rate	(% / sec)	109	2.9	3.0	2.5	0.9

Table 37. Proctogram results.

A rectocoele was demonstrated in 88 patients. The mean size of these was 2.49cm (sd 1.26, range 0.90 – 5.90 cm). Fifteen (13%) of these rectocoeles were deemed to be significant on proctographic grounds (Radiologically significant rectocoele, RSR).

There was no difference between patients with RSR and Non-RSR with respect to age, duration of constipation, exposure to childbirth or exposure to surgery (Table 38). Furthermore, there was no difference between PAC-QOL scores between subjects with RSR and Non-RSR (Table 39).

	Radiologically Significant Rectocoele (RSR)	Non Radiologically Significant Rectocoele (Non-RSR)	p value
Mean age (years)	40.1 (sd 11.7)	42.9 (sd 14.3)	0.50
Exposed to childbirth	Exposed = 12 Not exposed = 3	Exposed = 71 Not exposed = 32	0.55§
Exposed to abdominal / pelvic surgery	Exposed = 6 Not exposed = 9	Exposed = 36 Not exposed = 67	0.78§
Duration of constipation (years)	23.7 (sd 11.8)	17.2 (sd 15.7)	0.12

Table 38. Radiologically significant rectocoele and Non-Radiologically significant rectocoele.
§ Fisher's Exact test

	RSR n= 15		Non RSR n= 73		p value
	mean	sd	Mean	sd	
Overall PAC-QOL score	2.56	0.69	2.54	0.67	0.91§

Table 39. Effect of radiologically significant rectocoele on PAC-QOL.
§ Student's T test

Results of the patient self assessment of disease specific QOL (PAC-QOL) and symptoms (PAC-SYM) symptoms are shown in Table 40. The subject's perception of mental and physical general health is also displayed in Table 40.

The mean overall PAC-QOL score was 2.43 (sd 0.73) and mean overall PAC-SYM score was 2.13 (sd 0.68). Regarding specific PAC-SYM domains: stool score 2.34 (sd 0.90), abdominal score 2.43 (sd 0.86) and rectal score 1.42 (0.97).

The mean physical component summary (PCS) score of SF-36 was 42.07 (sd 8.62). Mean mental component summary (MCS) was 35.87 (sd14.80).

Table 41 shows the correlation coefficients between the variables and overall PAC-QOL score. Although the strength of association was weak in several instances, many of the correlations achieved statistical significance.

	Possible scores	mean	sd
PAC QOL			
Overall PAC-QOL	0-4	2.43	0.73
PAC SYM			
Overall PAC-SYM	0-4	2.13	0.68
Abdominal symptoms	0-4	2.43	0.86
Rectal symptoms	0-4	1.42	0.97
Stool symptoms	0-4	2.34	0.90
SF-36			
Physical component score	0-100	42.07	8.62
Mental component score	0-100	35.87	14.80

Table 40: Mean scores for QOL, symptom and health perception measures.

Variable	Overall PAC-QOL score				
	mean	sd	Correlation coefficient	Strength of association	p value
Age (years)	42.54	13.08	-0.267	Weak	0.010
Cumulative constipation score	22.81	4.85	0.358	Moderate	0.011
Total colon transit time (hours)	57.20	17.30	0.050	Weak	0.601
%Evacuation	68.30	20.90	-0.106	Weak	0.266
Evacuation time (seconds)	70.60	87.80	0.168	Weak	0.083
Rectocoele size (cm)	2.49	1.26	0.169	Weak	0.068
Physical Component Summary	42.07	8.62	-0.265	Weak	0.010
Mental Component Summary	35.87	14.80	-0.509	Moderate	0.010
PAC-SYM stool symptom score	2.34	0.90	0.466	Moderate	0.012
PAC-SYM Abdominal symptom score	2.43	0.86	0.553	Moderate	0.006
PAC-SYM Rectal symptom score	1.42	0.97	0.243	Weak	0.013

Table 41. Correlation between variables and overall PAC-QOL

Disease specific QOL (overall PAC-QOL) was no different between groups of patients defined by exposure to child birth, exposure to abdominal-pelvic surgery, presence of a coexisting medical condition, or a psychiatric history (Table 42 and Table 43).

Parameter	Overall PAC-QOL score		
	Mean (sd)	Mean (sd)	p value
Childbirth	**Exposed** (n = 81)	**Not exposed** (n = 37)	0.33
	2.42 (0.76)	2.57 (0.68)	
Abdominal-pelvic surgery	**Exposed** (n = 42)	**Not exposed** (n = 76)	0.08
	2.62 (0.75)	2.37 (0.71)	

Table 42. PAC-QOL scores and exposure to childbirth and surgery.
Student's T test

Parameter	Overall PAC-QOL score		
	Mean (sd)	Mean (sd)	p value
medical conditions	**Coexisting medical condition** (n = 45)	**No coexisting medical condition** (n = 73)	0.91
	2.43 (0.67)	2.45 (0.86)	
Psychiatric illness	**History of psychiatric illness** (n = 14)	**No history of psychiatric illness** (n = 104)	0.28
	2.56 (0.82)	2.49 (0.72)	

Table 43. PAC-QOL scores and presence of medical conditions and psychiatric history.
Student's T test

7.9 Regression analyses

The variables that were entered in to the regression model comprised:

Clinician assessment of symptoms;

- expressed as the cumulative constipation score (higher score indicative greater severity of constipation).

Demographics and patient characteristics;

- including age, onset age of constipation, duration of constipation, exposure to surgery, exposure to childbirth, presence of coexisting medical problems and presence of psychiatric history.

Proctography results;

- including evacuation time, % evacuation, rectocoele size and presence of radiologically significant rectocoele.

Colonic transit;

- total colonic transit time and classification into STC / NTC.

Perceived health;

- expressed as the MCS and PCS (higher score indicates better QOL).

Patient self assessment of symptoms;

- PAC-SYM Stool score, PAC-SYM Abdominal symptom score and PAC-SYM Abdominal symptom score (higher score indicates more severe symptoms).

Details of the methods for coding and units for continuous variables are included in Appendix B, Table 4. Descriptive statistics for the variables used in the regression analyses are displayed in Appendix B, Table 5. The data from subjects 29,39,76,97 and 107 were not included in the regression analyses because of the aberrant nature of their transit study results (Table 32).

Forward regression models

The forward regression produced three models (Table 44). The descriptive data regarding the variables and a summary of the model are displayed in Appendix B, Table 6.

The third model accounted for 55% of the variance in the overall PAC-QOL score ($R^2 = 0.56$, adjusted $R^2 = 0.55$).

Model	R	R^2	Adjusted R^2	Standard error of the estimate
1	0.61	0.40	0.39	0.60
2	0.71	0.50	0.49	0.55
3	0.75	0.56	0.55	0.52

Model	Predictor variables in each model
1	PAC-SYM Abdominal symptom score
2	PAC-SYM Abdominal symptom score, Mental Component Summary
3	PAC-SYM Abdominal symptom score, Mental Component Summary, PAC-SYM stool symptom score

Table 44. Forward regression models.

Table 45 describes model 3 of the forward regression. The variables have highly significant p values ($p < 0.01$) suggesting that they all contribute significantly to the model.

Variable	Unstandardized Coefficients B	Standard error	Standardized Coefficients Beta	t statistic	p value
Constant	1.69	0.27		6.12	< 0.01
PAC-SYM Abdominal symptom score	0.38	0.06	0.44	5.85	< 0.01
Mental Component Summary	-0.02	0.00	-0.32	-4.30	< 0.01
PAC-SYM stool symptom score	0.21	0.06	0.25	3.48	< 0.01

Summary of variance	Sum of Squares	Degrees of freedom	Mean Square	F statistic	p value
Regression	31.57	3	10.52	39.40	< 0.01
Residual	24.83	93	0.26		
Total	56.30	96			

Table 45. Forward regression analysis (model 3).
Forward regression analysis of overall PAC-QOL score on PAC-SYM Abdominal symptom score, Mental Component Summary and PAC-SYM stool symptom score.

The unstandardised regression coefficients (B) can be used to produce the regression equation for disease specific QOL;

$$\text{Overall PAC-QOL} = 1.69 + 0.38 \times (\text{PAC-SYM Abdominal symptom score}) - 0.02 \times (\text{Mental component summary score}) + 0.21 \times (\text{PAC-SYM stool symptom score})$$

As expected, the regression coefficient for Mental Component Summary (MCS) has a negative value because a high MCS score suggests better psychological wellbeing (associated with better generic QOL) whilst a high PAC-QOL suggests worse constipation specific QOL. The standardised coefficients (Beta) suggest that the PAC-SYM abdominal symptom score is the main contributor to PAC-QOL followed by Mental Component Summary (MCS), and PAC-SYM stool symptom score.

The values of the unstandardised regression coefficients (B), reflect the original units in which the variables were measured. In regression modelling the units for each

variable are not always the same. The standardized coefficients (Beta) are an attempt to make the regression coefficients for each variable more comparable. They can provide more information about the relative importance and contribution of each predictor to the dependent variable than the unstandardised coefficients (B). The standardized coefficients (Beta) represent the change in response in dependent variable for a change of one standard deviation in a predictor variable.

Therefore, a change of one standard deviation in PAC-SYM Abdominal score will produce a change of 0.44 of a standard deviation in overall PAC-QOL, whilst a change of one standard deviation in PAC-SYM Stool score produces a change of only 0.25 of a standard deviation in PAC-QOL.

Since PAC-SYM Abdominal score has the largest Beta weight, it also has the largest correlation with the dependent variable (PAC-QOL).

Table 46 displays collinearity diagnostics for the forward regression. Overall, model 3 performs well although the eiganvalues for dimensions 3 and 4 could be considered close to zero. This could suggest that the variables are highly inter-correlated. The Condition Index for Dimension 4 is 11.57, but not of a large enough magnitude to suggest a series problem with multi-collinearity.

Residual statistics for the model are summarised in Appendix B, Table 7. Appendix B, Figure 2, Appendix B, Figure 3 and Appendix B, Figure 4 confirm that the residuals follow a normal distribution and have the same variance throughout the range.

Overall it appears that model 3 offers the best model under the circumstances explaining 55% of the variance in the overall PAC-QOL score. The contributory variables are PAC-SYM abdominal symptom score, Mental Component Summary (MCS) and PAC-SYM stool symptom score, in order of their relative contribution to disease specific QOL.

Model	Dimension	Eigenvalue	Condition Index	Variance Proportions			
				(Constant)	PAC-SYM Abdominal symptom score	Mental Component Summary	PAC-SYM stool symptom score
3	1	3.68	1.00	0.00	0.01	0.10	0.10
	2	0.20	4.28	0.00	0.12	0.39	0.07
	3	0.09	6.49	0.00	0.48	0.00	0.76
	4	0.03	11.58	0.99	0.40	0.60	0.16

Dependent Variable: Overall PAC-QOL score

Table 46. Collinearity diagnostics for forward regression model 3

Stepwise regression models

The stepwise regression also produced three models that confirmed the results of the forward regression strategy. The third stepwise model accounted for 55% of the variance in the overall PAC-QOL score ($R^2 = 0.56$, adjusted $R^2 = 0.55$) (Table 47 and Table 48).

Again, the standardised regression coefficients (Beta) in this model, suggest that PAC-SYM abdominal symptom score is the main contributor followed by Mental Component Summary (MCS) and PAC-SYM stool symptom.

A summary of the stepwise regression is displayed in Appendix B, Table 8. Collinearity diagnostics and residual statistics for the stepwise regression are displayed in Appendix B, Table 9 and Appendix B, Table 10. The residuals follow a normal distribution and have the same variance throughout the range.

Model	R	R^2	Adjusted R^2	Standard error of the estimate
1	0.61	0.40	0.39	0.60
2	0.71	0.50	0.49	0.55
3	0.75	0.56	0.55	0.52

Model	Predictor variables in each model
1	PAC-SYM Abdominal symptom score
2	PAC-SYM Abdominal symptom score, Mental Component Summary
3	PAC-SYM Abdominal symptom score, Mental Component Summary, PAC-SYM stool symptom score

Table 47. Stepwise regression models.

Variable	Unstandardized Coefficients B	Standard error	Standardized Coefficients Beta	t statistic	p value
Constant	1.69	0.27		6.12	<0.01
PAC-SYM Abdominal symptom score	0.38	0.06	0.44	5.85	<0.01
Mental Component Summary	-0.02	0.00	-0.32	-4.30	<0.01
PAC-SYM stool symptom score	0.21	0.06	0.25	3.48	<0.01

Summary of variance	Sum of Squares	Degrees of freedom	Mean Square	F statistic	p value
Regression	31.57	3	10.52	39.40	<0.01
Residual	24.83	93	0.26		
Total	56.30	96			

Table 48. Stepwise regression analysis (model 3).
Stepwise regression analysis of overall PAC-QOL score on PAC-SYM Abdominal symptom score, Mental Component Summary and PAC-SYM stool symptom score.

Model	Dimension	Eigenvalue	Condition Index	Variance Proportions			
				(Constant)	PAC-SYM Abdominal symptom score	Mental Component Summary	PAC-SYM stool symptom score
3	1	3.68	1.00	0.00	0.01	0.10	0.10
	2	0.20	4.28	0.00	0.12	0.39	0.07
	3	0.09	6.49	0.00	0.48	0.00	0.76
	4	0.03	11.58	0.99	0.40	0.60	0.16

Dependent Variable: Overall PAC-QOL score

Table 49. Collinearity diagnostics for stepwise regression model 3.

Backwards regression models

The backwards regression strategy produced seventeen models. The seventeenth model accounted for 55% of the variance in the overall PAC-QOL score ($R^2 = 0.56$, adjusted $R^2 = 0.55$) (Table 50). The same three predictor variables were identified (PAC-SYM Abdominal symptom score, Mental Component summary and PAC-SYM Stool symptom score), confirming the findings of the forward and stepwise regression strategies.

Model	R	R^2	Adjusted R^2	Standard error of the estimate
1	0.79	0.62	0.53	0.53
2	0.79	0.62	0.53	0.52
3	0.79	0.62	0.54	0.52
4	0.79	0.62	0.54	0.52
5	0.79	0.62	0.55	0.51
6	0.79	0.62	0.55	0.51
7	0.79	0.62	0.56	0.51
8	0.78	0.61	0.56	0.51
9	0.78	0.61	0.56	0.51
10	0.78	0.61	0.56	0.51
11	0.78	0.60	0.56	0.51
12	0.77	0.60	0.56	0.51
13	0.77	0.60	0.57	0.50
14	0.77	0.59	0.57	0.50
15	0.76	0.58	0.56	0.51
16	0.76	0.57	0.55	0.51
17	0.75	0.56	0.55	0.52

Model	Predictor variables in final model
17	Mental Component Summary, PAC-SYM stool symptom score, PAC-SYM Abdominal symptom score

Table 50. Backwards regression models.

The regression equation from the final model in the backwards strategy expressed constipation specific QOL as;

$$\text{Overall PAC-QOL} = 1.67 + 0.44 \times (\text{PAC-SYM Abdominal symptom score}) + 0.21 \times (\text{PAC-SYM stool symptom score}) - 0.02 \times (\text{Mental component summary score})$$

The standardised coefficients (Beta) suggest that PAC-SYM Abdominal symptom score is the main contributor to PAC-QOL (Beta 0.44), followed by Mental Component Summary (Beta -0.32), followed by PAC-SYM Stool symptom score (Beta 0.25). These results are displayed in Table 51.

Collinearity diagnostics and residual statistics for the stepwise regression are displayed in Appendix B, Table 11 and Appendix B, Table 12. The residuals follow a normal distribution and have the same variance throughout the range.

Variable	Unstandardized Coefficients	Standard error	Standardized Coefficients	t statistic	p value
	B		Beta		
Constant	1.67	0.27		6.19	<0.01
Mental Component Summary	-0.02	0.00	-0.32	-4.30	<0.01
PAC-SYM stool symptom score	0.21	0.06	0.25	3.48	<0.01
PAC-SYM Abdominal symptom score	0.38	0.06	0.44	5.85	<0.01

Summary of variance	Sum of Squares	Degrees of freedom	Mean Square	F statistic	p value
Regression	31.57	3.00	10.52	39.42	<0.01
Residual	24.83	93.00	0.27		
Total	56.40	96.00			

Table 51. Backwards regression analysis (model 17).
Backwards regression analysis of overall PAC-QOL score on Mental Component Summary, PAC-SYM stool symptom score and PAC-SYM Abdominal symptom score.

7.10 Discussion

This study has used a larger group of patients in comparison to all but one of the previous studies that have examined the relationship between QOL in constipation and the results of objective tests. In contrast to previous studies, it has utilised well validated QOL measures that are specific to idiopathic constipation, rather than relying on more generic measures. Furthermore, the disease specific measures of QOL and symptom assessment have been validated in our own study population.

The population studied represents an extreme part of the spectrum of idiopathic constipation. It is made up of subjects who have remained refractory to medical therapy in both primary and secondary care who were referred to a dedicated clinic. Consequently, these subjects are not representative of the majority of patients who can manage symptoms themselves or through consultation with their GP. There was a female preponderance in the cohort. Female gender is associated with a higher prevalence of constipation and has also been associated with increased health seeking behaviour compared to males with constipation[24]. These influences result in a predominant female population being referred to the constipation clinic. Our convenience sample only contained 4 male subjects. These were removed from the analyses and our findings only relate to female patients with severe refractory idiopathic constipation.

The majority within the cohort had no coexisting medical conditions. Despite this the Physical Component Summary PCS (a measure of the physical effect of the condition) was less than norm referenced values for the general population. In addition, the Mental Component Summary MCS (a measure of the psychological effect of the condition) was less than norm referenced values. It is recognised that constipation is a problem in patients with a formal diagnosis of psychiatric illness, such as depression [41]. It might be expected that MCS would be low in subjects with known depression. However, only a minority of subjects (14) in our cohort had any history of psychiatric illness. The diminished MCS in our subjects suggests that a hidden or undiagnosed psychological burden exists within the constipation clinic.

The deleterious affects of constipation, evidenced by a diminished MCS, has also been noted by Wald et al in a multinational survey of general populations. In UK

subjects, the norm referenced MCS was 46.4 in the constipated and 49.9 in the non-constipated [155].

The proctographic investigations performed show that rectocoele is common in our cohort but again selection bias exists. Only a small proportion of subjects had a radiologically significant rectocoele. Suggested risk factors for the development of significant rectocoeles include exposure to childbirth and increasing age. However, we found that patients exposed to childbirth or surgery were no more likely to have a significant rectocoele than a non significant rectocoele. There was no difference in age between the groups.

The main aim of the study was to consider which of several parameters would be predictors of disease specific QOL. These parameters included a clinician assessment of symptom severity (expressed as a cumulative score) and the results of transit study and proctography. Traditionally, these have been held as important for assessing severity in constipation. Patient perception of health and symptoms were also studied.

The major findings are that: disease specific QOL in idiopathic constipation is associated with the intensity of symptoms assessed by the patient rather than assessed by the clinician; patient perception of their own mental health is associated with QOL; and proctography and transit study results are not associated with QOL.

Forward and stepwise regression strategies, suggested that the predictors of disease specific QOL (in order of contribution) were PAC-SYM abdominal symptom score, Mental Component Summary (MCS) and PAC-SYM stool symptom score. The backward regression strategy confirmed that these variables accounted for the variance in PAC-QOL.

The PAC-SYM abdominal discomfort domain contains 4 items that consider the severity of abdominal discomfort, pain, cramping and bloating. The domain is scored 0 to 4 with a higher score representing more severe symptoms. The PAC-SYM stool symptom domain contains 5 items. Subjects are asked to score how severe the following symptoms are; passage of bowel movements that require straining, bowel movements that are too hard, too small, that result in a sensation of incomplete evacuation and the feeling of having to pass a bowel movement but being unable (false alarm). Interestingly, frequency of defecation is not explicitly considered in the

PAC-SYM. In the development process of the PAC system, item deletion regarding stool frequency occurred in the psychometric validation of the measure. Although bowel frequency has long been held as an important marker of disease severity by clinicians, in the rigorous patient driven development process of the PAC-SYM it did not remain as a variable.

The rectal symptom domain for PAC-SYM was not found to be a significant predictor of disease specific QOL. This domain considers symptom intensity related to the passage of painful bowel movements, rectal burning, bleeding or tearing during or after bowel movements. Of all of the domains of PAC-SYM, the rectal domain scored the lowest (less severe symptoms). This suggests that rectal symptoms were not a significant problem for the patients and consequently did not affect disease specific QOL.

The MCS is a psychometrically validated score that summarises the SF-36 domains of Vitality, Social functioning, Role emotional and Mental Health[148]. The MCS measures the impact of a disorder on the subject's psychological wellbeing. MCS was lower compared to norm references in the healthy population suggesting that constipation was causing psychological morbidity. Mason et al also encountered psychological morbidity in female patients with idiopathic constipation[40]. That reduced QOL in constipation is associated with impaired psychological wellbeing is an important observation since in addition to managing symptoms of constipation, tackling psychological morbidity may provide an additional route for ameliorating the effects of this condition. In our subjects, what is not yet clear is whether the presence of psychological morbidity is a consequence of constipation or a trigger leading to constipation or whether psychological morbidity is a separate phenomenon. These issues require further study.

Previous studies have shown an association between symptoms intensity (measured by a cumulative score) and QOL. Damon et al found a moderate correlation ($r = 0.45$) between symptoms assessed by the clinician (Cleveland Clinic Score) and GIQLI but ultimately concluded that symptom scoring alone was insufficient to provide a precise assessment of the impact of constipation on QOL[37].

In our study the clinician assessment of symptoms, expressed as a cumulative score, was rejected from the models as a predictor of disease specific QOL. The assessment

was based on the Cleveland Clinic Score that evaluates symptoms traditionally held to be important markers of severity. Higher scores equate with worse symptom intensity. A criticism of using a system like the Cleveland Clinic Score is that the items were chosen by clinicians rather than through a patient centred approach (as used in PAC-SYM). It could be argued that a patient developed symptom measure has more meaning since it evaluates symptoms that are important to the patient themselves.

A further criticism of the Cleveland Clinic Score is that although statistical testing was used to select items for the final system, item development, item reduction and psychometric validation was not as rigorous as that employed in the PAC system. In addition, the Cleveland Clinic Score was not validated against QOL measures to confirm that increasing symptom intensity was associated with a worse QOL. These criticisms also apply to our own constipation score that was based on the Cleveland Clinic system. Certainly the results of our regression analyses would suggest that PAC-SYM, rather than the cumulative constipation score, is more appropriate for evaluating symptoms with regard to their affect on QOL.

A limitation of our regression models is that they tell us little about the association of individual clinician assessed symptoms and QOL. For example, we cannot comment specifically on whether stool frequency predicts PAC-QOL because this factor was not included as an individual variable in the regression models but formed part of the cumulative constipation score. Regarding the decision to include the cumulative symptom assessment rather than individual symptoms, a compromise had to be reached to avoid problems of multiple testing in a small data set[154] and problems of variable overlap. In the latter, where variables share similarities and overlap with other variables they may not be entered into the regression model. For example, the individual clinician assessed symptoms of straining during defection, painful defecation, sensation of incomplete evacuation abdominal pain, abdominal bloating etc potentially overlap with the individual items in the PAC-SYM questionnaire. Once one of these variables is in the regression model it is unlikely that other variables that overlap will be entered. Entering in the cumulative score, a single variable, avoided this problem. However, to investigate the relative importance of

each individual clinician assessed symptom on PAC-QOL, further regression analyses using only these as the predictor variables would need to be performed.

The other problem alluded to was multiple-testing large numbers of variables (from a small data set) that has the potential to produce an over optimistic model. To limit this problem it has been suggested that *n*/10 should be the number of variables included (where *n* is the sample size) [154]. In our current study 19 variables were examined (all of which were felt to be worthy of study). If all of the individual clinician assessed variables had been included in addition, then more than 30 variables would have been studied. This would have potentially led to inaccuracy from over optimistic models and problems with overlap.

Demographic factors such as age, duration of constipation, age of onset were studied. These variables did not explain variance in the overall PAC-QOL score. Damon et al also found that duration of constipation was not associated with QOL[37]. Two thirds of our patients had been exposed to childbirth and a third exposed to surgical intervention. However, bivariate analyses showed no differences in QOL between groups of patients defined by whether they had been exposed to surgery or child-birth. Furthermore, neither of these factors was found to be an independent predictor of QOL. In their paper, Damon et al did not explore whether age, gender, history of surgical intervention or delivery predicted QOL[37].

The importance of demographic factors in relation to QOL in constipation has been highlighted by Wald et al. QOL was lower in unemployed subjects and singles living with their parents [155]. A limitation of our current study is that the effect of marital status, household size, education status and employment on PAC-QOL was not studied.

Slow colonic transit was demonstrated in 86.4% of the subjects, using a cut off limit of greater than 40 hours. Glia et al have previously shown that patients with normal transit constipation have a poorer QOL. Our results do not support this observation. Firstly, simple comparisons of disease specific QOL showed no differences between subjects with NTC and STC and secondly, through regression modelling, neither colonic transit time nor classification according to transit time explained variance in PAC-QOL.

The results of transit study were aberrant in five subjects with disproportionately low numbers of radio-opaque markers retained. The most likely explanation for this is that the capsules containing the markers were not taken according to protocol. Results for these subjects were not used in the regression analyses. Transit studies may also be inaccurate in patients who inadvertently take laxatives or continue medications that alter colonic transit. These issues illustrate the problems inherent in the use of this investigation. Since transit studies do not predict QOL, their role in assessing severity is questionable. Further criticisms can be levelled regarding the use of arbitrary cut offs for defining slow transit and whether the studies accurately reflect colonic physiology. However, there may still be a role for radio-opaque transit studies for diagnosing pseudo-constipation[156].

No previous studies have examined proctographic parameters as predictors of QOL. In our study, neither evacuation time or % evacuation were independent predictors. The presence of a significant rectocoele and the size of the rectocoele were not associated with QOL. Bivariate analysis did not show differences in QOL between those with a radiologically significant rectocoele and those without. Overall, these results do not support the use of proctography for assessing severity. Proctography should be reserved for those patients with severely disordered defecation in which surgery for anatomical abnormalities would be contemplated. Considered wisdom is that surgery should only be offered to patients with radiologically significant rectocoele have also use manual manoeuvres to defecate. Pigot et al have shown that disease specific QOL can be improved after surgery in such selected patients[134].

It is clear that multi-factorial elements are at play when the effect of constipation on QOL is considered. Previous studies of QOL have looked for associations between variables (such as symptom scores or colonic transit) in isolation without considering the effect of coexisting variables. To overcome this problem, Multiple Linear Regression was used to evaluate the relationships between the dependent variable (overall PAC-QOL score) and several predictor variables. The variables for inclusion were chosen on pragmatic grounds, based on clinical experience of managing constipation. Variables involving colonic transit and proctography were included because they have long been accepted as important objective assessments of constipation. This is despite the fact that their utility has not been proven formally.

Some of the variables included were shown to have significant association with PAC-QOL in bivariate analyses. However, bivariate analysis was not used as a strict method of selecting variables. This is because we were keen to include variables of interest considered to be worthy of study. Although, pre-selection of variables by bivariate analysis is a common approach, a potential problem is that excluded variables may contribute to a multiple regression model in unforeseen ways because of the presence of complex interrelationships.

Ultimately, the results of a regression model are reliant on the variables entered. We have identified independent predictors of disease specific QOL but it will be desirable to undertake further study to look at the predictive influence of the demographic and socioeconomic variables not already studied in our models. In addition, it will be interesting to study the individual clinician based symptoms to evaluate their association with PAC-QOL. Importantly, this should include stool frequency as well as frequency of laxative use, frequency of unsuccessful attempts, time spent attempting to defecate, straining, pain on defecation, sensation of incomplete evacuation, use of manual manoeuvres, frequency and intensity of abdominal pain and bloating.

7.11 Conclusion

An understanding of predictors of disease specific QOL will hopefully enable targeting of interventions to improve overall QOL in patients with refractory constipation. Our findings suggest that symptoms (abdominal and stool symptoms) and the impact of constipation on mental health are important predictors. Therapeutic strategies that reduce abdominal and stool symptoms may offer a way of improving QOL in constipation. Addressing problems in mental health with psychiatric and psychological interventions may also be beneficial.

The results of transit studies and proctography are unhelpful for identifying subjects who are suffering the most from their constipation. In addition, it would appear that if symptom intensity is used to evaluate the impact on QOL, it is preferable to use the psychometrically validated, patient administered PAC-SYM, rather than using a cumulative clinician based assessment of symptoms.

7.12 Future directions

The search for predictors of disease severity is important so that interventions can be targeted and best use be made of limited resources. Confirmation of our findings will be an important further step. The impact of additional demographic details needs to be studied within our population.

Our findings present us with avenues for prospective studies to test hypotheses regarding QOL and natural history in groups defined by symptom patterns, demographics and treatments. Studies of therapies that specifically deal with abdominal and stool symptoms would be interesting. Data has emerged suggesting that Tegaserod can ameliorate symptoms of abdominal discomfort, pain, cramping, and bloating in patients with IBS and functional constipation [70,157,158]. A study of Tegaserod in our cohort would add to the understanding of the efficacy of this drug in severe refractory idiopathic constipation. Despite the fact that Tegaserod is effective in treating some of the predictors we have identified (abdominal symptoms), because of safety concerns (increased risk cerebrovascular and cardiovascular events) a study in our subjects seems unlikely [73].

Other emergent therapies such as Lubiprostone and Linaclotide have been shown to improve stool frequency and consistency [159,160]. However, their effectiveness in treating abdominal symptoms such as pain and bloating is less certain.

Lubiprostone is a member of a class of compounds called prostones. It activates type-2 chloride channels (ClC-2) thus increasing the chloride concentration of intestinal fluid. This increases intestinal fluid secretion (without disturbing serum electrolyte balance) facilitating intestinal transit. Johanson et al studied 129 patients in a randomized, double-blind, placebo-controlled trial of Lubiprostone versus placebo for treatment of idiopathic constipation. Frequency of spontaneous bowel movements was higher with Lubiprostone than with placebo. Severity of straining and stool consistency improved in the treated patients. However, results for abdominal discomfort and bloating were less encouraging. Although the intensity of abdominal pain and bloating did improve with Lubiprostone, the differences compared to placebo did not achieve statistical significance [159]. It would be interesting to study the affects of Lubiprostone in our own population to determine whether it improved any of the predictor symptoms we have identified.

The other potential candidate for future study is Linaclotide, a guanylate cyclase-C (GC-C) receptor agonist. Activation of the GC-C receptor (present on the luminal membrane of enterocytes) results in increased chloride and bicarbonate secretion into the intestinal lumen. Anderson et al studied the pharmacological effects of Linaclotide in 36 female patients with IBS-C [160]. There was a significant decrease in colonic transit time with Linaclotide compared to placebo. Stool frequency, stool consistency and ease of passage were improved by treatment. However, the affects of Linaclotide on abdominal symptoms (bloating, pain etc) were not specifically studied.

Data is emerging in the literature regarding therapies that enhance intestinal motility, such Methylnaltrexone and Alvimopan (peripherally acting mu-opioid antagonists). These drugs have been studied in a limited way for the management of opiate-related constipation and post operative ileus [161,162]. These treatments could form the basis of future studies in our population.

The issue of psychological wellbeing in patients referred to the constipation clinic deserves further attention. It is possible that an unrecognised burden of psychological morbidity exists, evidenced by low MCS scores (the MCS is a summary of SF-36 domains dealing with mental well being). The Mental Health (MH) domain contains 5 questions that have previously been combined to form the Mental Health Inventory (MHI-5). The raw scores (0-30) are transformed to a score of 0 to 100, where 100 represents good mental health. A cut off score of less than 52 has been shown to accurately predict the presence of depression and other psychiatric conditions[163-165]. In this way, SF-36 could be used as an initial screening tool to identify those patients who may benefit from psychiatric or psychological treatment. A further future study would be to assess the impact of psychological wellbeing on QOL, prognosis and response to treatment in severe refractory idiopathic constipation.

8 EXPLORING THE PATHOPHYSIOLOGY OF A REDUCED URGE TO DEFECATE IN IDIOPATHIC CONSTIPATION

8.1 Abstract

Introduction Patients with idiopathic constipation can be separated into groups depending on their urge to defecate. Approximately 60% of patients have a reduced rectal urge to defecate. These patients perceive the urge as abdominal sensations or have no urge at all. It is possible that these patients represent a distinct group defined by differences in the sensation, motility or physical properties of the anorectum compared to those with a normal urge.

The role of the sampling reflex has not been studied in these patient groups. The sampling reflex describes relaxation of the anal sphincter that allows rectal contents to come into contact with sensory receptors in the proximal anal canal. This event is thought to have a role in appreciation and discrimination of rectal contents prior to evacuation and therefore may have a role in creating a rectal urge to defecate. Patients with a reduced rectal urge may have less frequent episodes of the sampling reflex compared to those with a normal urge.

To test this hypothesis a technique for measuring the frequency of sampling events was developed and a comparative study of patients with reduced urge and normal urge was performed.

Methods Semi-ambulatory continuous anorectal manometry using solid state transducers was performed in 5 subjects to test the feasibility and tolerability of the technique. The 5 subjects were heterogeneous group with a variety of gastrointestinal disorders. A prospective study was then performed in patients with idiopathic constipation to compare the frequency of the sampling reflex in 11 with a normal rectal urge and 11 patients with a reduced rectal urge to defecate. Comparisons of symptom severity, anorectal sensation and colonic transit were also made.

Results The developmental study demonstrated the feasibility of semi-ambulatory anorectal manometry. The duration of recording that was acceptable to subjects was 4 hours. Three distinct types of events were identified. A reproducible method with satisfactory inter-observer agreement was developed to analyse the manometry results.

In the prospective study of constipated patients, the frequency of sampling events was 8.71/hr in the normal rectal urge group and 8.95/hr in the reduced urge group

(NS). There were no differences in type of events occurring in the two groups. Also no differences in anorectal sensation, colonic transit time were found.

Conclusion The frequency of the sampling reflex can be studied using semi-ambulatory continuous anorectal manometry. The cause of a reduced rectal urge in constipated patients was not infrequent sampling events. The factors determining the urge to defecate remain unclear. Further study is required to evaluate the role of rectal compliance, rectosigmoid motility and central processing of sensory perceptions.

The frequency of the sampling response does not determine urge to defecate in patients with constipation: A study using semi-ambulatory anorectal physiology.
Cowlam S, Saunders P, Wooff D, Yiannakou Y.
Neurogastroenterology and Motility. 2006. 18 (8); 676

Oral presentation at the European Society of Coloproctology.
Lisbon, Portugal, September 2006.

Data collection	SRC, PS
Data entry	SRC
Data Analysis	SRC (advice from TH)
Data interpretation	SRC, YY

8.2 Introduction

Patients with idiopathic constipation can be separated into distinct groups depending on their perception of the urge to defecate. One group experience the urge to defecate as a sensation in the rectum. This group can be described as having a normal rectal urge to defecate (NRUD). In contrast, the other group experience the urge to defecate as sensations in the abdomen (abdominal fullness, bloating or pain) or do not perceive any urge to defecate at all. This group can be described as having a reduced rectal urge to defecate (RRUD). Some patients lose their normal rectal urge at the same time as the onset of constipation. The explanation for this phenomenon is not known. Harraf et al found that 61% of patients with constipation had no rectal urge to defecate, instead describing abdominal sensations[166]. Hawkes et al studied patients with chronic constipation and found that 58% had a RRUD[167] whilst in the constipation clinic at Durham, 63% of patients with idiopathic constipation were found to have a RRUD[168]. The fact that constipated patients can be separated into groups raises the possibility that distinct pathophysiological processes exist that may have an impact on prognosis and outcome.

Rectoanal sampling is part of a sensory pathway that appears to be involved with perception of the rectal urge to defecate. The possibility that the frequency of sampling is different in patients with a normal urge compared to those with a reduced urge has not been studied.

It is postulated that sampling occurs when faeces distends the distal rectum and initiates a reflex relaxation of the anal sphincter. Faeces enters the rectum as a result of propulsive forces in the colon, sigmoid and rectum. Reduced motor activity has been found in some patients with constipation and it is interesting to speculate whether a reduced urge to defecate (occurring because of infrequent sampling) is a surrogate marker of this dysmotility[169].

It is known that some patients with slow transit constipation have a poor outcome (pain, bloating, rectal discomfort) following colectomy and ileorectal anastomosis (IRA)[170]. This might be related to disordered rectal motility so that despite removal of the colon, rectal abnormalities contribute to ongoing distressing symptoms. If it was shown that a reduced urge to defecate was associated with a clinical marker of rectal dysmotility (reduced urge) this would have implications for patient selection for colectomy and IRA.

8.3 The urge to defecate

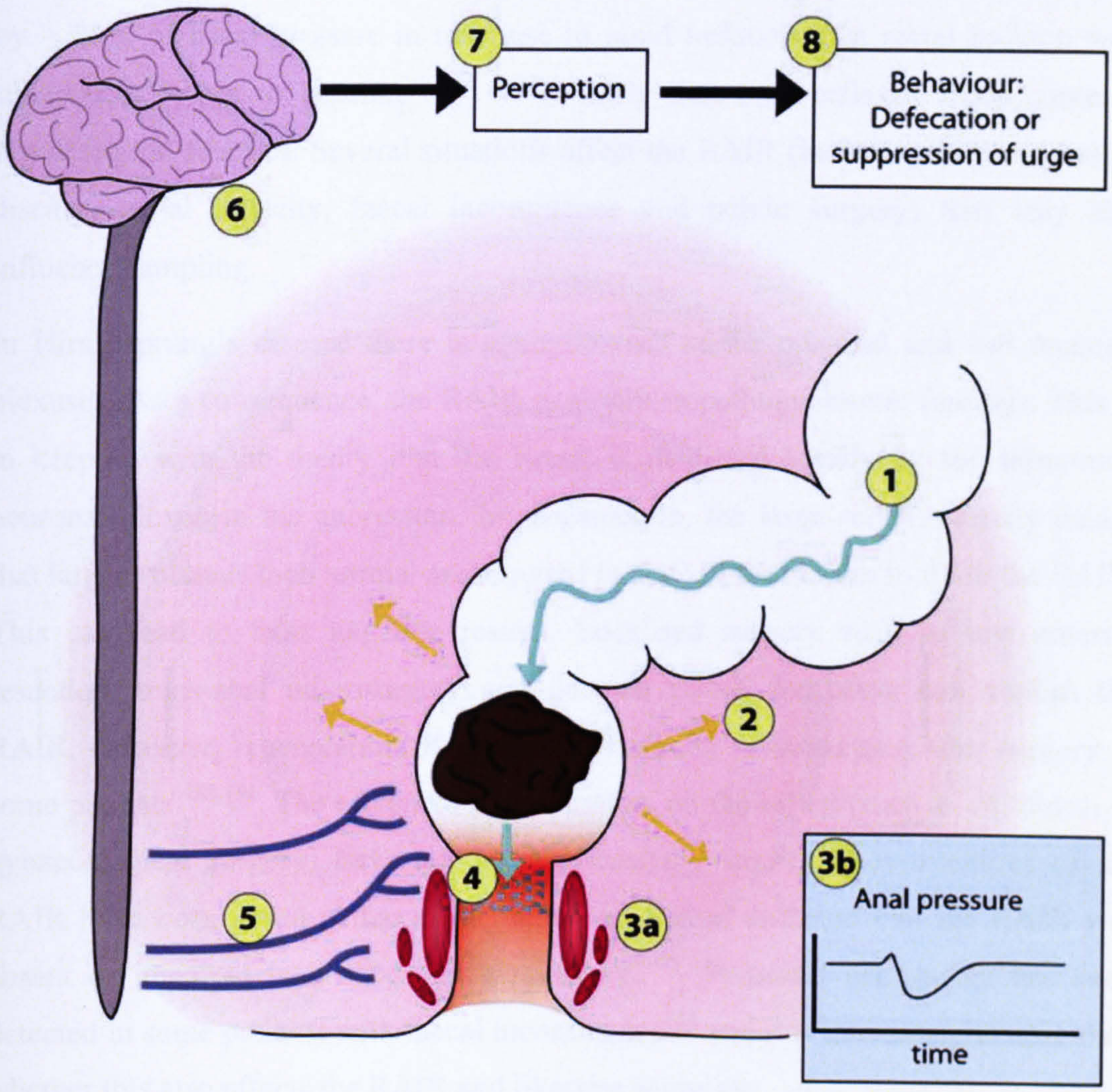
In normality, a sensation of rectal fullness generally precedes the act of defecation. The perception of this rectal urge depends on a sensory pathway (Figure 15). In this process there is activation of sensory apparatus in the rectum, initiation of local inhibitory and activation of sensory receptors in the anus. Sensory afferents carry information via the spinal cord to the brain for processing. Centres in the brain dictate the behaviour of the individual in terms of how they deal with the rectal content (e.g. whether they choose to defecate).

Propulsive contractions in the colon move material into the rectum which leads to rectal distension [171,172]. This activates stretch receptors and an intrinsic inhibitory reflex is initiated. This causes relaxation of the internal anal sphincter (IAS). This rectal anal inhibitory reflex (RAIR) can be induced by balloon inflation in the rectum. Interstitial cells of Cajal and nitric oxide have been implicated in the relaxation of the IAS[173,174]. Other neurotransmitters may have a role such as vasoactive intestinal peptide and adenosine triphosphate [175].

Relaxation of the IAS allows rectal material to come into contact with the proximal part of the anal canal. This allows sampling to occur to discriminate faeces from flatus and has been described as the "sampling reflex" [176]. During this process, continence is maintained by simultaneous contraction of the external anal sphincter (EAS) in normal subjects. The proximal part of the anal canal is sensitive to touch, pain, temperature and movement. Sensory nerve endings identified in this area include Meissner corpuscles, Pacinian corpuscles and corpuscles of Golgi and Mazzoni [177]. Sensation from the anus and rectum is carried by afferent fibres running via the pelvic and sacral nerves and through the spinal cord to the cortical brain for processing.

The urge to defecate can therefore be influenced by factors affecting this pathway at several points. Possible factors include mechanical changes in the anus and rectum or disruption of the inhibitory reflex. Aside form "local" disturbances in the anorectum, disruption may occur in the spinal column. Injury to the spinal column has been associated with diminished rectal sensory responses and changes to RAIR[178]. Such changes may affect the urge to defecate.

Central processing of the sensory information in the brain can also influence whether an urge to defecate is perceived. For example, central control can allow urge to be suppressed or disregarded. In this situation, accommodation within the rectum allows faeces or flatus to be stored until a convenient time for evacuation. During this time, continence is maintained by a combination of voluntary contraction of the EAS, the efforts of the puborectalis muscle, the effect of the ano-rectal angle and rectal compliance [179]. It is possible that learned behaviour in childhood or adolescence (such as volitional stool retention due to painful defecation [180,181]) leads to a diminished call to stool. Here the sensation of a rectal urge is suppressed or lost.



1. Propulsive contractions in the sigmoid and proximal rectum move faeces into the distal rectum.

2. Rectal distension activates mechano receptors in the rectal wall and initiates an intrinsic inhibitory reflex via the myenteric plexus.

3a & 3b. Relaxation of the internal anal sphincter occurs.

4. As the anal sphincter relaxes, faeces enters the proximal anal canal and activates sensory receptors.

5. Afferent nerve fibres carry sensory information to the spinal cord.

6. Processing of sensory afferent information occurs in the brain.

7. A sensation of rectal fullness is perceived as an urge to defecate.

8. A behavioural response is triggered; either the act of defecation or the suppression of the urge so that defecation is delayed to until a more convenient time.

Figure 15. Sensory perception of the normal urge to defecate.

8.4 The Rectoanal Inhibitory Reflex (RAIR)

Both the RAIR and the sampling reflex refer to transient decreases in anal sphincter pressure. Lowry defined the RAIR as "the transient decrease in resting anal pressure by $\geq$ 25% of basal pressure in response to rapid inflation of a rectal balloon with subsequent return to baseline" [182]. It is likely that both reflexes share common physiological features. Several situations affect the RAIR (including Hirschsprung's disease, rectal capacity, faecal incontinence and pelvic surgery) that may also influence sampling.

In Hirschsprung's disease there is aganglionosis in the mucosal and sub mucosal plexuses. As a consequence, the RAIR is absent (a pathognomonic finding). This is in keeping with the theory that the RAIR is mediated locally by the intramural neuronal plexus in the anorectum. In megarectum, the large rectal capacity means that larger volumes then normal are required to distend the rectum to illicit the RAIR. This can lead to false negative results. Localised surgery such as low anterior resection, trans-anal microsurgery and ileoanal pouch formation can abolish the RAIR. However, regeneration of the reflex has been demonstrated after surgery in some patients [183,184]. The effects of pelvic trauma on the reflex (such as childbirth or gynaecological surgery) have not been extensively studied. Abnormalities of the RAIR have been noted in faecal incontinence. Sun et al found that the RAIR was absent or impaired in a subgroup of patients [185]. Pudendal neuropathy has been detected in some patients with faecal incontinence[186] and it is interesting to speculate whether this also effects the RAIR and likewise sampling.

8.5 Defining the Sampling Reflex

Duthie et al demonstrated reflex lowering of anal pressure caused by balloon distension and postulated that this mechanism was involved in sampling of rectal content. During the "sampling reflex" resting anal sphincter pressure dropped with or without a rise in rectal pressure and returned quickly to basal values over the following 30-60 seconds [176].

Miller also studied spontaneous sampling events and identified two situations; firstly a fall in anal sphincter pressure occurring with or without the patient being aware and secondly, a fall in pressure associated with the sensation of the presence or passage of flatus[187].

In the first situation, he described "...falls in sphincter pressure to such an extent that it was equal or less then rectal pressure" and also "falls in pressure that did not result in equalisation with rectal pressure". In the second situation, " where flatus was noted it was associated with a fall in sphincter pressure of 30mmHg (20-50mmHg) and a rise in rectal pressure of only 7 mmHg (0-15 mmHg). Sphincter pressure was equal to or lower then rectal pressure in 80% of these (flatus) cases". The work of Duthie and Miller has provided definitions for sampling events that include quantitative and qualative elements. These descriptions have been used by other authors studying these phenomena [169,188,189].

8.6 Previous studies regarding the sampling reflex

Duthie studied 19 normal male subjects and mapped out a sensitive area in the proximal anal canal using a fine bristle[176]. Rectal distension with a balloon was performed whilst anal sphincter pressure was measured with a non-perfused water filled manometric system. They demonstrated relaxation that produced equalisation with rectal pressure that they postulated would allow the sensitive anal mucosa to be exposed to the rectal contents.

Miller and Bartolo found that the spontaneous sampling reflex occurred in 89% of controls but only in 35% of incontinent patients [187]. They suggested that defective anorectal sampling might be an important factor in the control of continence. Manometric measurements in this study were made over short periods of time in the

left lateral position in a laboratory and therefore cannot be assumed to mirror natural physiological conditions. In an attempt to address these limitations, the authors developed an ambulatory technique of anorectal manometry. A micro transducer was inserted into the anal canal and rectum and secured at the anal verge. A portable device was carried by the subjects to record pressure changes over a 3 hour period. In 15 normal subjects sampling occurred 7 times per hour. The subjects did not perceive 60% of these events. In one subject the rectum filled with stool during recording producing a characteristic pressure trace. The authors concluded that several times an hour, the anal sphincter relaxes allowing entry of rectal contents into the anal canal so that its presence and nature can be determined [187].

Waldron et al studied 12 control subjects and 8 patients with intractable idiopathic constipation with slow colonic transit[169]. Ambulatory anorectal manometry was performed using a micro transducer attached to a portable recorder. A mean of 23.25 hours of recorded activity per subject was available for analysis. The portable nature of the equipment meant that recording could occur in the patients own home rather than in a laboratory. Sampling occurred 2.4 times per hour in the constipated patients and 7.4 times per hour in the controls.

Farouk et al studied 48 patients with faecal incontinence and 44 controls. The median length of recording was 8 hours[188]. The median frequency of sampling during the daytime was 4 per hour in controls. Sampling occurred in all of the incontinent patients at a frequency of 9 per hour. This result is in contrast to those reported by Miller [187] (sampling in only 35% of incontinent patients) and Sun et al (only 18% of patients) [190]. These studies however, were non-ambulatory with short periods of recording performed in a laboratory rather then in the patients' natural environment. Another explanation for these differences is patient selection; Farouk's subjects had neurogenic faecal incontinence and were theoretically dissimilar to the patients with idiopathic faecal incontinence studied by Miller and Sun.

An attractive explanation for why patients with faecal incontinence sample more then controls or constipated individuals is that the increased frequency allows a greater appreciation of rectal content so that episodes of incontinence are reduced.

Ronhalt et al performed ambulatory manometry using solid state equipment in 10 normal subjects (3 women)[189]. Recordings for 20 to 24 hours were made. Analysis

of anorectal activity was made by a computer programme and by visual inspection of the pressure traces. The frequency of sampling events was 14.5 /hr whilst awake and 4.3 / hr during sleep.

8.7 Previous studies regarding the urge to defecate

The pathophysiological explanation for why some patients have abdominal urge and others a rectal urge remains unclear. There are few reports comparing subjects from the two groups.

Harraff et al studied 44 consecutive patients with constipation attributable to IBS and evaluated symptoms, colonic transit and rectal sensation[166]. Included were 17 patients with an abdominal urge and 27 patients with a rectal urge. There were no differences between groups defined by urge with respect to age, sex, stool frequency, passage of pellet like stools or laxative use. There was no difference in psychological symptoms between the groups. However, a greater proportion of patients with a rectal urge rated their symptoms of constipation as "severe" in comparison to abdominal urge patients.

Sensation was assessed by balloon distension using ramp and phasic inflation protocols to test for the sensations of "stool" and "discomfort". Perceptual responses to phasic distension were no different between the two groups. However, both urge groups displayed hypersensitivity for discomfort thresholds compared to normal controls. Responses to continuous ramp distension were different between groups. Stool and discomfort thresholds were significantly higher in abdominal urge compared to the rectal urge group and controls. The results suggest a degree of rectal hyposensitivity to ramp distension in patients with abdominal urge compared to those with rectal urge. With regard to colonic transit, Harraff found no difference in total or segmental transit between the groups [166].

Hammonds et al tested sensory perceptions to distension in the oesophagus, jejeunum, ileum, colon and rectum[191]. Patients with IBS constipation were studied. Comparisons were made between 10 patients with urge, 21 patients with no urge and 31 normal controls. For all regions of the bowel, the constipated patients had hypersensitivity to distension compared to controls. This finding was irrespective of

their urge. The no urge patients showed diminished sensitivity to distension in the rectum compared to those with urge but there were no differences in sensation in the other regions of the bowel.

Yiannakou et al studied 23 constipated patients with rectal urge and 33 patients with a reduced urge. The groups were well matched for age and duration of symptoms. Sensory perceptions to rectal distension were comparable in the domains of initial sensation, desire to defecate and maximum tolerated volume. Rectal compliance was not assessed.

Mertz et al commented on 26 patents obtained from a convenience sample of patients with idiopathic constipation who described rare or no urge. Total colonic transit time was slower in patients with no urge group (85 hours) compared to patients with urge (60 hours, $p < 0.05$). Rectal compliance was comparable in the two groups as was rectal sensation to balloon distension[192].

8.8 Summary

Patients with constipation can be separated into groups dependent on their urge to defecate. The pathophysiological determinants of whether a patient has a RRUD or NRUD are not fully explained. Demographics, symptoms, psychological state, and colonic transit appear to be comparable. Conflicting results exist regarding rectal sensation; some authors reporting no differences between the two groups and others reporting hyposensitivity in RRUD. The role of the sampling reflex in determining the urge to defecate has not been studied. In the following two sections, a technique for recording sampling events using semi-ambulatory anorectal manometry and a study comparing the frequency of sampling events in RRUD and NRUD patients, are described.

9 DEVELOPMENT OF A SEMI-AMBULATORY TECHNIQUE FOR CONTINUOUS ANORECTAL MANOMETRY

9.1 Abstract

Introduction It is postulated that the sampling reflex is involved in determining the urge to defecate in patients with constipation and that in those with a reduced urge, the frequency of sampling is less compared to patients with a normal urge. The frequency of sampling events has not previously been measured in groups of patients defined according to whether they have a normal or reduced urge to defecate.

Aims The primary aim was to develop a semi-ambulatory technique for performing continuous anorectal manometry to measure the frequency of the sampling reflex. The secondary aim was to evaluate the tolerability and acceptability of the technique to patients with gastrointestinal conditions.

Method An explorative study of semi-ambulatory anorectal manometry was undertaken. Semi-ambulatory anorectal manometry was performed using a catheter with 2 solid-state transducers positioned at 1cm and 5cm (Gaeltec). This was inserted so that the distal transducer was placed in the rectum and the second transducer positioned in the proximal anal canal. Subjects were ambulatory within the department during recording and were closely supervised. A detailed diary was completed by each patient. Subjects were interviewed after the recording to ascertain they views on the tolerability and acceptability of the procedure. The recordings were analysed independently by two different observers.

Results Five subjects with a gastrointestinal conditions were studied (alternating IBS =3, functional abdominal pain =1, idiopathic constipation =1). The mean age was 38.5 years. Four subjects were female. The mean duration of recording was 4.4 hours (range 3.7 hrs – 5.7 hrs). Mean sampling event frequency 7/hr (range 2-17/hr). Only 6% of sampling events were perceived by the subjects. Three distinct types of sampling events were identified (defined by the variation in anal sphincter pressure). All of the subjects found the procedure to be acceptable and felt that a recording time of 4 hours was tolerable. Good agreement was found between the two observers for reporting the frequency and type of sampling event.

Conclusion Semi-ambulatory continuous anorectal manometry is a tolerable and acceptable technique that can be used to measure the frequency of sampling events in patients with gastrointestinal conditions. Three distinct types of sampling events have been identified.

9.2 Introduction

Patients with constipation can be split into two groups depending on their urge to defecate. The pathophysiology of why one patient may have a rectal urge whilst another has a reduced rectal urge is not known. Although rectal sensation and compliance have been studied in patients with differing urges, the role of the sampling reflex has not been examined. Sampling events can be studied using anorectal manometry performed in a static patient in the left lateral position or by using ambulatory manometry. In the former method sampling events are not studied in the normal physiological state of the patient. Fully ambulatory study allows prolonged recording that can be undertaken in the subjects own home. However, outside of the supportive environment of the physiology laboratory, there is a risk that artifactual measurements are recorded due to probe displacement.

Semi–ambulatory continuous recording using solid state transducer technology in a dedicated environment represents a compromise. Recordings can be made in a physiological state that closely mirrors that of the natural condition. Close supervision of the subject can be provided to identify the problem of probe displacement so minimising recording artefact. Furthermore, detailed symptoms and sensation diaries can be recorded by the patients.

To address the question of whether there are differences in sampling reflex frequency in patients with RRUD and NRUD it was first necessary to develop a technique for semi ambulatory anorectal manometry that was acceptable to patients.

9.3 Aims

The primary aim was to develop a technique of continuous anorectal manometry that could be used to study the role of the sampling reflex in the determination of the urge to defecate. The secondary aim was to evaluate the tolerability of semi ambulatory anorectal manometry to determine the length of recording that would be acceptable to subjects. The third aim was to determine whether reproducible analysis could be performed of the manometry recordings.

9.4 Hypothesis

A solid state micro transducer catheter can be used to perform semi ambulatory continuous measurement of anal and rectal pressure so that the frequency of the sampling reflex can be calculated.

9.5 Materials and methods

9.5.1 Study design

Prospective explorative study of the tolerability and feasibility of performing semi ambulatory anorectal manometry. Appropriate ethical approval was sought (section 9.7).

9.5.2 Subjects

Five patients referred to a dedicated clinic for investigation of gastrointestinal disorders were studied. The subjects were invited to undergo semi ambulatory anorectal manometry in addition to their routine investigations.

9.5.3 Semi-ambulatory anorectal manometry

Recordings for all subjects began at 10am. No special dietary restrictions were imposed and subjects were advised to adhere to their normal diet and eating patterns in the evening and morning prior to investigation. Subjects were allowed to continue their normal prescribed medications. No bowel preparation was used although subjects were given the opportunity to empty their bowels before starting the study.

A soft, flexible transducer catheter, 2mm diameter was used (16C, Gaeltec Ltd, Isle of Skye, UK). The catheter carries two pressure sensitive transducers, one close to the tip and one 5cm proximally (Fig 1 & 2). It was connected to a Flexilog 3000/Flexisoft III (Oakfield Instruments Ltd) data acquisition system by a 4m flexible umbilical cable (4mm diameter). The system allowed an extended recording of pressure from the two channels that was displayed simultaneously on a visual

display unit. Pressure data were recorded and stored for later analysis. Events can be marked by the operator or patient and stored along with the pressure data (Fig 3, 4, 5)

Before insertion, *per rectum* examination was performed to confirm whether the rectum was empty. The distal transducer was positioned in the rectum and the other within the anal canal. The position of the transducers was confirmed by a manual pull through the rectum and anal sphincter to identify their characteristic pressure traces and to determine the length of the anal sphincter and location relative to the anal verge. The catheter was positioned so that the second transducer was situated in the middle part of the sphincter. The transducer catheter was secured externally to the natal cleft up to the anal verge with adhesive tape. The transducer catheter was initially inserted with the patient in the left lateral position. In this position, anal sphincter squeeze pressure was measured on three occasions. The patient was then allowed to move from the left lateral position. The flexible umbilical cable enabled the patient to dress normally and adopt comfortable, natural sitting or lying postures. In addition, participants were able to mobilise around the department and were encouraged to act naturally during the recording. A standard light meal was provided at lunchtime.

Subjects recorded a symptom diary during recording and were assessed on an hourly basis by an investigator. Recordings were continued until subjects felt unable to continue or a maximum of six hours of recording had elapsed.

At the end of the recording the subjects were interviewed to ascertain their views of the procedure. Subjects we asked to state their views regarding tolerability and acceptability of the test using the following descriptors; “tolerable”, “intolerable”, “an acceptable test” or “an unacceptable test”.

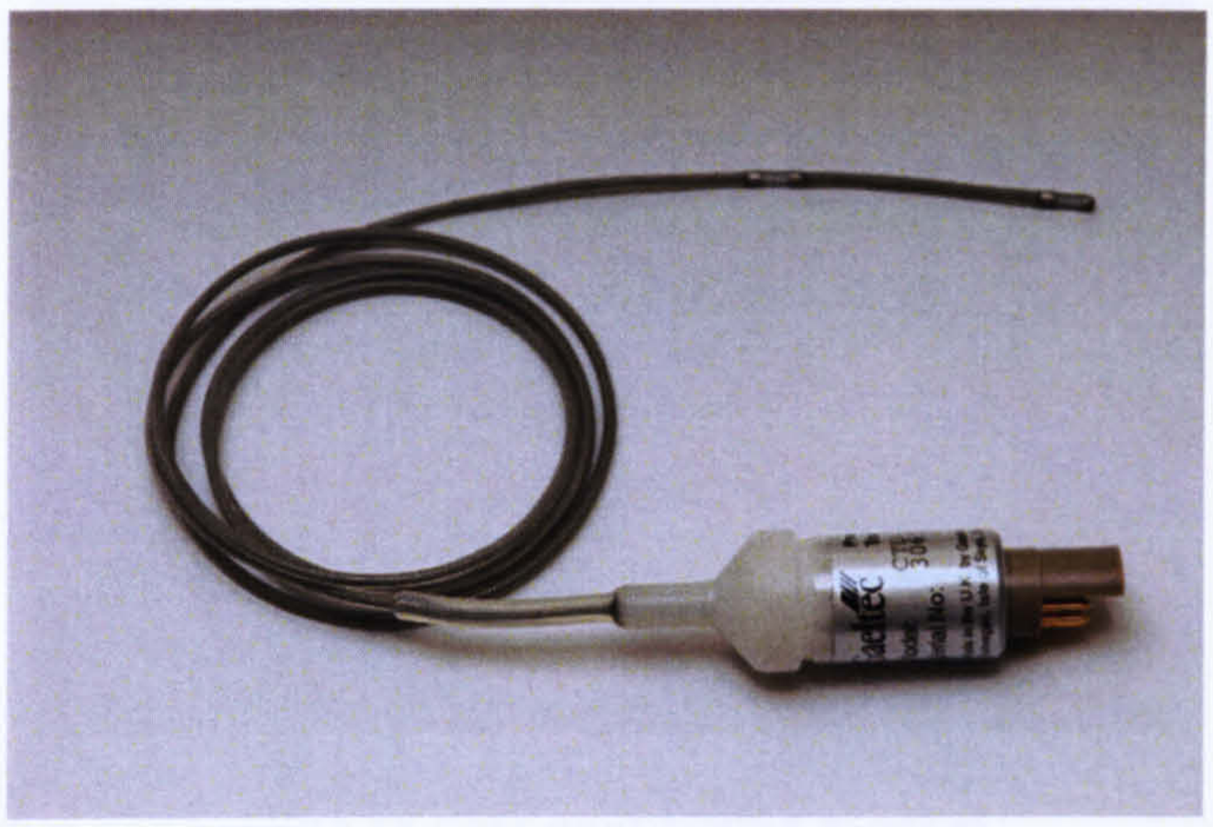


Figure 16. Transducer catheter

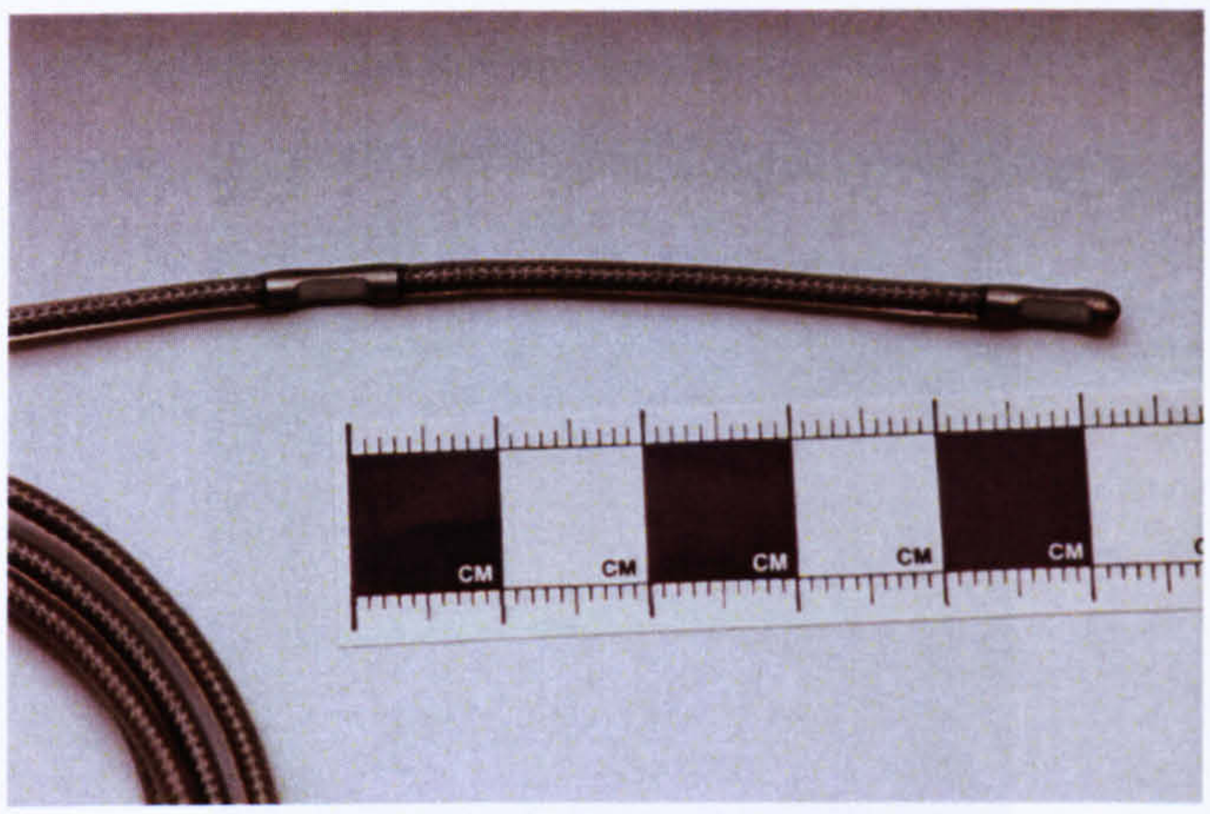


Figure 17. Solid state pressure transducers

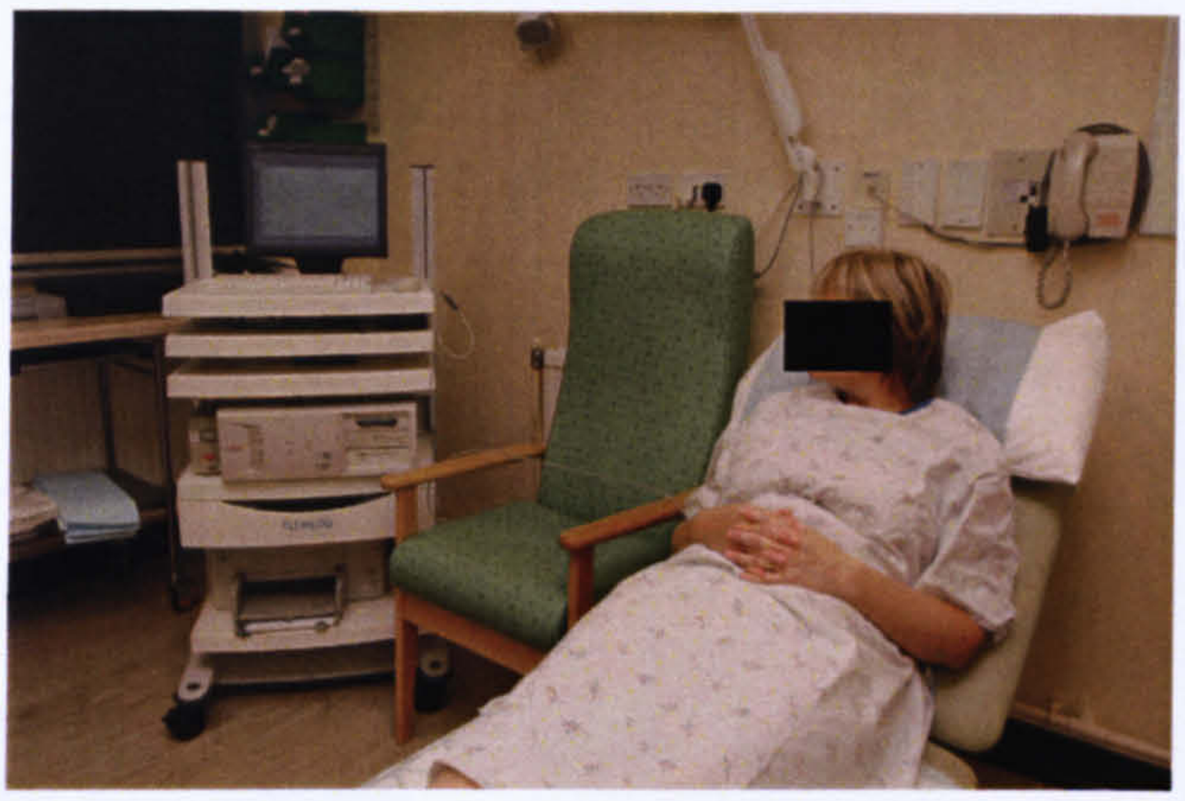


Figure 18. Umbilicus connection to data acquisition system

Figure 19. Flexilog 3000/Flexisoft III (Oakfield Instruments Ltd) data acquisition

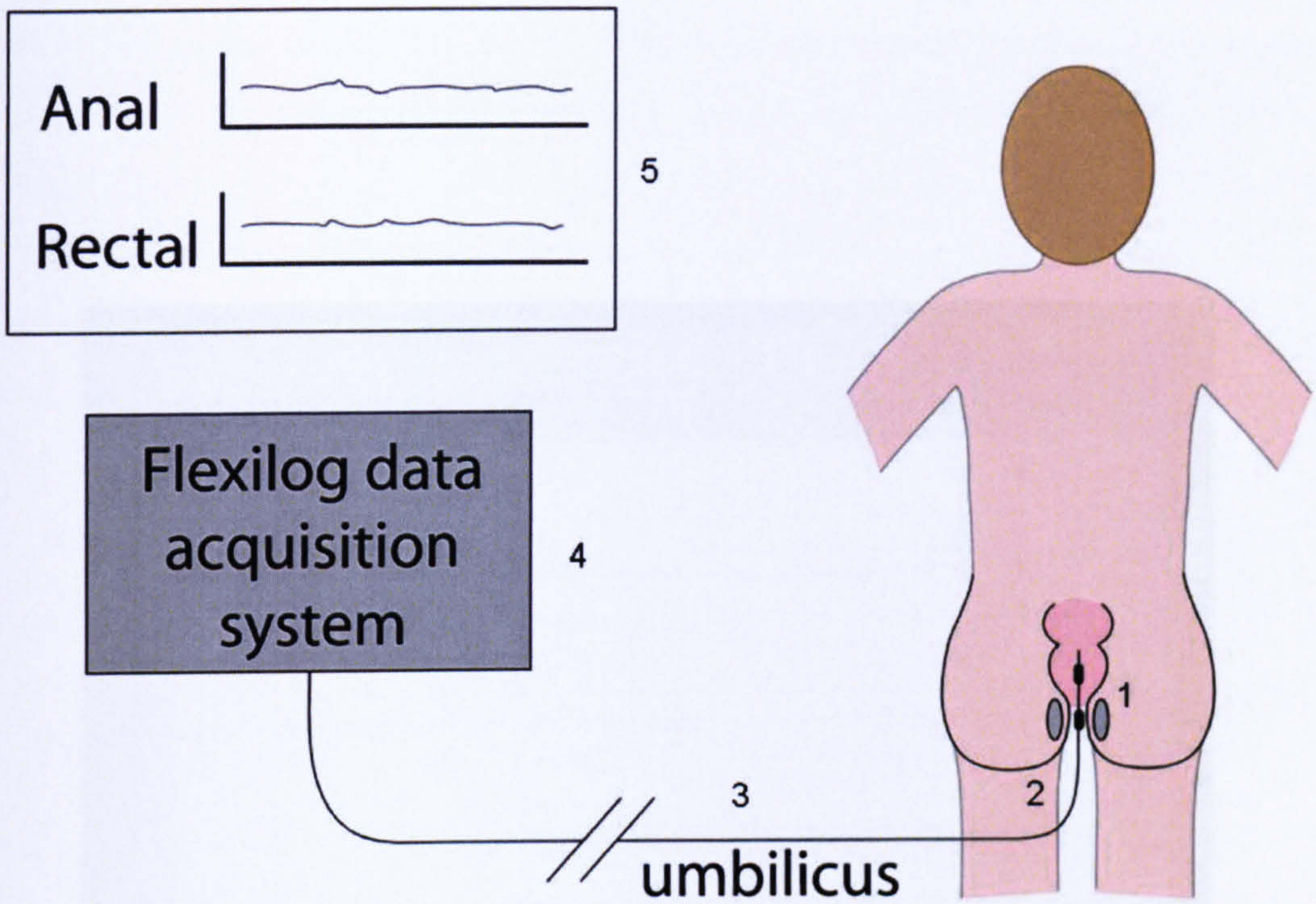


Figure 20. Illustration of semi-ambulatory anorectal manometry.
(1) Catheter with solid state pressure transducers inserted in the anorectum so that the proximal transducer is positioned in the mid point of the anal sphincter. The distal transducer is positioned in the rectum. (2) Catheter attached securely at the anal verge with adhesive tape to prevent displacement during recording. (3) 4m umbilical cable. (4) Flexilog 3000/Flexisoft III (Oakfield Instruments Ltd) data acquisition system that allows continuous measurement and recording of anal and rectal pressure. (5) Simultaneous display of pressure traces.

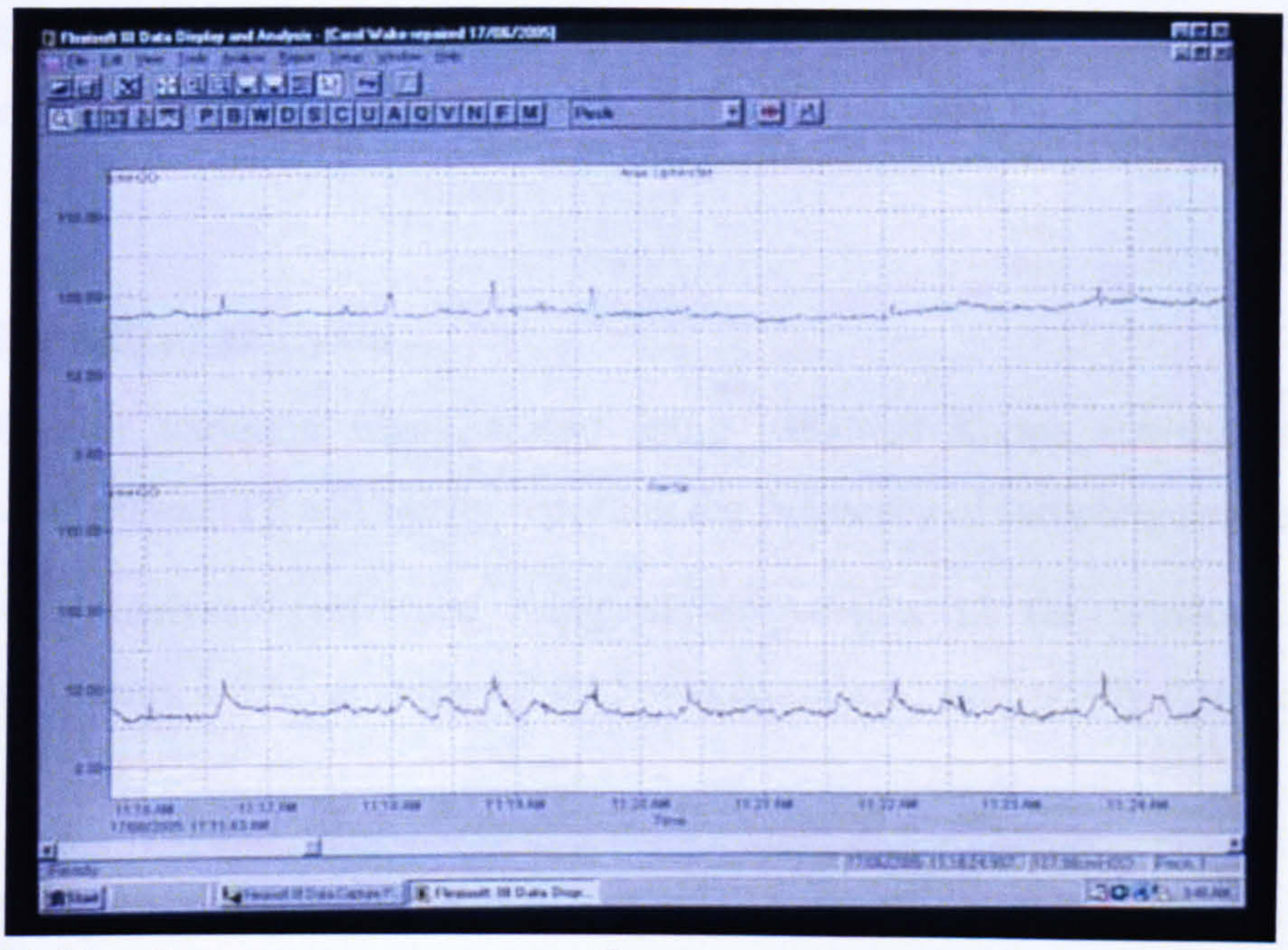


Figure 21. Simultaneous pressure recording.
Anal sphincter pressure (top) and rectal pressure (bottom).

9.5.4 Analysis of semi-ambulatory anorectal manometry

The traces were analysed on two separate occasions using Flexisoft III software (Oakfield Instruments Ltd). The analyses were performed independently of each other by different observers (PS and SC). Reported endpoints included, mean anal sphincter pressure, mean anal squeeze pressure, mean rectal pressure in the left lateral position. The frequency of sampling events was recorded. The descriptions of sampling events previously reported by Duthie and Miller were used to identify the sampling events in each recording [176,187].

9.6 Statistical analysis

Inter-observer variation was assessed using weighted Kappa statistic to assess agreement between PS and SC for reporting the frequency of sampling events.

Data were analysed performed using SPSS® version 12 for Windows (SPSS, Chicago, Illinois, USA). A value $p < 0.05$ was considered statistically significant.

9.7 Ethical considerations

The study was carried out in accordance with the 2004 Declaration of Helsinki and approval was granted by the local research ethics committee. All participants gave written informed consent.

9.8 Results

The clinical characteristics of the patients are summarised in Table 52. Mean age of all patients was 35.8 (sd 12.6) years. The group comprised 1 male (diagnosis of alternating IBS) and 4 females (2 cases of alternating IBS, one idiopathic constipation and one case of functional abdominal pain).

9.8.1 Anorectal manometry in the left lateral position

The mean anal sphincter pressure was 75.8 cmH_2O (sd 28.5) and mean rectal pressure was 26.6 cmH_2O (sd 8.9). The mean anal squeeze pressure for the group was 141.80 cmH_2O (sd 52.0).

9.8.2 Semi-ambulatory anorectal manometry

The mean duration of recording was 4.4 hrs (sd 0.87) with a range of 3.7 hours to 5.7 hours (Table 52). The pressure recordings were analysed in conjunction with the patient diaries by two investigators (SC and PS) on separate occasions. Pressure changes compatible with sampling events, were identified. The mean sampling event frequency was 7 per hour (range 2-17 per hour). Three distinct patterns of events were identified and classified as Type 1, Type 2 and Type 3 (summarised in Table 53, Figure 22, Figure 23 and Figure 24).

Correlation with the diaries allowed artifactual pressure changes (for example caused by cough or movement) to be disregarded (Figure 25, Figure 26 and Figure 27).

A total of 169 events were identified by PS. Very good agreement (weighted Kappa statistic 9.3) was demonstrated between the observers for identifying all types of events.

Parameter		
Number of patients		5
Mean age (sd)		35.8 (sd 12.6)
Sex (number of patients)	Male	1
	Female	4
Condition (number of patients)	IBS alternating	3
	Idiopathic constipation	1
	Functional abdominal pain	1
Mean anal sphincter pressure cmH_2O (sd)		75.8 (sd 28.5)
Mean anal squeeze pressure cmH_2O (sd)		141.80 (sd 52.0)
Mean rectal pressure cmH_2O (sd)		26.6 (sd 8.9)
Mean duration of recording (hours) (sd)		4.40 (sd 0.87)
Minimum duration of recording (hours)		3.7
Maximum duration of recording (hours)		5.7

Table 52. Patient characteristics.

Type of event	Description of anal sphincter pressure
Type 1	Anal sphincter pressure falls below rectal pressure
Type 2	Anal sphincter pressure falls and equals rectal pressure (equality of pressure sometimes achieved by simultaneous elevation of rectal pressure)
Type 3	Anal sphincter pressure falls and but remains greater than rectal pressure

Table 53. Description of sampling events.

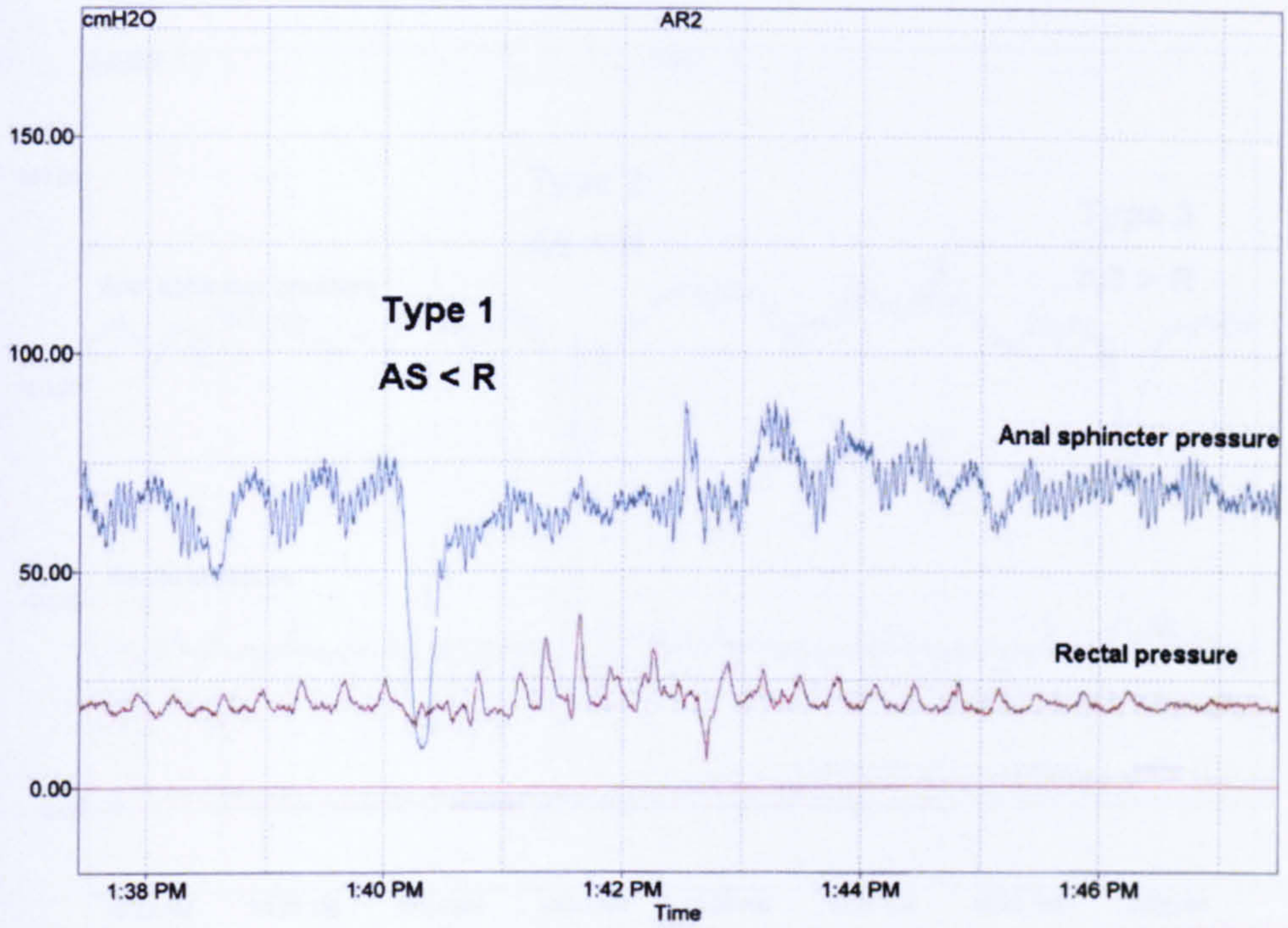


Figure 22. Type 1 sampling event

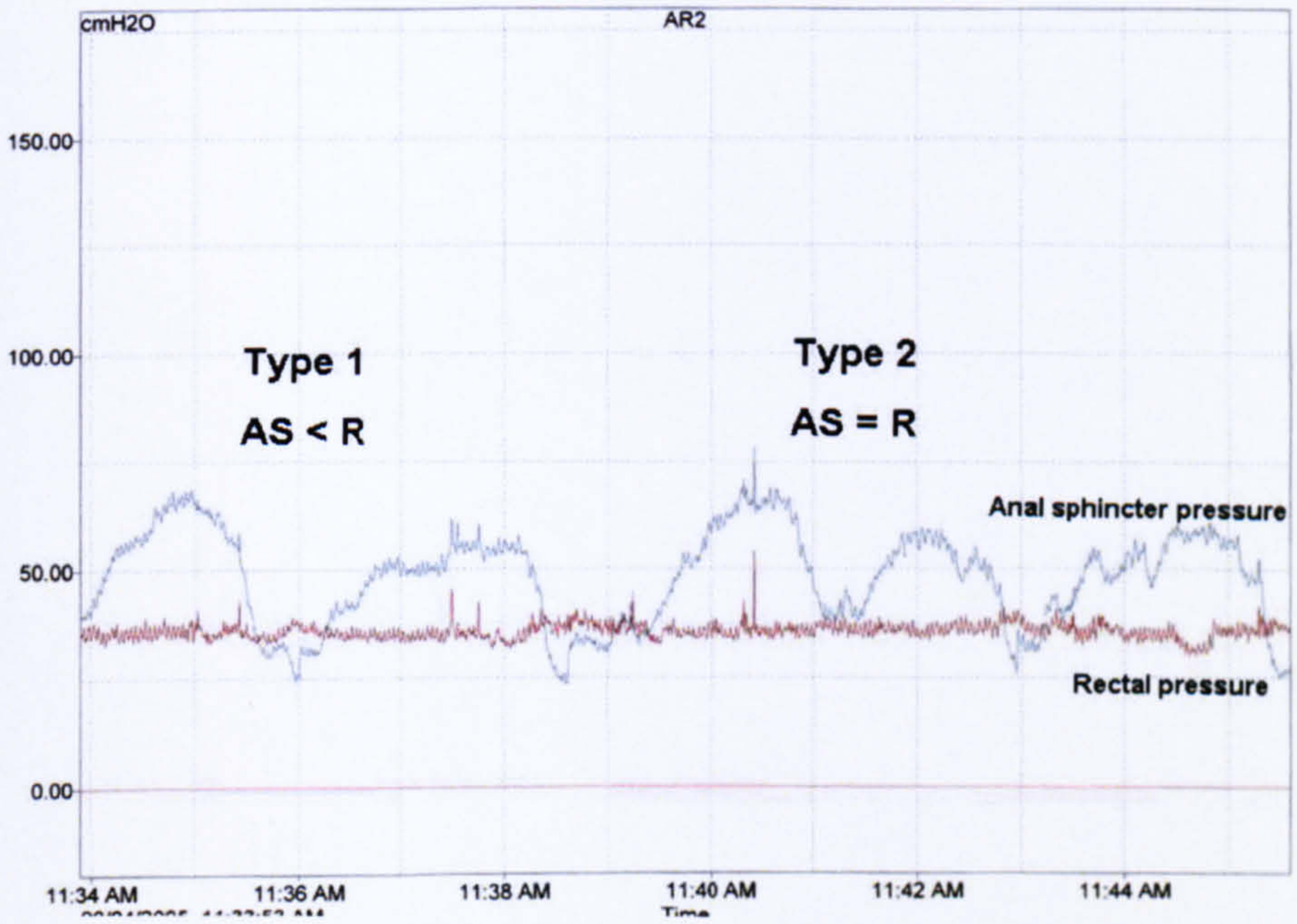


Figure 23. Type 1 and type 2 sampling events

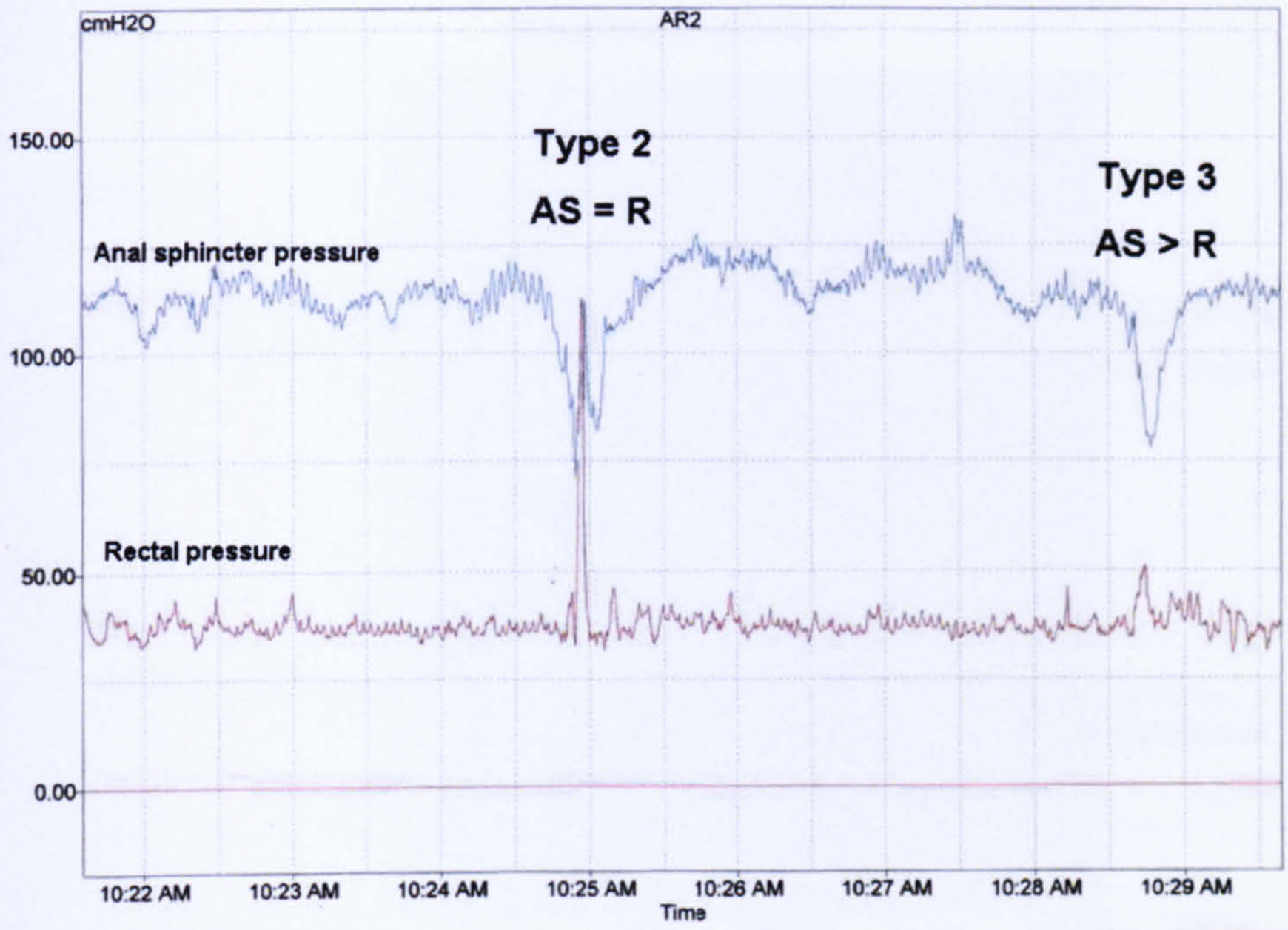


Figure 24. Type 2 and 3 sampling events

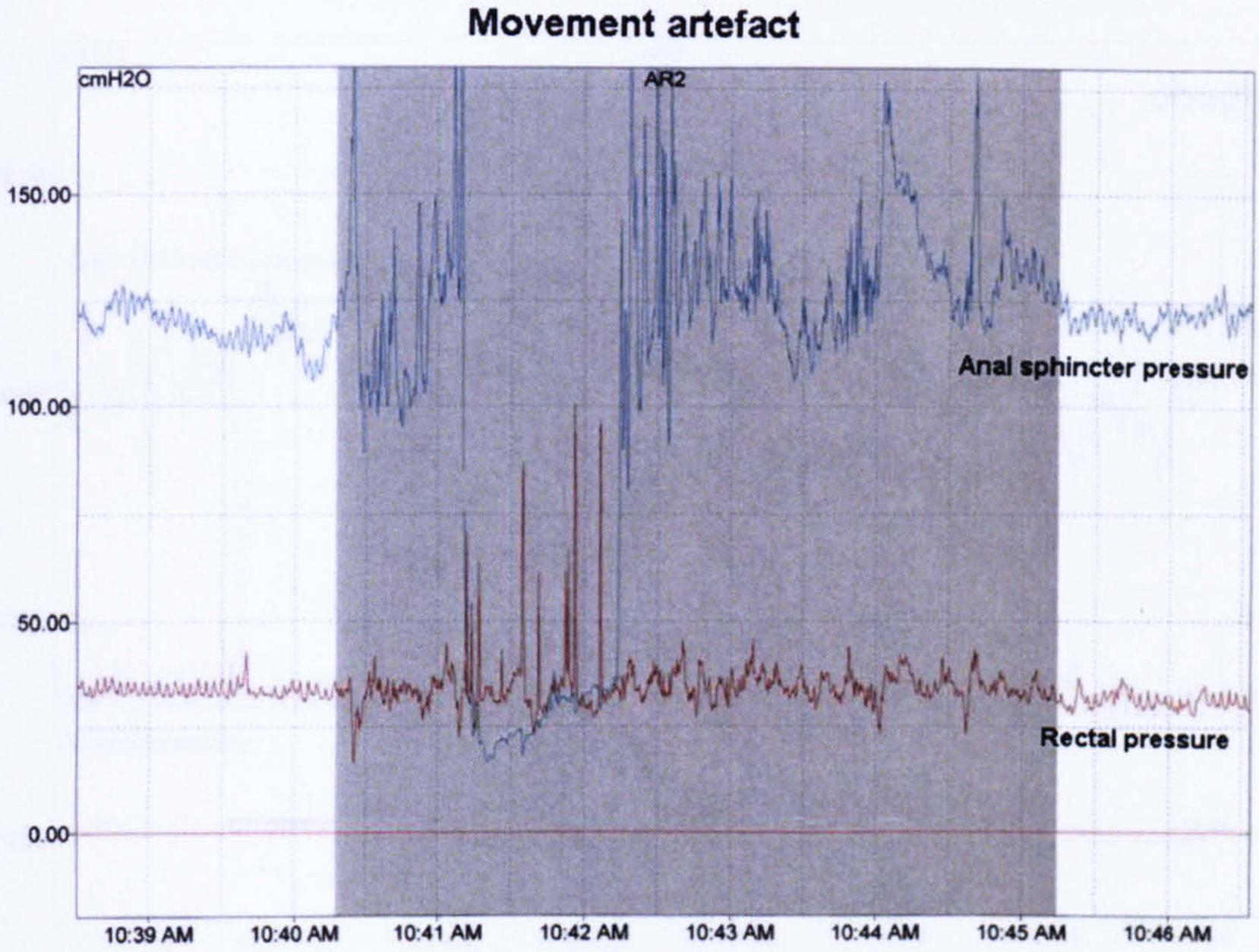


Figure 25. Movement artefact

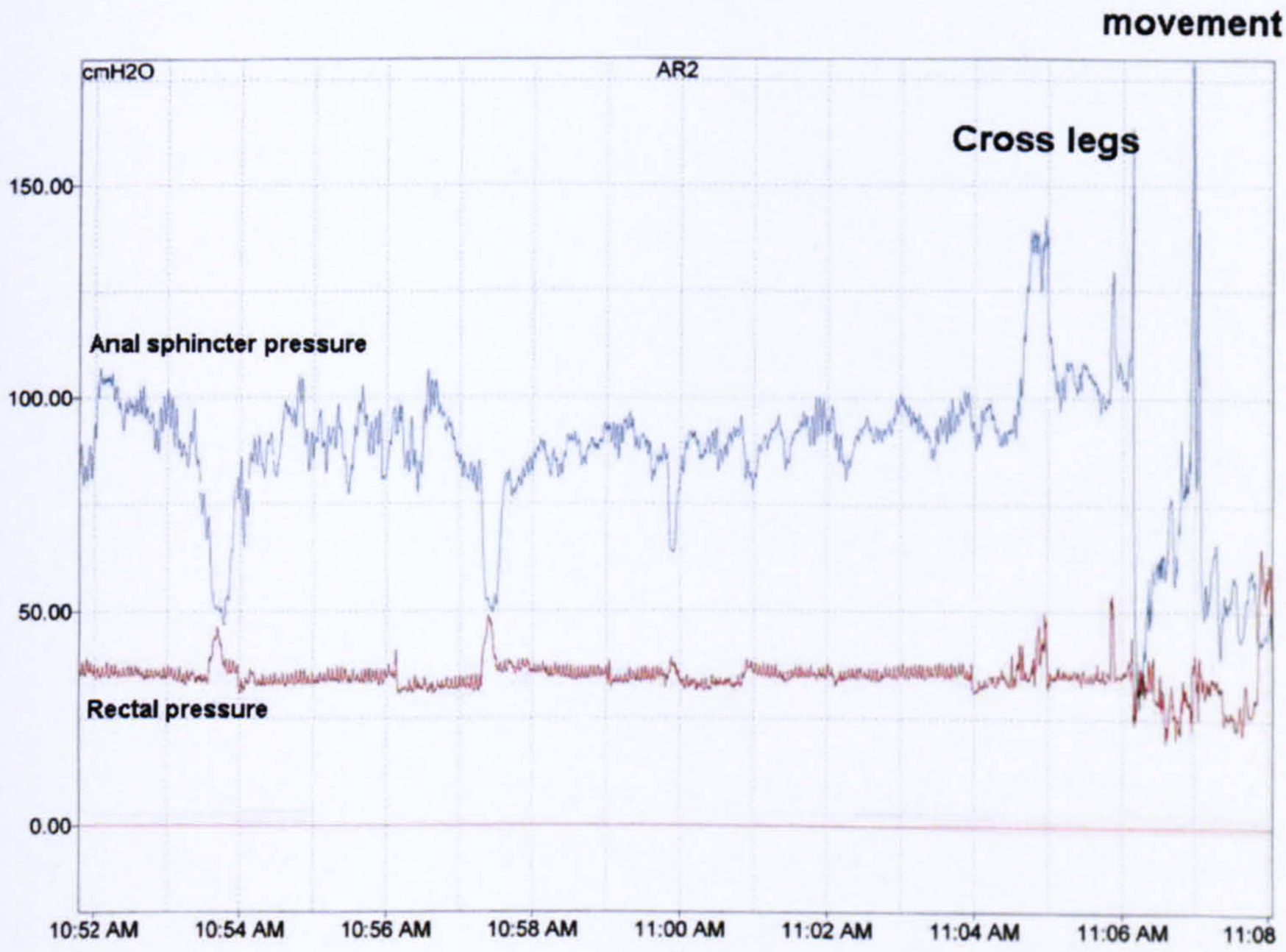


Figure 26. Specific movement artefact

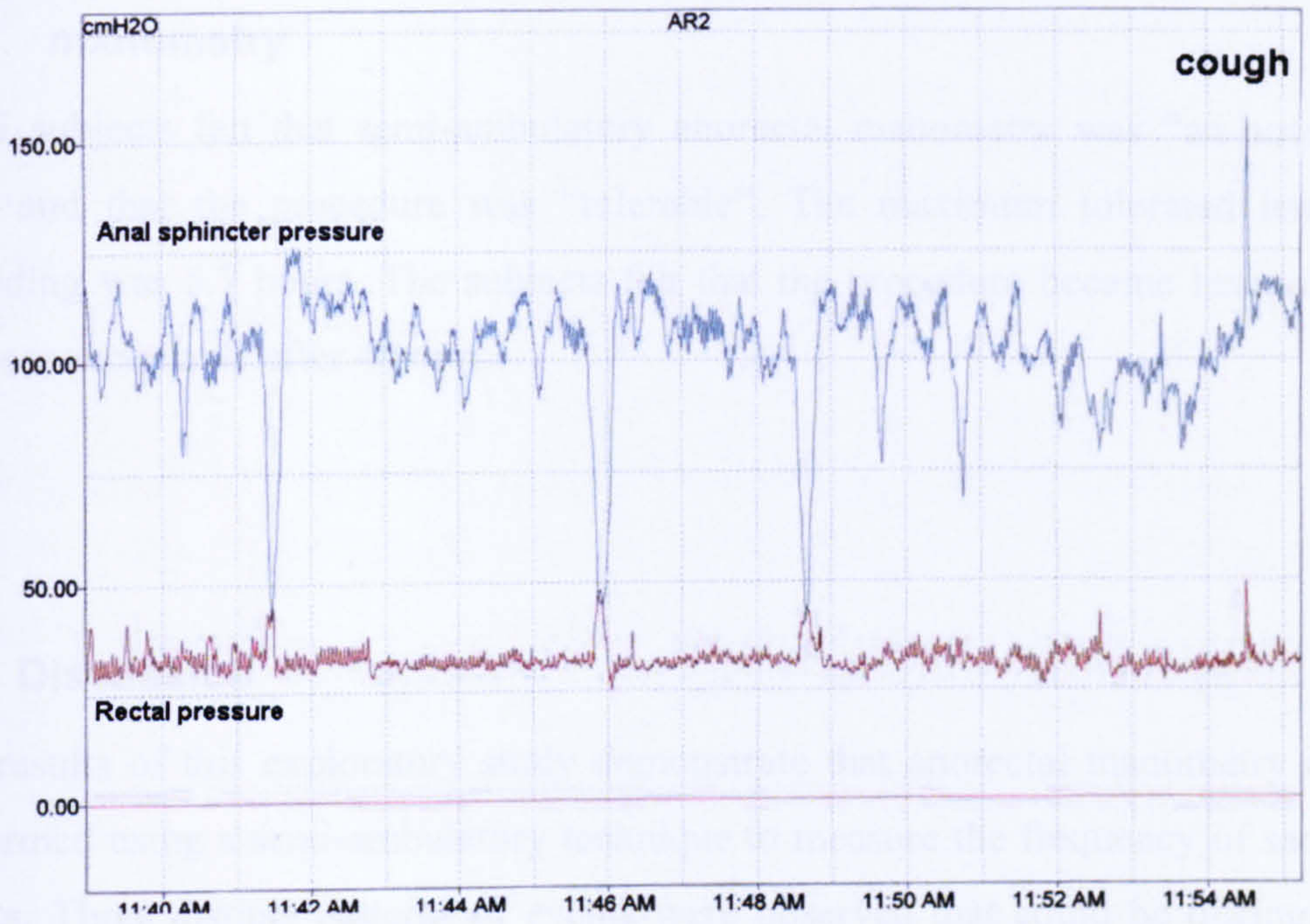


Figure 27. Cough artefact

9.8.3 Tolerability and acceptability of semi-ambulatory anorectal manometry

All 5 subjects felt that semi-ambulatory anorectal manometry was "an acceptable test" and that the procedure was "tolerable". The maximum tolerated length of recording was 5.7 hours. The subjects felt that the procedure became less tolerable and less acceptable after 4 hours.

9.9 Discussion

The results of this exploratory study demonstrate that anorectal manometry can be performed using a semi-ambulatory technique to measure the frequency of sampling events. Three distinct patterns of events were observed that could be distinguished from the background anorectal pressure recordings. The use of patient diaries to record activities meant that pressure variations caused by movement or coughing could be accurately recognised and not misreported as sampling events. The diaries also ensured meant that sampling events associated with the sensation or passage of stool could be identified.

This technique using solid state transducers was an effective way of observing the phenomena of sampling. It allowed the events to be studied in a more "natural" state then would have been possible using a water perfused pressure catheter in the left lateral position. The semi-ambulatory approach in conjunction with accurate patient diaries added a dimension of control so that artefact in the recordings could be readily distinguished from physiological changes in anal pressure.

Clearly, the longer the period of recording the more likely sampling evens are to be recorded. Fully ambulatory anorectal manometry using solid state transducers over 24 hours has been performed but this increases the likelihood of catheter displacement and movement artefact being included in the recording. The semi-ambulatory technique represents a compromise between recording anorectal pressure changes in a state that is close too "normal" as possible and ensuring accuracy of data collection.

The maximum time tolerated by patients was 5.7 hours although their opinion was that 4 hours represented the limit of overall tolerability and acceptability for the technique. Good agreement was shown between the two observers for identifying sampling events and classifying them into one of three different patterns.

9.10 Conclusion

This study has shown that semi-ambulatory simultaneous measurement of anorectal pressure can be used to identify and classify sampling events in patients with lower gastrointestinal disorders. The technique allows the recordings to be analysed and reported by different observers with a satisfactory level of agreement. The period of recording that is acceptable to patients appears to be 4 hours.

10 SAMPLING EVENTS IN IDIOPATHIC CONSTIPATION: A COMPARISON OF PATIENTS WITH NORMAL RECTAL URGE AND PATIENTS WITH REDUCED RECTAL URGE.

10.1 Abstract

Introduction Patients with constipation can be separated into groups depending on their urge to defecate. Approximately 60% of patients have a reduced rectal urge to defecate (RRUD). It is possible that these patients represent a distinct group defined by differences in the frequency of sampling events, sensation, motility or physical properties of the anorectum compared to those with a normal rectal urge to defecate (NRUD). A technique for measuring the frequency of sampling events using continuous semi ambulatory manometry was used to test the hypothesis that the frequency of sampling is less in patients with a reduced rectal urge to defecate.

Aims The primary aim was to compare the frequency of sampling events in two groups of constipated patients defined by their urge to defecate. Secondary aims were to establish whether anorectal sensation, symptom severity and colonic transit were involved in determining the urge to defecate.

Method Prospective study comparing frequency of sampling events in NRUD constipated patients with RRUD constipated patients. Subjects with idiopathic constipation were recruited. Each subject underwent a period of semi-ambulatory anorectal manometry using a catheter with 2 solid-state transducers at 1cm and 5cm (Gaeltec). The catheter was attached at the anal verge with the transducers in the rectum and anal canal. The subjects were ambulatory within the department during recording. The duration of recording (4 hours) was dictated by the results of a prior tolerability study. Analysis of recordings was made by an investigator blinded to whether the subject had NRUD or RRUD. Resting anal pressure, anal squeeze pressure, rectal pressure and anal electro-mucosal sensation were also assessed. Rectal balloon distension was performed to assess the RAIR. Rectal sensation was tested using barostat controlled inflation. Colonic transit was measured by radio-opaque marker studies

Results 22 female patients were studied; 11 RRUD and 11 NRUD. There were no differences between groups regarding age, duration and severity of symptoms or

mean duration of recording - NRUD group 3.95 hrs, RRUD 3.86 hrs (NS). All subjects had evidence of slow colonic transit. Mean sampling event frequency: NUD group 8.71/hr (range 2-20/hr), RUD 8.95/hr (range 0-21/hr) (NS). NRUD patients perceived 6% of sampling events; RRUD patients perceived 9% of events (NS). There was no difference in total or segmental (left, right, rectosigmoid) colonic transit time between the groups. No association between frequency of sampling events and segmental or total colonic transit time. No differences in resting anal pressure, anal squeeze pressure, rectal pressure or anal electro mucosal sensation were detected between the two groups.

Conclusion The cause of a reduced rectal urge to defecate is not infrequent sampling events. The factors determining whether constipated patients have RRUD or NRUD remain unclear. Further study is required to evaluate rectal compliance, rectosigmoid motility and higher cerebral function in determining the urge to defecate.

10.2 Introduction

In constipated patients a reduced rectal urge to defecate may be caused by differences in anorectal sensation or infrequent sampling events. It is postulated that sampling events occur as a result of faeculant material entering the rectal ampulla. Therefore, infrequent events may be associated with dysfunction of rectal motility.

Studies have not been performed to determine whether urge is dictated by the frequency of sampling events or whether a RRUD is a surrogate marker for rectal dysmotility. Rectal dysmotility may influence outcome following colectomy and ileorectal anastomosis performed to treat refractory slow transit constipation. The identification of a simple clinical parameter such as a reduced urge (caused by infrequent sampling) that was a surrogate marker of rectal dysmotility may have relevance for patient selection for surgery.

A technique for continuous semi ambulatory manometry was developed to test the hypothesis that the frequency of sampling is less in patients with a reduced rectal urge compared to patients with a normal rectal urge to defecate.

10.3 Aims

The primary aim was to compare the frequency of sampling events in two groups of with idiopathic constipation defined by their urge to defecate. Secondary aims were to establish whether other parameters (such as anorectal sensation, symptom severity and colonic transit) were involved in determining the urge to defecate.

10.4 Hypothesis

In idiopathic constipation the frequency of sampling events is less in patients with a reduced rectal urge to defecate compared to patients with a normal rectal urge to defecate.

10.5 Materials and methods

10.5.1 Study design

This was a prospective study of constipated patients meeting inclusion and exclusion criteria. Subjects were recruited from a dedicated clinic dealing with constipated patients. The planned duration of semi-ambulatory anorectal manometry was 4 hours (based on the results of the exploratory study described in section 9.8.3). Group size was determined on the assumption that constipated individuals with NRUD would experience a mean of 28 sampling events in 4 hours and a conservative assumption that RRUD is associated with a reduction of sampling events to 20 in 4 hours. Therefore, eleven patients per group would give 90% power at 5% significance to detect a difference.

10.5.2 Subject recruitment

Potential candidates for study were identified at the constipation clinic at the University Hospital of North Durham.

10.6 Inclusion criteria

Only patients with a diagnosis of idiopathic constipation (according to the definitions described in section 3.4) were considered for inclusion. In such patients systemic, biochemical, pharmacological, primary neurological, structural abnormalities of the colon or endocrinological explanations for symptoms of constipation had been excluded by appropriate investigation.

The affects of gender on the prevalence of constipation and healthcare seeking behaviour means that the majority of patients referred to the constipation clinic are female. This meant that the convenience sample for potential candidates was likely to be female. Therefore, it was decided to limit inclusion to women only. Patients over the age of 18 were considered.

To classify the subjects according to their urge to defecate a series of standardised descriptors were used at face to face clinician led interview (SC). These comprised;

1. In the last three months, the main reason that I go to the toilet to pass a motion is because of a feeling of fullness in my rectum.
2. In the last three months, I have not experienced any urge or feeling to pass a motion, in my rectum.
3. In the last three months, the main reason that I go to the toilet to pass a motion is because of a feeling of fullness or bloating in my abdomen.

10.7 Exclusion criteria

The presence of any of the criteria disqualified the patient for inclusion.

a) Age less than 18 years

b) Severe psychiatric disease

c) Known pregnancy, suspected pregnancy or patient trying to conceive.

d) Uncontrolled cardiac, respiratory, endocrine, metabolic, renal or hepatic diseases

e) Incapacity of higher mental function such that informed consent could not be achieved

f) Evidence of diarrhoea predominant Irritable Bowel Syndrome (IBS-D) according to Rome II criteria.

g) Previous ano rectal surgery

10.7.1 General assessment

In addition to details regarding urge to defecate, information regarding demographics, symptoms and history of constipation were assessed in all recruited patients using a standardised questionnaire based proforma. Severity of constipation was measured in terms of symptoms and QOL, assessed using the Patient Assessment of Constipation – Quality of Life (PAC-QOL) and the Patient Assessment of Constipation – Symptoms (PAC-SYM) [119,125] .

The subject's description of their urge to defecate was recorded at the time that they were identified as potential study candidates and at the time that they attended for

semi-ambulatory manometry. Therefore, the description of urge was assessed on two occasions using the same descriptor questions (section 10.6) by the same clinician (SC). This provided an opportunity to determine whether the the description of urge remained constatnt with time.

10.7.2 Semi ambulatory anorectal manometry

Semi ambulatory anorectal manometry was performed using the technique described in section 9.

Recordings for all subjects began at 10am after a 15 minute running in period performed in the left lateral position. No special dietary restrictions were imposed. Subjects were advised to adhere to their normal diet and eating patterns in the evening and morning prior to investigation. Subjects discontinued laxative therapy for 3 days before the study. No bowel preparation was used although subjects were given the opportunity to empty their bowels before starting the study. A *per rectum* examination was performed to confirm that the rectum was empty. The protocol allowed for the administration of an enema to clear the rectum if needed, however, this was not necessary in any of the subjects.

The transducer catheter (16C, Gaeltec Ltd, Isle of Skye, UK) was inserted with the patient in the left lateral position. It was connected to the Flexilog 3000/Flexisoft III (Oakfield Instruments Ltd) data acquisition system by a 4m flexible umbilical cable (4mm diameter). The catheter was positioned so that the distal transducer was positioned in the rectum and the second transducer was situated in the middle part of the anal sphincter.

A standard light meal was provided at lunchtime. Each subject completed a diary of their activities, movements, symptoms and sensations (including times). Information regarding abdominal symptoms, sensation or passage of flatus and sensation of urge were recorded. Defecation was not prohibited. Subjects were able to pass urine with the transducers in situ.

10.7.3 Resting anal pressure and anal squeeze pressure

Following the period of semi-ambulatory anorectal manometry a 10 min period of recording was performed in the left lateral position to record mean resting anal pressure. Following this mean anal squeeze pressure was determined by performing 3 episodes of volitional squeezing up to a maximum of 30 seconds with 2 minutes of rest between attempts.

10.7.4 Rectoanal inhibitory reflex (RAIR)

To test for the RAIR, a thin latex balloon was used for rectal distension (Mediplus, MED2301, Anorectal response catheter, 3cm by 5cm). This was inserted into the rectum so that the proximal part of the balloon was 10 cm from the anal verge. It was inflated rapidly via a short 14Fr catheter. The balloon was inflated with 10ml of air. If the RAIR did not occur the balloon was deflated and the process repeated using incrementally larger volumes of air (increasing by 10ml) or until 60ml of air was inflated. Anal sphincter pressure was measured continuously using a soft, flexible transducer catheter (2mm diameter) (16C, Gaeltec Ltd, Isle of Skye, UK).

10.7.5 Anal mucosal electro sensitivity

A 5mm diameter bipolar ring electrode was inserted into the proximal part of the anal canal [193]. The electrodes were spaced 1cm apart. Current pulses at 3Hz were passed between the electrodes from a constant current source (Medtronic, Keypoint) and increased linearly until the patient felt a sensation of tingling or pulsation. Averages of three recordings were taken to obtain a threshold value. The procedure was performed in both the right and left aspects of the anal canal.

10.7.6 Rectal sensation to distension

A latex rectal balloon was attached to a silastic tube (external diameter 4mm) and tied at the distal end with fine cord. The balloon was inflated and deflated prior to insertion to exclude leaks. Lubrication was used to insert the balloon so that the distal

tie attachment was 5cm from the anal verge. A barostat (volume displacement device) (Distender series II, G&J Electronics Inc. Toronto, Canada) was used to inflate the balloon continuously at a constant volume rate of 50ml/min (ramp distension). The device records pressures and volumes simultaneously. The subject was instructed to indicate their sensations to distension using the descriptors "first sensation of distension", "sensation of desire to defecate" and "maximum tolerated sensation or discomfort" (equating with maximum tolerated volume). At this point inflation was terminated and the balloon deflated and removed. To determine the sensory thresholds to distension, the indicated volume was corrected to find the true inflation volume by using Boyle's law at the indicated pressure.

10.7.7 Colonic transit

A validated method of assessing total and segmental colonic transit was performed in all subjects[53]. This is described in detail in section 7.5.3.

10.8 Analysis of semi-ambulatory anorectal manometry

The anorectal pressure recordings were analysed by an investigator (PS) blinded as to whether the subject had RRUD or NRUD. Sampling reflexes were reported using the definitions described in section 9.8.2. These included type 1 events (anal sphincter pressure falls below rectal pressure), type 2 events (anal sphincter pressure falls and equals rectal pressure) and type 3 events (anal sphincter pressure falls but remains greater than rectal pressure).

10.9 Statistical analysis

Normality of data was assessed by Kolmogorov-Smirnov tests. Normally distributed data were analysed with Student's *t* test for unpaired samples. Non-normally distributed data were analysed with the Mann-Whitney *U* test. Categorical data were compared using Fisher's exact test.

Reproducibility was evaluated by testing inter and intra-observer variability. The pressure recordings were re-analysed by SC and agreement between PS and SC was tested using weighted Kappa statistic to evaluate inter-observer variability. PS performed a second analysis (again blinded to the description of urge) of the traces two months after the original evaluation. Agreement between the first and second analyses made by PS was tested by weighted Kappa statistic to assess intra-observer variability.

Data were analysed using the SPSS® version 12 for Windows (SPSS, Chicago, Illinois, USA). A value $p < 0.05$ was considered statistically significant.

10.10 Ethical considerations

The study was carried out in accordance with the 2004 Declaration of Helsinki and approval was granted by the local research ethics committee. All participants gave written informed consent.

10.11 Results

10.11.1 Patient characteristics

The mean age of all patients was 40 years (sd 11) with a mean duration of constipation of 17 years (sd 14.7). All patients were female.

The description of urge remained stable with time. In all cases, the description of the urge to defecate recorded at the time of recruitement and at the time of semi ambulatory manometry was comparable. For the total group the mean time between recruitment and study was 4.3 weeks (sd 2.1). For NRUD, a mean of 4 weeks (sd 1.5) elapsed between recruitment and semi ambulatory manometry, for RRUD, a mean of 4.5 weeks (sd 2.6) elapsed ($p = 0.56$).

Semi-ambulatory anorectal manometry for the whole group

Regarding the whole group of 22 patients, the mean number of all types of sampling events was 34.82 (sd 25.3). The range was wide; one patient with zero events occurring in a 4 hour recording to 84 events occurring in another patient. The frequency of all types of sampling event in this group of patients with idiopathic constipation was 8.8 (sd 6.4) / hour.

10.11.2 Group comparisons

Clinical characteristics

Table 54 shows the characteristics of the two groups. The RRUD and NRUD groups were matched with regard to age, duration and severity of constipation (expressed as PAC-QOL and PAC-SYM score). There was no difference between the groups in terms of those exposed to labour or abdominal / pelvic surgery.

Parameter	**Normal Rectal Urge to defecate**	sd	**Reduced Rectal Urge to defecate**	sd	p value
Number of patients	11		11		
Mean age (years)	44.5	12.4	36	8.2	0.07
Mean Duration of constipation (years)	17	14.6	16.9	15.5	0.99
PAC-SYM score	1.93	0.61	2.32	0.72	0.18
PAC-QOL score	2.5	0.68	2.55	0.54	0.86

Table 54. Group characteristics.
Group sizes, age, duration and severity of constipation.

Semi-ambulatory anorectal manometry

In the whole group of 22 patients, the mean number of all types of sampling events was 34.82 (sd 25.3). The range was wide, from zero events in 4 hour period of recording to 84 events occurring in one of the patients.

The mean number of sampling events (all types) was 32.9 (sd 24.9) in NRUD and 32.6 (sd 27.4) in RRUD. There was no significant difference between the groups (p=0.98). Figure 28 shows a boxplot of all types of sampling events.

The frequency of sampling events in the two groups was comparable: 8.9/hr NRUD and 8.8/hr RRUD (p=0.96). Type 1, Type 2 and Type 3 events were recorded in both RRUD and NRUD patients. Type 3 events (anal sphincter pressure falls but remains greater than rectal pressure) accounted for 81% of all events recorded.

Figure 29 shows the frequency of each type of event in the two groups. There were no statistical differences in the frequency of Types 1, 2 or 3 events between NRUD and RRUD subjects.

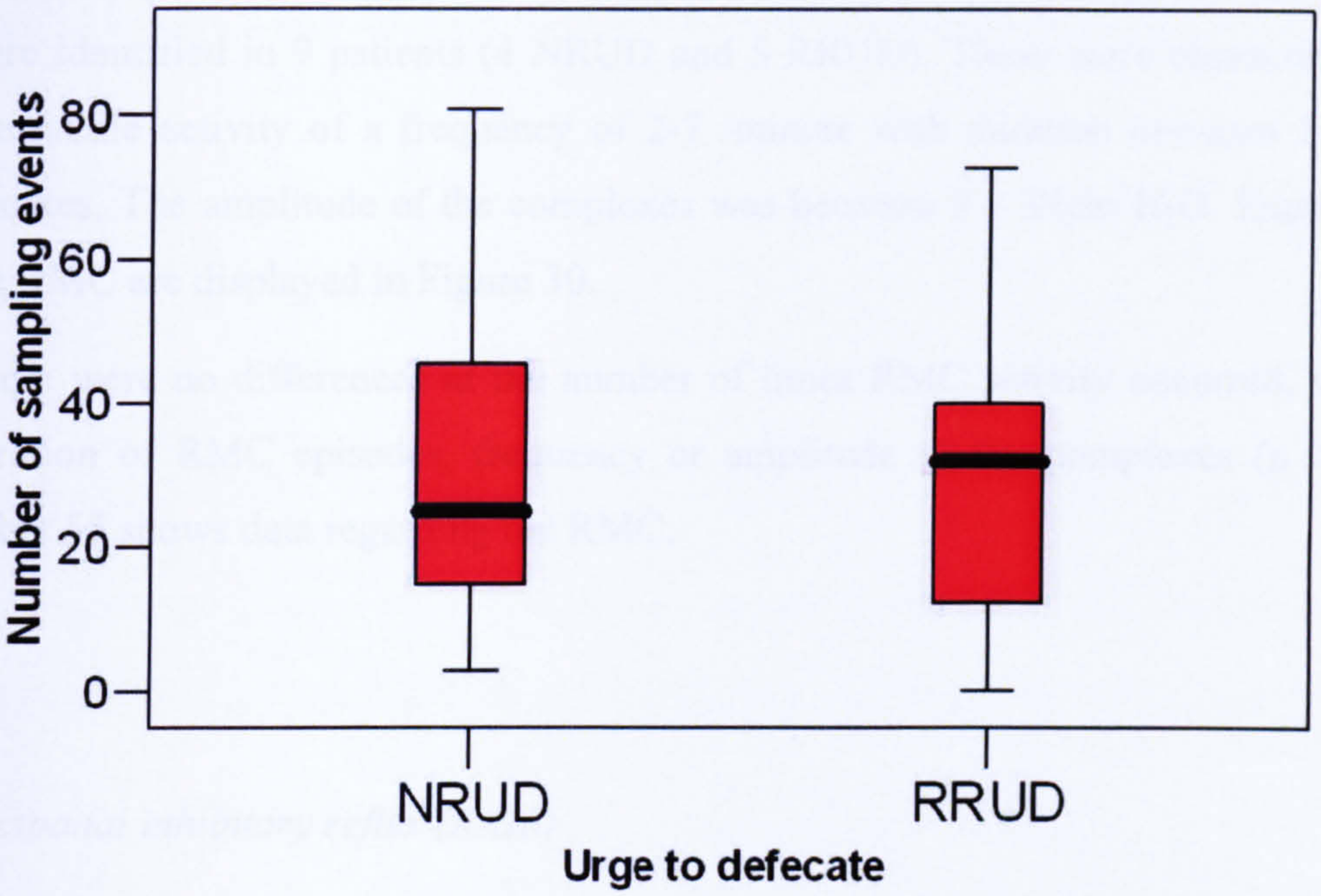


Figure 28. Boxplot of sampling events (all types).
The box plots include median bars. There was no difference between the mean number of events in NRUD 32.9 (sd 24.9) and RRUD 32.6 (sd 27.4) (p = 0.98).

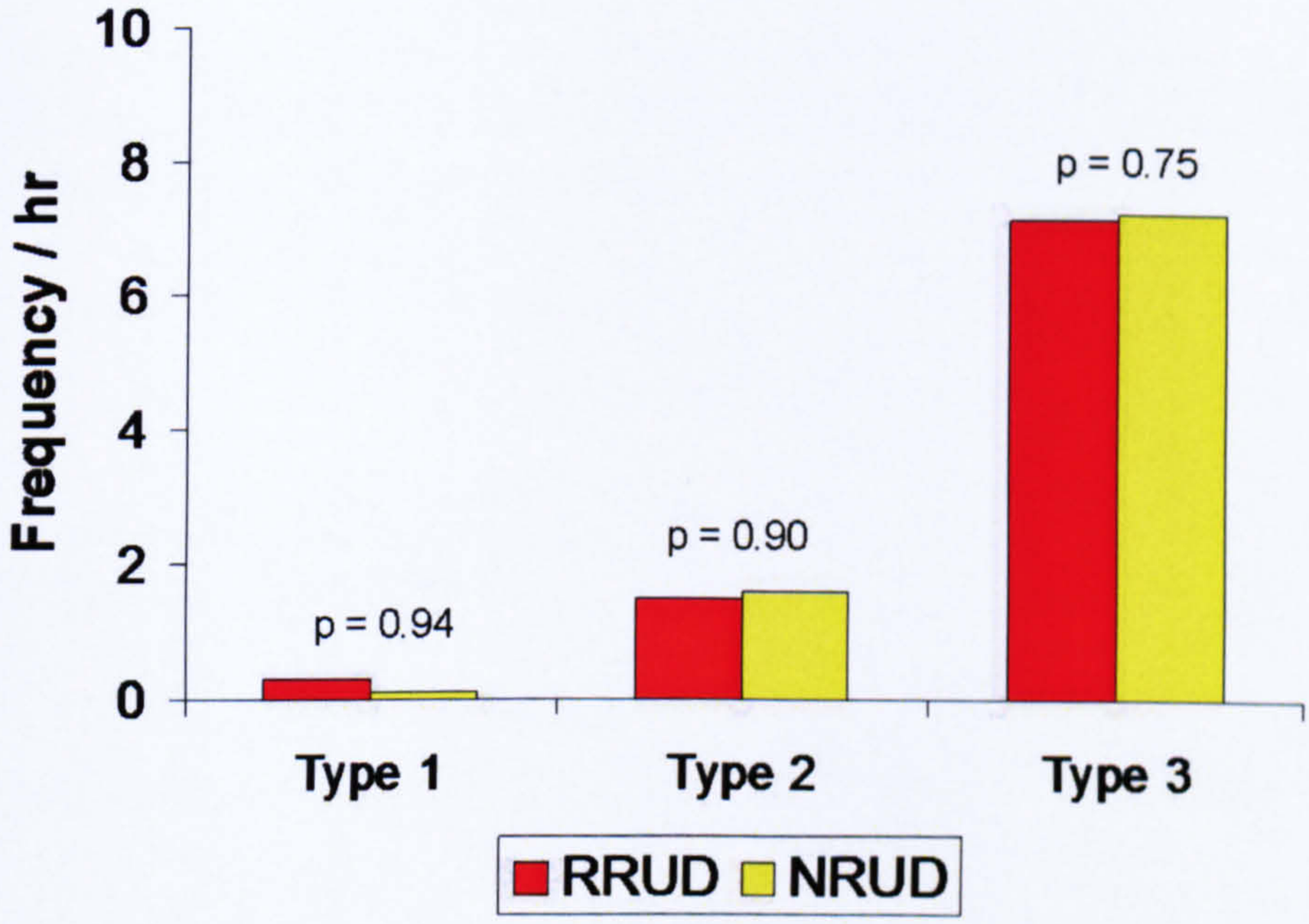


Figure 29. Frequencey of Types 1, 2 and 3 sampling events.
There were no differences between NRUD and RRUD regarding the frequency of Types 1, 2 and 3 events.

Periodic episodes of rectal motor activity – Rectal Motor Complexes (RMC)[172] - were identified in 9 patients (4 NRUD and 5 RRUD). These were characterised by contractile activity of a frequency of 2-7 /minute with duration between 1 and 15 minutes. The amplitude of the complexes was between 3 – 39cm H_2O. Examples of the RMC are displayed in Figure 30.

There were no differences in the number of times RMC activity occurred, the total duration of RMC episodes, frequency or amplitude of the complexes ($p > 0.15$). Table 55 shows data regarding the RMC.

Rectoanal inhibitory reflex (RAIR)

The RAIR was present in all subjects.

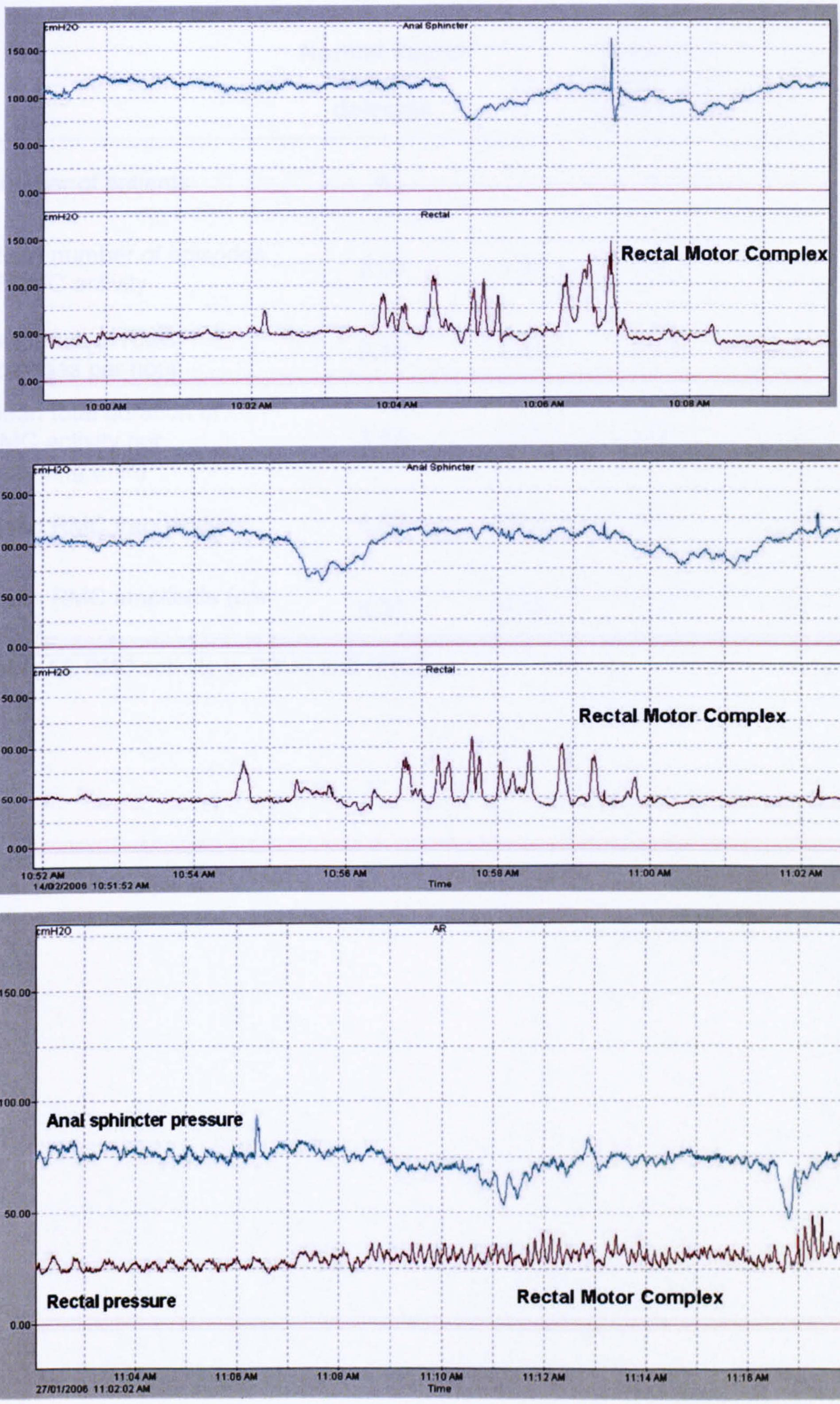


Figure 30. Examples of the Rectal Motor Complex.

	Normal Rectal Urge to defecate	sd	**Reduced Rectal Urge to defecate**	sd	p value
Number of patients	4		5		
Mean number of episodes of RMC activity	2.00	1.00	2.2	1.21	0.99
Incidence of RMC episodes per hour	0.18	0.28	0.26	0.57	0.57
Mean total duration of RMC activity per recording (min)	3.54	2.11	8.5	1.74	0.26
Mean RMC frequency	6.32	0.81	4.9	2.10	0.15
Mean RMC amplitude (cm H_2O)	6.31	8.14	2.4	3.23	0.25

Table 55. RMC activity in RRUD and NRUD.

Inter and intra observer variability

Very good agreement (weighted Kappa statistic 9.3) was demonstrated between PS and SC for identifying all types of events in the recordings. This result suggests minimal inter observer variability. Very good agreement (weighted Kappa statistic 9.1) was demonstrated between the first analysis by PS and the second analysis by PS (2 months later). This suggests minimal intra observer variability.

Anorectal physiology performed in the left lateral position

Figure 31 and Figure 32 show the results of anorectal physiology testing performed in the left lateral position. There were no differences between groups regarding mean anal sphincter pressure; 91.5cm H_2O (sd 26.0) in NRUD and 94.0cm H_2O (sd 21.5) in RRUD ($p = 0.81$). There were no differences regarding mean anal squeeze pressure; 129.4cm H_2O (sd 35.1) in NRUD and 143.7cm H_2O (sd 20.2) in RRUD ($p = 0.26$).

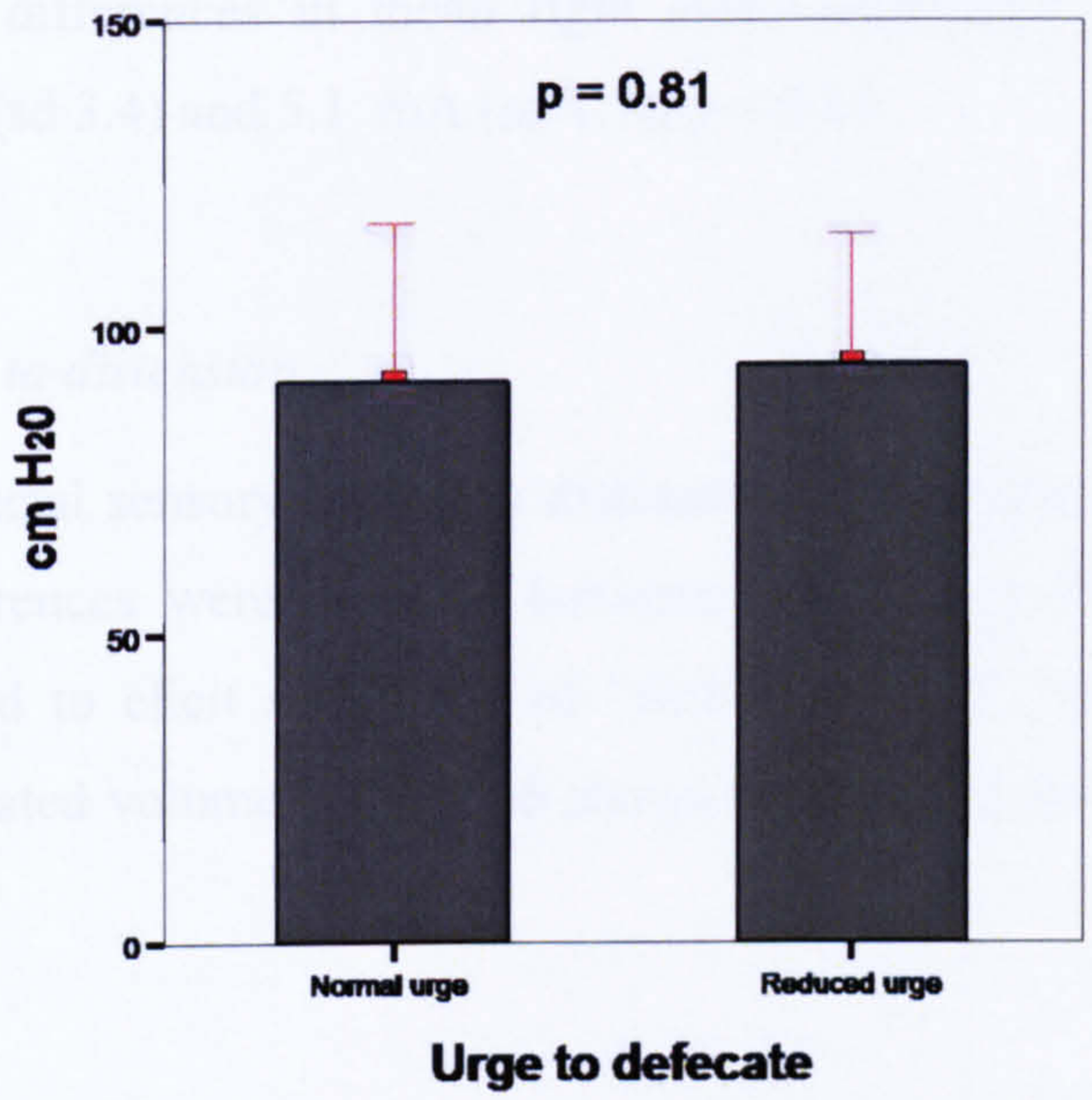


Figure 31. Resting anal sphincter pressures.

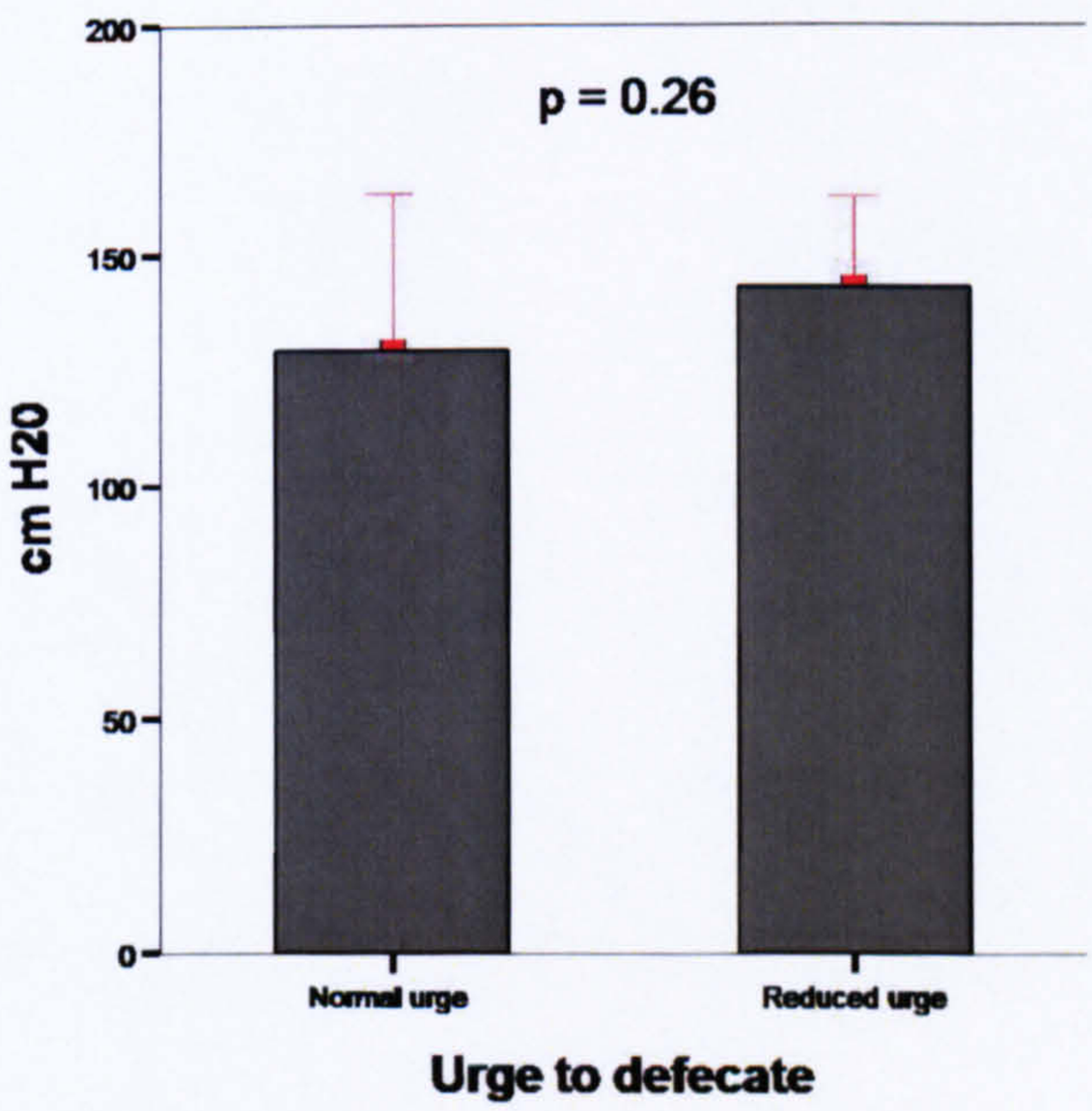


Figure 32. Anal squeeze pressures.

Anal mucosal electro sensitivity

Figure 33 and Figure 34 show the results of electro mucosal sensory testing. There were no differences in mean left sided anal mucosal sensitivity between NRUD and RRUD groups; 6.5 mA (sd 2.9) and 5.5 mA (sd 2.0), p = 0.26.

There were no differences in mean right sided sensitivity between NRUD and RRUD; 6.8 mA (sd 3.4) and 5.1 mA (sd 1.7), p = 0.15.

Rectal sensation to distension

The results of rectal sensory testing to distension are summarised in Figure 35. No significant differences were detected between NRUD and RRUD with regard to volumes required to elicit sensations of "first sensation", "desire to defecate" or "maximum tolerated volume". Table 56 shows the mean volumes in the two patient groups.

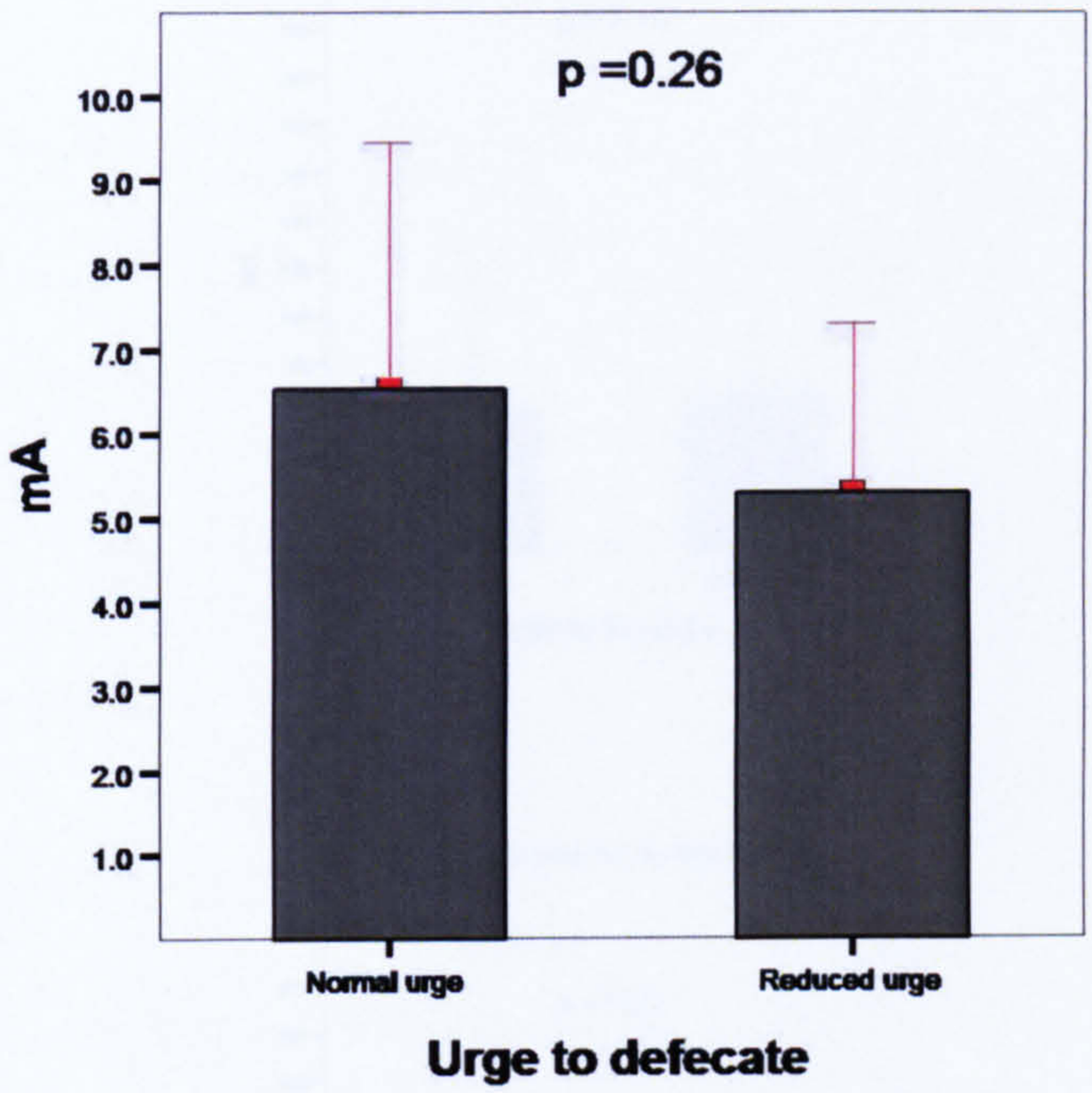


Figure 33. Left sided anal mucosal sensation.

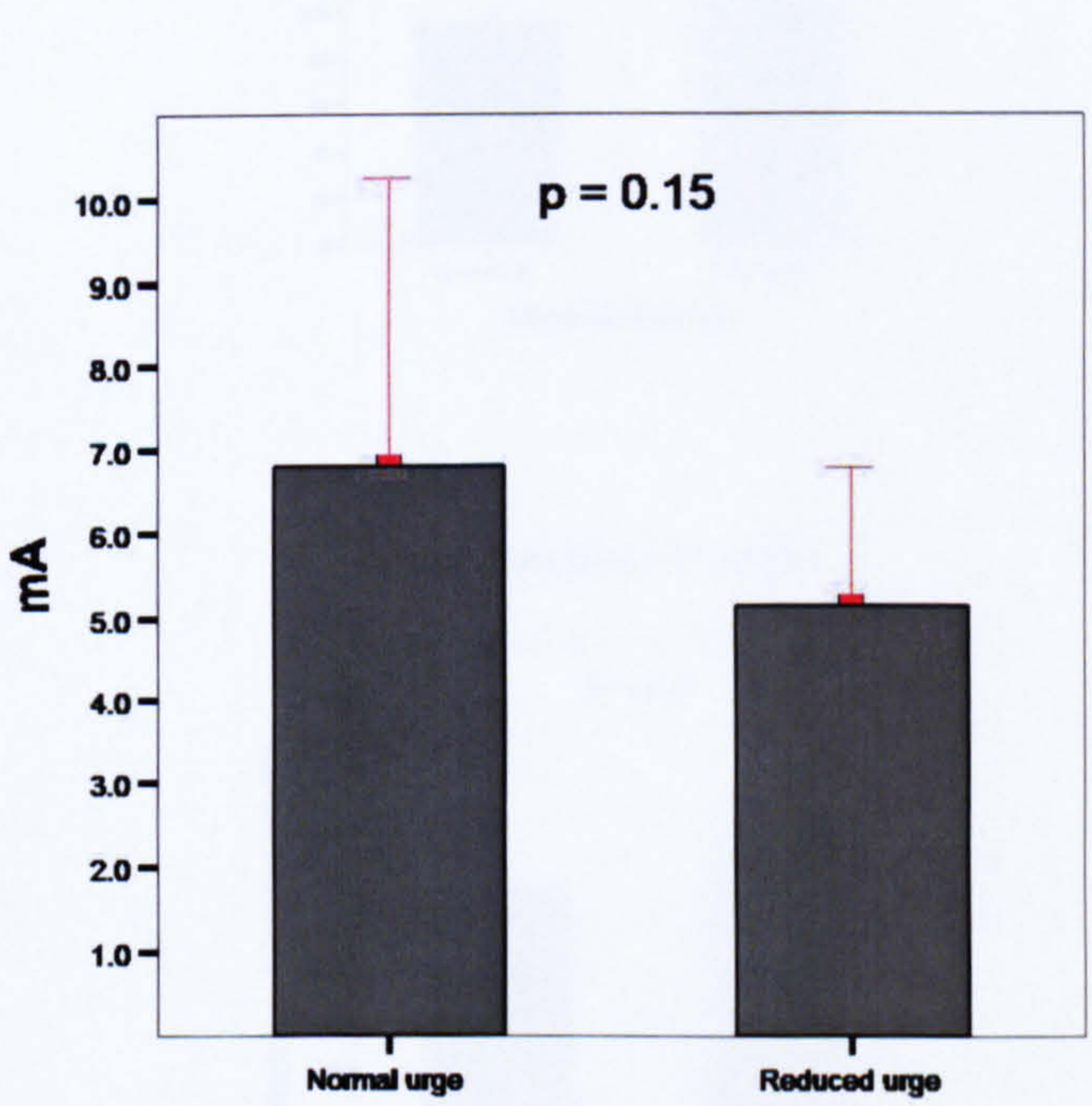


Figure 34. Right sided anal mucosal sensation.

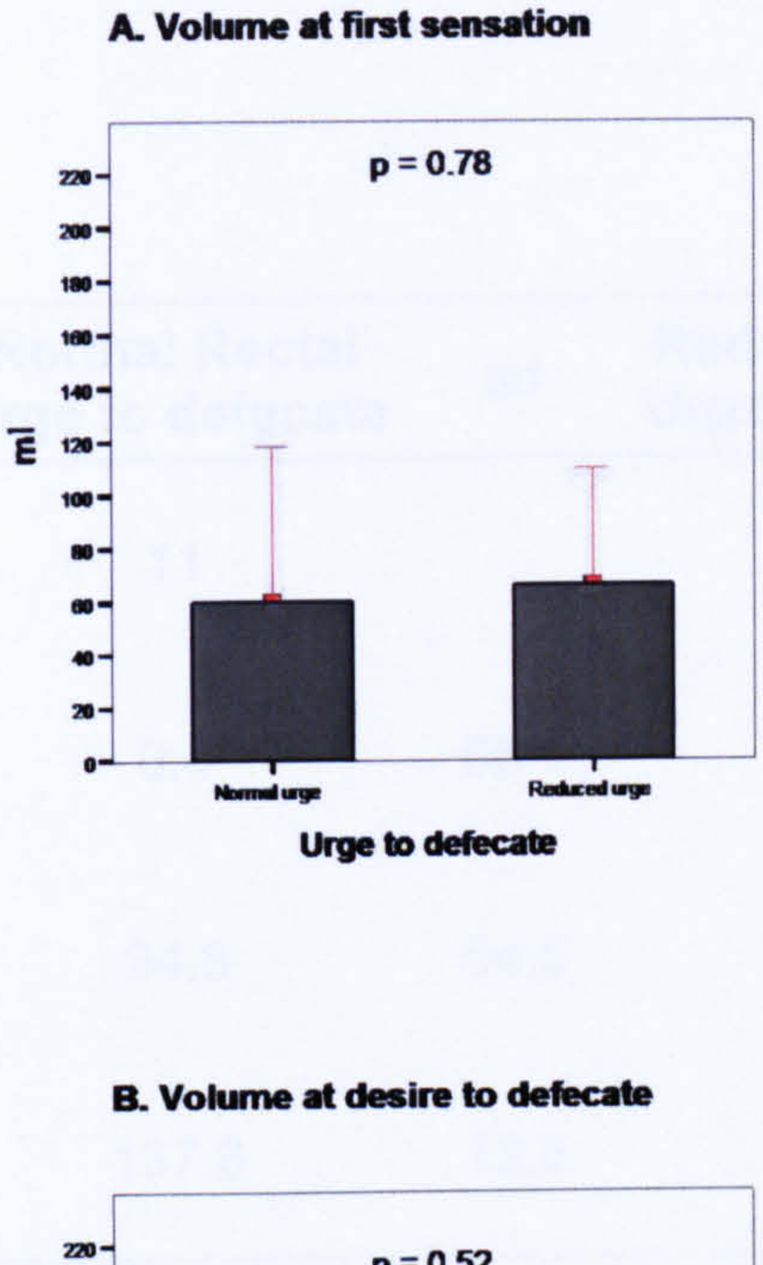


Figure 35. Rectal balloon distension in RRUD and NRUD.

	Normal Rectal Urge to defecate	sd	Reduced Rectal Urge to defecate	sd	p value
Number of patients	11		11		
Volume at first sensation	0.4	58.1	66.6	43.4	0.78
Volume at desire to defecate	94.8	54.5	108.6	43.0	0.52
Maximum tolerated volume	137.6	12.6	161.6	67.0	0.35

Table 56. Rectal sensation to distension.

Colonic transit

The mean total colonic transit for the total group was 50 hours (sd 11.9) suggesting prolonged colonic transit in the subjects compared to reference values for normal females (upper limit of normal 38.9 hours)[53].

The mean total colonic transit time was comparable in the two groups; 47.5 hours (sd 15.1) in NRUD and 52.6 hours (sd 7.5) in RRUD patients ($p = 0.33$). There were no differences between the groups with regard to right colonic, left colonic and rectosigmoid transit time ($p > 0.4$). Results of total and segmental colonic transit in NRUD and RRUD are summarised in Figure 36.

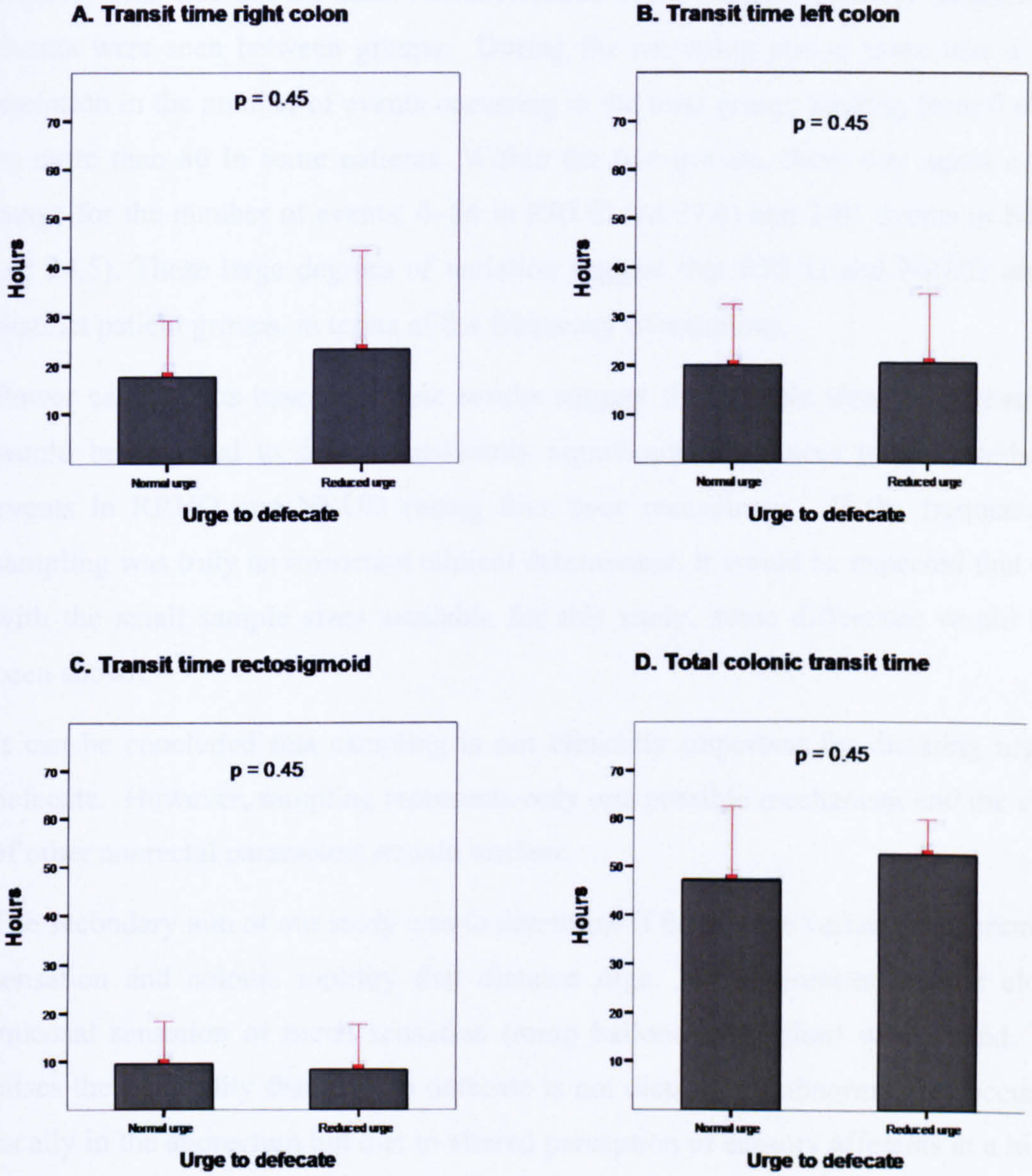


Figure 36. Colonic transit in NRUD and RRUD.

10.12 Discussion

The primary aim of this study was to confirm whether sampling was less frequent in RRUD. This was not the case. No differences in the mean number or frequency of events were seen between groups. During the recording period there was a great variation in the number of events occurring in the total group; ranging from 0 events to more than 80 in some patients. Within the two groups, there was again a large range for the number of events; 0–84 in RRUD (sd 27.6) and 2-81 events in NRUD (sd 24.5). These large degrees of variation suggest that RRUD and NRUD are not distinct patient groups, in terms of the frequency of sampling.

Power calculations based on these results suggest that sample sizes of at least 174 would be required to detect statistically significant differences in the number of events in RRUD and NRUD (using four hour recordings). If the frequency of sampling was truly an important clinical determinant, it would be expected that even with the small sample sizes available for this study, some difference would have been shown.

It can be concluded that sampling is not clinically important for dictating urge to defecate. However, sampling represents only one possible mechanism and the effect of other anorectal parameters remain unclear.

The secondary aim of our study was to determine if there were variations in anorectal sensation and colonic motility that dictated urge. No differences in anal electro mucosal sensation or rectal sensation (ramp balloon distension) were found. This raises the possibility that urge to defecate is not dictated by abnormalities occurring locally in the anorectum but due to altered perception of sensory afferents at a higher level. Positron emission tomography (PET) and dynamic MRI scanning have shown that visceral perception of bowel sensations (such as distension and pain) is associated with activation of different parts of the brain in IBS patients compared to controls [194-196]. The possibility that a reduced urge is associated with different patterns of brain activation compared to normal urge is intriguing. However, dynamic imaging comparing the two groups has not been performed.

The role of rectal sensation in urge has not been fully established and published results of sensory testing vary. In contrast to our findings, Harraf found greater

sensitivity to ramp distension in patients with rectal urge compared to those with abdominal urge [166]. No differences in sensation to phasic distension were demonstrated. Hammonds et al studied constipated patients with urge and no urge and also found increased rectal sensitivity in the urge group[191]. Although these two groups could be separated from each other by rectal sensory testing, it was more difficult to separate urge and no urge patients from controls. Hammonds et al found that 50% of urge patients were hypersensitive and 50% normosensitive compared to control values. Regarding no urge pateints, 33% were hypersensitive, 57% normosensitive and 10% hyposensitive compared to controls. In keeping with our results, Yiannakou et al found no differences in rectal sensation between reduced and normal rectal urge patients[197]. To definitively study rectal sensation in RRUD and NRUD, it will be necessary to study larger patient groups using validated distension protocols that assess reproducible endpoints and that can be compared to normative data[198].

Another factor that might influence rectal sensation and therefore urge to defecate is compliance. A highly compliant rectum may need large volumes of stool to achieve sufficient rectal pressure to activate sensory receptors. Gladman et al have demonstrated rectal hyposensitivity in patients associated with increased compliance [199]. It is possible that a reduced urge to defecate is similarly due to increased compliance. However, Mertz et al found no differences in compliance in patients with urge and patients in whom urge was rare [192]. Further study of rectal compliance and the urge to defecate would be interesting but it must be remembered that rectal hyposenitivity can occur in the presence of normal compliance suggesting that this is not the only factor that could influence the urge to defecate [199].

It was postulated that a RRUD might be associated with colonic dysmotility manifesting as prolonged total colonic transit or right sided delay. However, there were no differences in either total or segmental transit times in RRUD and NRUD patients. This finding is in keeping with the findings of Harraf et al who also found no difference in transit time in urge and non-urge patients [166]. In contrast, Mertz et al found that total colonic transit time was slower in patients with no urge compared to those with urge. They postulated that absent urge could be due to reduced delivery of stool to the rectum (occurring because of slower colonic transit) rather than

abnormalities of perception in the rectum. This suggestion was supported by the fact that they demonstrated no difference in rectal sensation in patients with normal urge or no urge[192].

It has been suggested that diminished Rectal Motor Complex (RMC) activity is a marker of colonic dysmotility in constipation[169]. RMC activity can be propulsive and it is possible that this initiates sampling by moving faeces through the rectum. It might be expected that reduced RMC activity would be associated with RRUD. In our study, RMC was observed in both groups. However, no differences were detected in terms of the duration, amplitude or interval between the RMC in the two groups. However, there are limits to the strength of the conclusions that can be drawn from the results of a 4 hour of recording. To fully test the hypothesis that rectal dysmotility (evidenced by changes in RMC) dictates urge, larger sample sizes would be required. Ambulatory manometry for at least 24 hours would be needed since it is recognised that RMC activity varies in intensity according to the time of day [200]. To assess the propulsive characteristics of the rectosigmoid, a catheter with multiple transducers fixed in the splenic flexure would be preferable to the single rectal transducer used in our study [201,202]. The development of impedance planimetry may also allow more detailed assessment of motility and the urge to defecate [60].

The above issues highlight the main limitation of our study; namely that only a 4 hour period of semi ambulatory recording was possible (using a catheter with only 2 transducers), as opposed to a 24 hour fully ambulatory recording with multiple transducers. Our use of a 2 transducer catheter was dictated by the availability of equipment. The duration of the recording was dictated by the tolerability of the semi ambulatory manometry equipment. Patients were only able to tolerate 4 hours of recording. An advantage of this was that subjects could be studied in a controlled and secure environment and that the symptom diaries of the recordings were completed comprehensively. Another limitation is that the study relates to females only. Gender issues regarding the urge to defecate have not been studied in depth.

Our results suggest that the description of urge remains static with time. At recruitment, subjects were specifically asked descriptor questions regarding their urge in the preceding three month period. During that time frame, the description of the urge to defecate (either RRUD or NRUD) was constant. Furthermore, the

description at the time of recruitment was the same as that recorded 4 weeks latter when they attended for their manometry. However, further study is required to confirm the clinical impression that the description of urge remains constant in the longer term.

We have demonstrated sampling events occurring at a frequency of 8.8 (sd 6.4) per hour in constipated individuals. Waldron et al, studying 8 patients with slow transit constipation, found sampling occurring 2.4 (sd 0.3) per hour [169] . Ambulatory solid state manometry was performed without the use of a patient diary over a 24 hour period. In their study, normal controls sampled at a frequency of 7.4 (sd 2.0) per hour. Waldron et al demonstrated a lower frequency of sampling compared to our study with a smaller standard deviation.

One explanation for these discrepant results relates to the use of patient diaries. Our experience suggests that without correlation with diaries, some events are misinterpreted as movement artefact and mistakenly ignored. It is possible that Waldron under reported events because no diary was used.

Another explanation relates to the criteria used to define sampling during analysis. Events can be identified by quantitative definitions (that use the amplitude of anal sphincter relaxation) or qualitative definitions (based on characteristic patterns of pressure change). In our study all events with characteristic pressure changes were included without the use of predetermined amplitude criteria. A quantitative approach may underestimate the frequency of sampling because small amplitude changes that still fit the descriptions of sampling are ignored. Likewise, computer analysis using definitions set by predetermined amplitudes may underestimate sampling [189]. There is an element of subjectivity associated with visual analysis using qualitative definitions. This may lead to inter observer variation and over estimation of sampling. Existing studies have used the descriptions suggested by Duthie and Miller as a broad definition of sampling [176,187]. Specific details regarding whether qualitative or quantitative definitions were also used for analysis in these studies are not clearly described. These issues may explain why discrepant results have been reported between units. For example, Ronhalt reported sampling in normal subjects as 14.5/hr whilst Waldron and Farrouk reported 7.4/hr and 4/hr respectively [169,188].

There is a need to develop agreed methods for analysis that use both quantitative and qualitative definitions of sampling. Computer analysis should not be performed alone and should be supported with visual reporting. By adopting agreed analysis protocols reproducibility between centres could be assessed and inter and intra unit variability evaluated.

On the whole we believe that our method of reporting the manometry traces is robust. We have demonstrated good intra and inter observer reliability as well as reproducibility and do not believe that the number of events has been overestimated. What is not known is whether the insertion of a manometer catheter into the anal canal and rectum will actually trigger sampling events, increasing the natural frequency. Furthermore, the question of whether the diameter or the materials used in a catheter could increase frequency by an irritant effect has not been studied. Differences in catheter design are unlikely to explain why our sampling frequency was higher than that reported by Waldron et al since the catheters were of identical dimensions and produced by the same manufacturer.

With regard to the wide range of sampling seen in this study it is not clear why one constipated patient should sample more than 80 times in the recording whilst another does not sample at all. Clearly, further study with large numbers of patients with recordings for a minimum of 24 hours compared against controls would improve our understanding of the physiology of sampling. However, this would be a great undertaking which may not produce clinically relevant findings. Further analysis of our data looking for differences between groups of patients at the extremes of the sampling range (i.e. those who sample the least and those that sample the most) would involve comparisons between small numbers of patients, such that the meaning of the results would be questionable.

10.13 Future directions

The explanation of why some patients have RRUD remains unclear. The perception of rectal urge involves a complicated pathway that has been described in section 8.3 and summarised in Figure 15. The current study results (using 4 hours of semi ambulatory recording) suggest that the frequency of sampling does not dictate urge.

Further studies are required to examine each part of the pathway to look for differences between those with RRUD, those with a NRUD. Comparison with normal controls will also be needed. Areas for future study include; rectosigmoid motility and further assessment of anorectal properties (sensation and compliance). These studies will require sufficient sample sizes to identify differences and use reproducible and validated protocols. Studies involving functional brain imaging may also be interesting.

More study could be performed, specifically examining the frequency of sampling, in constipated patients, in normal and reduced urge subjects and in normal healthy controls. However, it could be argued that using the current protocol of 4 hours recording in such studies would potentially limit the ability to examine the phenomena of sampling and motility. The duration of 4 hours was dictated by our use of semi ambulatory recording in a secure environment and the results of the tolerability study. The advantage of this was that it facilitated accurate completion of diaries. However, our experiences of this technique would suggest that in future studies, a minimum of 24 hours recording (necessitating ambulatory recording) would be preferable.

Further study of rectal motility in RRUD and NRUD may still be of value. It is recognised that poorer outcomes after colectomy and IRA are associated with pre operative anismus, proximal bowel dysmotility and elevated rectal compliance [203,204]. Despite selecting out such patients, surgery may still not be universally successful [98,170]. It is possible that some patients have persistent abnormalities of rectal function that contribute to impaired evacuation leading to persistent troublesome symptoms. If it could be shown that urge was a surrogate marker for dysmotility and reduced propulsive contractions, this could help refine selection further. Again, larger sample sizes will be required and fully ambulatory manometry for a minimum of 24 hours would be desirable.

There has been increased recognition that constipated patients can be separated into groups according to urge and that this division may reflect the presence of distinct pathophysiological processes [166,167,197]. Despite this, there has been little or no assessment of the effect of RRUD on severity, prognosis or response to treatment.

Further study of these issues will be important and may influence the design of future treatment trials.

10.14 Conclusion

A description of the urge to defecate can be used to separate constipated patients into two distinct groups, those with a normal rectal urge and those with a reduced rectal urge. This description appears to remain static with time.

The role of sampling in dictating urge was examined using semi-ambulatory simultaneous measurement of anorectal pressure. The results did not support the hypothesis that a reduced urge to defecate is caused by infrequent sampling events. To detect significant differences in sampling, unfeasibly large sample sizes would be required. Further study of the frequency of sampling in these patients is not recommended using the current technique.

Fully ambulatory recording for a minimum of 24 hours may give us the opportunity to learn more about RRUD and NRUD. Further study is also required to definitively examine the anorectum in these two groups, including assessment of rectal sensation, compliance and rectosigmoid motility.

It is possible that urge is determined by the way sensory afferent information is processed in the brain rather then because of differences in anorectal properties. This aspect has not previously been evaluated. Developments in dynamic imaging of parts of the brain involved in the sensory perception may make this possible.

The effect that RRUD has on prognosis has not been studied. This represents an important area for future work, to determine the true clinical significance of the observation that constipated patients can be separated according to their urge to defecate.

11 EVALUATION OF A NOVEL THERAPY FOR THE MANAGEMENT OF IDIOPATHIC CONSTIPATION: PERCUTANEOUS ENDOSCOPIC COLOSTOMY (PEC).

11.1 Abstract

Background: Percutaneous Endoscopic Colostomy (PEC) in the left colon is a minimally invasive endoscopic technique that can be used to irrigate the left colon and relieve constipation. The efficacy of the technique in the management of refractory idiopathic constipation has not been studied in depth.

Aim: To evaluate efficacy and safety of PEC insertion for the management of refractory idiopathic constipation. The initial step was a retrospective data collection of all patients who had PEC inserted at the unit. The results were to be used to inform the design of a prospective study.

Methods: Retrospective data collection

Results: Between 2001 and 2005, 31 patients attended for PEC. Insertion was possible in 27. Indications included idiopathic constipation, recurrent sigmoid volvulus, colonic pseudo-obstruction and neurological constipation.

Although symptoms were improved in the majority of patients and recurrent sigmoid volvulus prevented, complications were common. Infection and abdominal pain necessitated the removal of PEC in the majority of patients. Patients with refractory idiopathic constipation were particularly susceptible to these complications. Two deaths occurred due to faecal peritonitis occurring after insertion.

Conclusion: Insertion was associated with significant morbidity and mortality. Recurrent infection was a common problem necessitating removal. The findings did not support the initiation of a prospective study to assess efficacy in patients. Consequently the aim of the project could not be fulfilled.

The widespread use of PEC is not recommended and insertion should be restricted to specially selected cases.

Percutaneous Endoscopic Colostomy (PEC) of the left colon is effective at preventing sigmoid volvulus and treating symptoms of constipation but insertion is associated with morbidity and mortality. S Cowlam, C Watson, M Elltringham, I Bain, P Barrett, S Green, Y Yiannakou Gastrointestinal Endoscopy, 2007, 65(7):1007-14	
Data collection	SRC
Data entry	SRC
Data Analysis	SRC (advice from TH)
Data interpretation	SRC, YY

11.2 Overall aims

The overall aim of the study was to evaluate the efficacy and safety of PEC in the left colon to treat patients with idiopathic refractory constipation. The initial step was a retrospective data collection of all patients who had undergone PEC insertion.

It was intended that the results of this assessment would inform the feasibility of a prospective study of the effectiveness of PEC. However, the findings suggested that a prospective study in patients with refractory idiopathic constipation was not feasible.

11.3 Design

The prospective study of PEC was to involve constipated patients meeting inclusion and exclusion criteria. Subjects were to be recruited from a dedicated clinic dealing with constipated patients. The primary endpoint for assessing efficacy was to be colonic transit time pre and post insertion of PEC. Previous unpublished data from the unit had shown that colonic transit was reduced on average by 24 hours following insertion. This result was used in a power calculation to determine sample size. A conservative assumption was made that following insertion would be a reduction of transit time by 10 hours. Therefore, 28 patients would need to be assessed pre and post insertion to give 80% power at 5% significance to detect a difference in colonic transit after PEC.

Secondary endpoints were to be symptom severity assessed using the Patient Assessment of Constipation – Symptoms (PAC-SYM)[125] and a subjective global assessment made by both patients and clinician. Quality of Life was to be evaluated pre and post insertion using the Patient Assessment of Constipation – QOL (PAC-QOL) questionnaire[119]. Assessments after insertion were to occur at 1, 3 and 6 months.

11.4 Introduction

Percutaneous Endoscopic Colostomy (PEC) is a minimally invasive endoscopic procedure in which a plasticised tube is inserted in the left colon. Through this, the bowel can be irrigated or decompressed. Percutaneous insertion of a tube into the colon has in the past been undertaken radiologically [205,206]. In 1986 Ponsky et al described an endoscopic technique in the caecum; Percutaneous Endoscopic Caecostomy [207]. Endoscopic methods have also been used for insertion in the left colon, where the technique has been termed PEC; Percutaneous Endoscopic Colostomy [208-211]. PEC has been used to treat a variety of conditions including colonic pseudo-obstruction, functional constipation and patients with constipation and faecal incontinence caused by neurological disorders [209-213]. PEC insertion has also been used to fix the sigmoid colon to the abdominal wall in recurrent sigmoid volvulus, so offering an alternative to surgical sigmoidopexy or resection [213-216].

11.5 Historical perspective

The formation of a conduit into the colon can be undertaken percutaneously by radiological and endoscopic means or directly by surgery. Traditionally the site for undertaking such procedures was the caecum.

Malone described a surgical procedure in which a conduit was created by appendicocaecostomy fashioned in such a way to prevent reflux[93]. Through this irrigation could be performed and the concept of antegrade colonic enema (ACE) irrigation was developed. Percutaneous insertion using conscious sedation and radiological techniques have also been performed. Casola et al used Computed Tomography (CT) guidance to perform percutaneous caecostomy in colonic pseudo-obstruction in 1986[205]. More recently, Chait et al reported the use of fluoroscopy for the procedure [217].

In 1986 Ponsky described an endoscopic method for insertion in the caecum that was termed Endoscopic Percutaneous Caecostomy [207]. Further case reports followed[218,219]. Ganc et al used a gastrostomy tube to create the caecostomy[218]. Insertion was under direct vision. The technique had an advantage over the

radiological approach because the problem of inadvertent insertion into the terminal ileum could be avoided.

Following on from these early attempts in the right colon, endoscopic methods have been used for insertion in the left colon, where the technique has been termed PEC; Percutaneous Endoscopic Colostomy. Review of the existing literature suggests that percutaneous endoscopic insertion in the left colon (including left and right colon) has been performed in approximately 80 adults and 33 children (Table 57, Table 58, Table 59, Table 60).

Author & institution	Design	Indication	Patient numbers	Age years	Outcome	Follow up
Ganc, AJ[218] 1988 SP,Brazil	Case report of Transcolonoscopic extraperitoneal cecostomy	Acute Colonic pseudo-obstruction	1	-	Radiological and symptomatic resolution	-
Salm R[219] 1988 Frieburg, Germany	Case series Endoscopic percutaneous cecostomy (EPC).	Acute Colonic pseudo-obstruction	2	-	Radiological and symptomatic resolution	-
Wills JC[220], 2003 Salt Lake city,USA	Case report of Percutaneous Endoscopic Caecostomy	Chronic constipation due to malignancy with spinal cord metastases and opiate medication	1	36	Improved symptoms Death due to progressive malignancy	3 weeks
Ramage JI[221], 2003 Mayo clinic, USA	Retrospective series of Percutaneous Endoscopic Caecostomy	Chronic Constipation due to neurological conditions and Acute colonic pseudo-obstruction	5	59 mean	Improvement of symptoms	mean 6.6 months
Uno Y[222], 2006 Muroran Japan	Retrospective series of Percutaneous Endoscopic Caecostomy	Chronic colonic pseudo-obstruction (n=1) Neurological constipation (n=14) Acute colonic pseudo-obstruction (n=5)	20	67 mean	Improvement of symptoms	-

Table 57. Published reports regarding Percutaneous Endoscopic Caecostomy in adults

Author & institution	Design	Indication	Patient numbers	Age years	Outcome	Follow up
Daniels IR[211] 1999 Chichester, UK	Case report of PEC	Chronic constipation Faecal incontinence due to MS	1	46	Symptom resolution	-
Brown SR[208], 2000 Sheffield,UK	Retrospective series of PEC	Acute Colonic pseudo-obstruction	2	72 mean	Radiological and symptomatic resolution	12 months
Daniels IR[214], 2000 Chichester, UK	Retrospective series of PEC	Recurrent sigmoid volvulus	14	78 mean	No recurrence n=8 Recurrence after early removal n=3	mean12.6 months
Heriot AG[209], 2002 Chichester, UK	Case report of PEC	Obstructed defecation	1	52	Symptomatic resolution	6 months
Davis BQ,[212] 2003 Chichester UK	Retrospective series of PEC	Chronic constipation Faecal incontinence due to neurological disease MS n=6 Other n=3	9	38-72	Improved Wexner incontinence score, improved QOL, reduced toilet time, reduced laxative use	2-40 months
Thompson RA[210] 2004 Chichester, UK	Retrospective series of PEC	Chronic Colonic pseudo-obstruction	3	54 mean	Symptomatic resolution	5weeks – 2.5 yrs
Baraza et al[223], 2007 Sheffield, UK	Prospective series of PEC	Chronic Colonic pseudo-obstruction, Recurrent sigmoid volvulus, Idiopathic constipation	19	–	Symptom resolution in CPO & control of RSV	Median 35 months

Table 58. Published reports regarding Percutaneous Endoscopic Colostomy (PEC) in adults

Author & institution	Design	subjects	Age	Indication	Outcome	Follow up
Rivera MT[224] et al, 2001 Wisconsin, USA	Retrospective series of Percutaneous Endoscopic Caecostomy	12 children	17months to 22 years	Chronic constipation Faecal soiling	Improved bowel management in all patients	Average FU 13 months
De Peppo F[225] 1999 Rome, Italy	Retrospective series Percutaneous Endoscopic Caecostomy	3 children	-	Faecal incontinence	Complete control of defecation in all patients	-

Table 59. Published reports regarding Percutaneous Endoscopic caecostomy in children

Author & institution	Design	subjects	Age	Indication	Outcome	Follow up
Rawat DJ[226] et al, 2004 London, UK	Retrospective series of PEC	14 children 12 boys, 2girls	Median 5.5 yrs	Refectory constipation Faecal soiling	Improved QOL at 2 months No faecal soiling at 12 months	Median FU 12.5 months
Guaderer MW[227], 2002 Greenville USA	Retrospective series of PEC	4 children	-	Chronic evacuation disorders	Improved symptoms and ability to evacuate	-

Table 60. Published reports regarding Percutaneous Endoscopic Colostomy (PEC) in children

11.6 The technique of Percutaneous Endoscopic Colostomy in the left colon

The approach favoured by most operators is full bowel preparation 24 hours before insertion. Intravenous antibiotics are administered before the procedure as prophylaxis against infection. The procedure is performed under conscious sedation. Colonoscopy is performed to identify a site for insertion. This site is the point of maximal transillumination and indentation on the abdominal wall suitable for placement of the tube. The area is infiltrated with local anaesthetic. A Seldinger needle is passed through the abdominal wall and its entry into the lumen of the colon observed endoscopically. A guide wire can then be passed grasped by a polypectomy snare. The guide wire is then pulled through the anus by withdrawing the colonoscope. The PEC tube is attached to the guide wire and pulled through the abdominal wall via the anus. This method is termed the "pull through" technique.

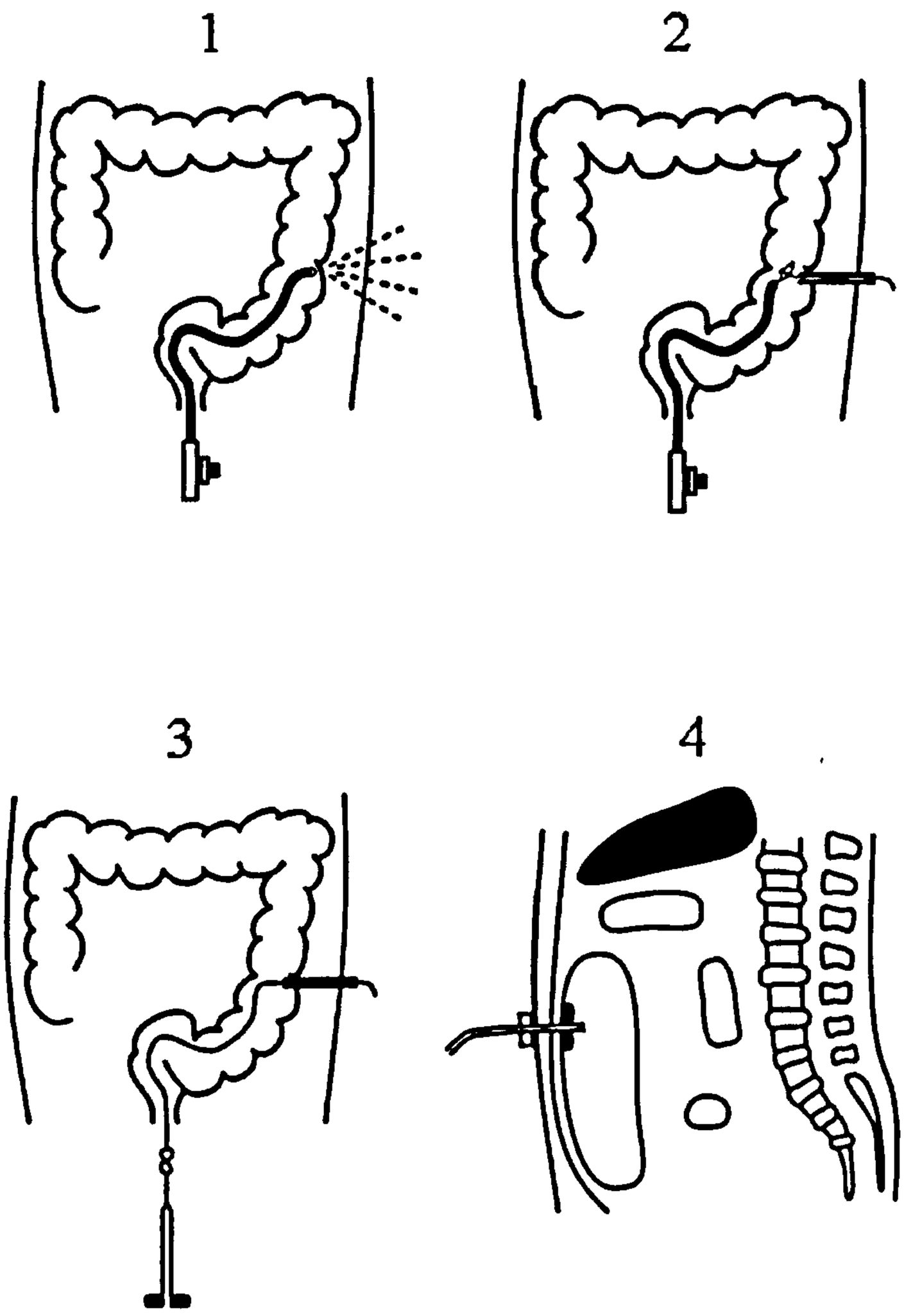
The type and diameter of tube is dictated by the clinical situation. Typically, 20 Fr gastrostomy tubes (Merck Pharmaceuticals, UK) or specifically designed 12 Fr PEC tubes (Merk Pharmaceuticals, UK) are used. The latter tubes utilise a plasticised guide wire to reduce the risk of "cheese wiring" the colon and abdominal wall during "pull through". In addition, the diameter of the internal bumper (or bolster) is increased in comparison to standard tubes to reduce the risk of the bumper becoming buried in the colon wall.

The colonoscope is reinserted to check the position of the internal bumper and adjust the tension on the tubing. Finally, the tube is attached to the abdominal wall to avoid inadvertent dislodgement. Patients are generally admitted after the procedure for observation and antibiotic therapy continued. Figure 37 shows schematic diagrams illustrating the technique. Figure 38 shows images taken during PEC insertion.

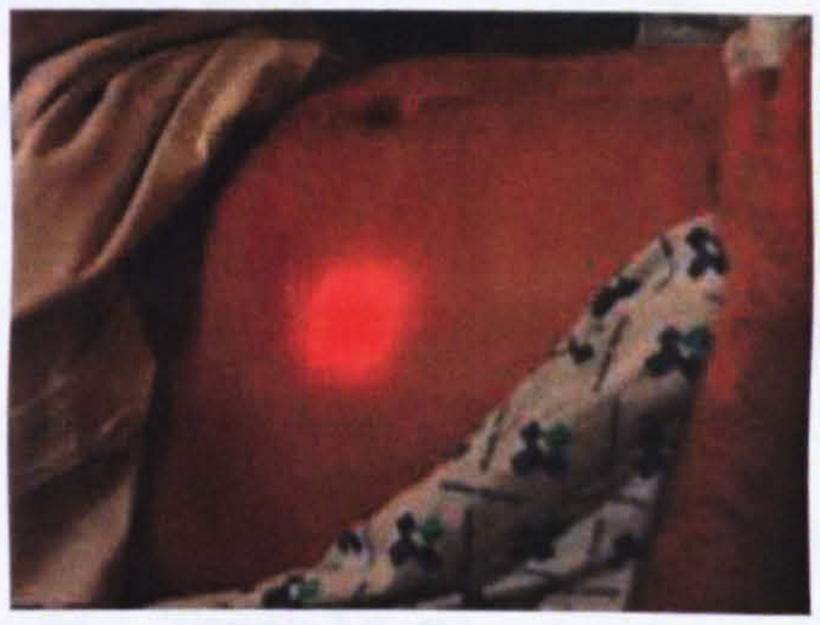
The "pull through" technique has been used for insertion in both the right and left colon. An "introducer" method of percutaneous endoscopic caecostomy insertion has also been described [222].

Figure 37. Schematic diagrams of the technique for PEC insertion

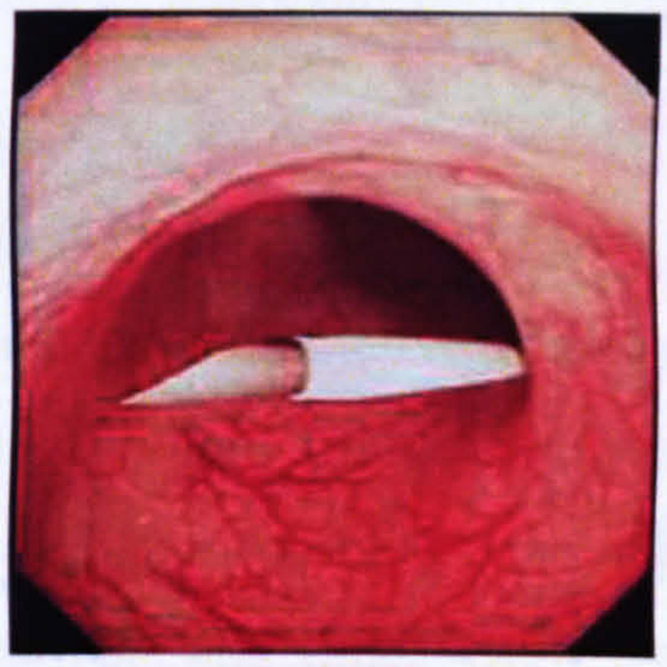
1. Colonoscope passed into left colon. Seldinger needle inserted into left colon (under colonoscopic vision). 2. Guide wire passed through Seldinger needle into left colon and grasped with polypectomy snare. Colonoscope is withdrawn so that the guide wire is pulled out through the anus. 3. PEC tube attached to the guide wire and pulled back into the left colon. 4. PEC tube fixes left colon to the inner surface of the abdominal wall and held in place by the internal and external bolsters.



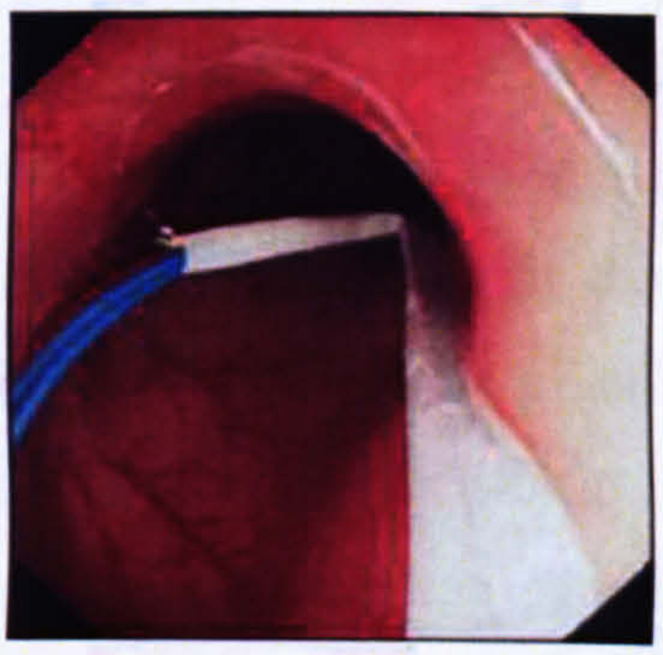
Insertion site demonstrated by maximal transillumination.



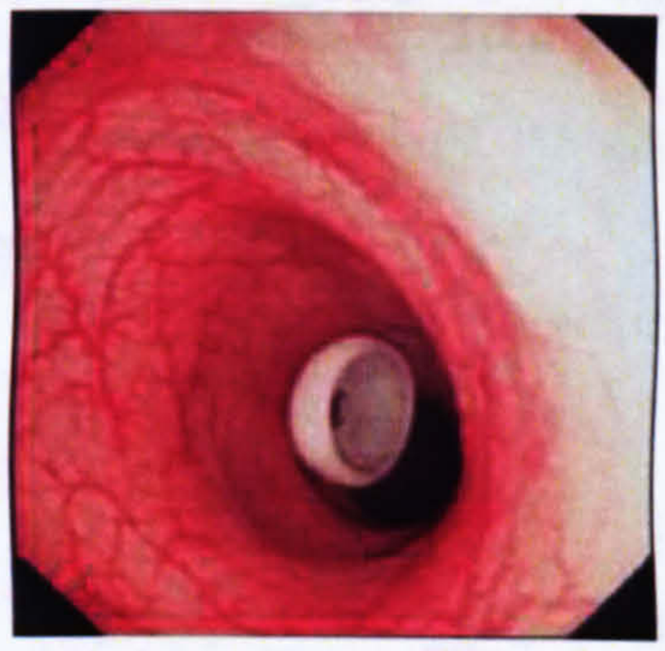
18-gauge Seldinger needle passed into lumen of the colon.



Guide wire passed into the lumen of the colon.



Position of the internal bolster checked endoscopically



PEC tube secured to the abdominal wall

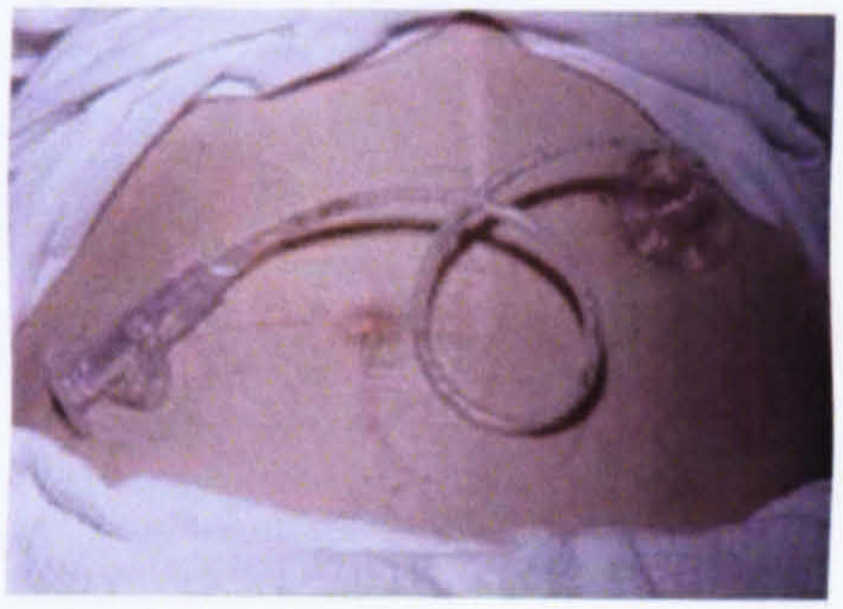


Figure 38. Images of PEC insertion.

11.7 PEC and the management of recurrent sigmoid volvulus

Sigmoid volvulus is a potentially life-threatening condition that may occur in elderly patients who often have other comorbidities. An overall mortality of 7% has been reported[228]. Decompression by colonoscopy can be performed but maybe associated with a recurrence rate of approximately 40%. A mortality of 10% has been observed for operative reduction. In the presence of colonic ischaemia mortality can rise to 60%[229]. PEC provides an alternative to surgical intervention in a potentially high-risk, frail and elderly population.

Daniels et al [214] reported on 14 patients with a mean age of 78 years with recurrent volvulus. Colonoscopy was performed to reduce the acute volvulus and PEC was inserted. Two tubes were used to fix the sigmoid to the inner surface of the abdominal wall (inserted in the proximal and distal sigmoid). There were no deaths associated with the procedure. In five patients the tubes were left in situ and volvulus did not reoccur (mean follow up 12.6 months). Tubes were removed at an early stage in 8 patients; in 3 of these volvulus reoccurred. It was concluded that PEC was safe and effective for treating RSV and had a role in those patients in whom "conventional surgery was considered unsafe or inappropriate". Baraza et al reported on 19 patients with recurrent sigmoid volvulus in whom there were no further episodes of volvulus with tubes in situ. In 6 of these patients tubes were removed between 5 and 26 months with no subsequent recurrence[223]. The authors again concluded that PEC had a role for the management of RSV particularly in patients who were unfit for surgical intervention.

11.8 PEC and the management of colonic pseudo-obstruction

Colonic pseudo-obstruction describes a clinical syndrome characterised by clinical and radiographic appearances suggestive of mechanical obstruction of the colon but where no physical obstruction can be demonstrated. Acute colonic pseudo-obstruction; often termed Ogilvie's syndrome[230] can be associated with systemic conditions (metabolic derangements, systemic infection, electrolyte disturbance, trauma or surgery)[231]. The chronic form may be a feature of intestinal pseudo-obstruction. In this pan-intestinal disorder neuropathic or myopathic changes in the bowel wall can occur as a primary illness or in association with other conditions (scleroderma, bronchial carcinoma and amyloidosis) as a secondary phenomena [232]. The most feared complication of acute pseudo-obstruction is caecal perforation. Conservative and supportive treatments may not be effective. Prokinetics including neostigmine have been used with variable results [233-236]. Decompression by colonoscopy can be considered but the rate of recurrence ranges from 20% to 40% [236,237]. Furthermore, colonoscopy in the presence of pseudo-obstruction, is associated with an increased risk of perforation and complications [235]. Surgical caecostomy or colectomy may be indicated in cases of emergency perforation or threatened perforation. Surgery is however associated with significant mortality rates of between 26-36% [238].

Treatment of chronic intestinal pseudo-obstruction is difficult with no guarantees of success. Overall, the effect of medical treatment is disappointing. Surgical options for managing chronic CPO include resection, stoma formation or decompression with enterostomy tubes. However, after reviewing the prognosis and response to treatment in 20 patients Mann et al concluded that the role of surgery was poorly defined. The authors suggested that the main aims of management included avoiding unnecessary surgery, symptom control and commitment to the long-term care of patients[239]. Percutaneous Endoscopic Colostomy of the left colon can be used to provide decompression in both acute and chronic CPO. PEC offers an alternative to surgery.

Acute colonic pseudo-obstruction

Brown et al, reported their experience of using PEC to treat acute CPO[208]. They presented two cases. The first was a retired miner with severe Chronic Obstructive

Pulmonary Disease who suffered episodes of recurrent abdominal distension. Conservative management was successful in the initial episodes but subsequent presentations required colonoscopic decompression. On the final admission PEC was inserted in the sigmoid colon. This allowed decompression of the bowel. The patient remained symptom-free and avoided re-admission during a 12 month follow up period. The second case was 73-year-old patient with ischaemic heart disease. Ten days following aortic valve replacement and coronary artery bypass grafting, they developed CPO. Repeated colonoscopic decompression was unsuccessful. PEC was inserted, allowing decompression of the bowel. The tube was removed 28 days later and the patient remained well at three months.

The "pull through" technique was used to perform percutaneous endoscopic caecostomy in 5 patients with acute CPO in a Japanese series [222]. Decompression was achieved in these patients but the duration that tubes were in situ was not stated.

Chronic colonic pseudo-obstruction

Thompson et al[210], reported three consecutive cases of chronic CPO treated with PEC. In all cases, diagnosis of chronic colonic pseudo-obstruction was confirmed by contrast enema and treatment had included flatus tube. After PEC placement in the left colon, all three patients noted symptom improvement. In each case PEC allowed decompression of the colon and relieved symptoms of bloating and discomfort. There were no PEC related complications in any of the cases. The period of follow-up ranged from five weeks to 2.5 years. Four patients with CPO were studied prospectively by Baraza et al. These patients with a median age of 75 had not responded to medical management. Three had a satisfactory result with resolution of symptoms[223]. Both sets of authors concluded that PEC is an effective treatment in selected patients with chronic CPO.

11.9 PEC and the management of constipation and faecal incontinence

Chronic constipation and faecal incontinence are significant problems for clinicians, patients and carers. These conditions can have a detrimental effect on the physical, social and psychological well-being of patients with significant impairment of quality of life. Although many patients can be treated successfully with laxative therapy, some do not respond. Behavioural therapy with biofeedback and rectal irrigation has been used with variable degrees of success to manage these conditions[240,241]. Experience with sacral nerve stimulation is so far limited to relatively small numbers [242]. In patients who do not respond, surgical intervention can be considered. The type of surgery is dictated by the cause of the chronic constipation. The functional results of rectocoele repair and internal anal sphincterotomy can vary with no guarantee of long-term success [243,244]. Subtotal colectomy and ileorectal anastomosis is accepted as a definitive procedure for managing slow transit constipation. Functional improvement of up to 90% has been reported[245]. Further detailed long-term follow up is required to fully appreciate the role of invasive surgery in patient management. However, for patients with proximal intestinal dysfunction and slow colonic transit or patients with obstructed defecation such surgery is unlikely to be beneficial. Irrigation via an appendicocaecostomy – antegrade colonic enema (ACE) – is another surgical option. Although encouraging long term results are reported [246] the procedure is again, invasive and requires general anaesthesia. The long length of colon that must be irrigated could theoretically compromise the efficacy of ACE. This maybe of relevance in those patients with predominantly left sided colonic dysfunction [247,248]. It is plausible that antegrade irrigation of the left colon via PEC would be beneficial in these cases. Furthermore, PEC offers a less invasive, reversible alternative to colectomy and ileorectal anastomosis or ACE procedure.

Herriot et al reported on the case of a 52-year-old woman with a chronic history of obstructed defecation in whom standard treatment had failed[209]. The patient refused a colostomy. PEC was inserted in the descending colon using conscious sedation and irrigated with one to two litres of water twice a day. She was able to evacuate within 10 minutes and had no further abdominal pain. The original 14 French gastrostomy tube (Freka, Frenius, UK) was replaced with a flat Mic-key tube (Vygon, UK). The

patient remained asymptomatic at six months. Baraza et al treated 10 patients with slow transit constipation but had variable success with the procedure with three patients choosing to have their tubes removed and return to conservative treatment[223].

11.10 PEC and the management of incontinence and constipation in adults with neurological disease

Severe bowel dysfunction with intractable constipation and or faecal incontinence is common in neurological diseases such as multiple sclerosis, spinal cord injury or cerebrovascular disease[249,250]. As in idiopathic constipation, conservative treatments are not always successful.

Options for intractable disease unresponsive to conservative therapy include ACE procedure[251,252], sacral nerve stimulation[253] or colostomy formation[254]. The inherent risks of surgery and general anaesthesia exist with no absolute guarantee of success.

Daniels reported on one patient with MS who was treated by PEC for her refractory constipation[211]. Following discharge the patient's carers irrigated the sigmoid colon on alternate days to remove faeces. The irrigation took approximately 20 minutes to perform and improved the patient's quality of life by removing the incontinence and easing the distressing symptoms of constipation.

Davis et al, reported on a series of nine patients, age 38-72 years with severe neurological disease[212]. Six of the patients were suffering from multiple sclerosis. Symptoms included severe constipation and faecal incontinence. After insertion the subjects were followed up for a period ranging from two to forty months. All reported significant improvement in their Wexner incontinence score, reduction in use of bowel regulating medications, reduction in toilet time and improved quality of life. The combined experience of several centres in the use of PEC for the management of faecal incontinence caused by central neurological disease has been reported as an abstract[255]. Twenty six patients aged between 7 and 86 years were studied. Nine patients suffered from MS, seven with spina bifida, four with tetraparesis, three with parkinsonism, one with Alzheimer's disease, one motor neurone disease and one patient suffered from dystonia. Eighty five percent of

patients had good outcome with PEC. There was improvement of incontinence score using irrigation on alternate days. Two patients did not benefit from PEC and underwent surgery.

11.11 Percutaneous Endoscopic Colostomy in children

Rawat et al, reported on a series of 15 children who underwent PEC procedure for the management of refractory constipation and concurrent faecal incontinence[226]. PEC was inserted into the left colon using the "pull through" technique. In contrast to the adult population, the procedure was performed under general anaesthesia. Following insertion, washout of the distal colon was performed with water (and enema if necessary).

The outcome measure to assess response was a "clean score". This recorded the state of daily soiling between spontaneous or washout induced evacuations. At two-month follow up all 13 patients reported significant improvement in their continence. The PEC was tolerated well by the children and parents. Rivera et al, similarly treated children with chronic constipation and faecal soiling caused by neurological handicaps. Average follow-up was 13 months. All patients and families were pleased with the PEC. The authors concluded that PEC was a safe and effective method for treatment of intractable constipation. They recommended the procedure for selected patients with spina bifida, spinal cord injury, anorectal abnormalities and severe neurological handicaps[224].

11.12 Percutaneous endoscopic caecostomy

Following the early case reports concerning percutaneous endoscopic ceacostomy [207,218,219], two case series have been published. Ramage presented 5 patients (3 with neurological constipation and 2 with acute colonic pseudo-obstruction) in whom there were improvement in symptoms. The mean follow up was 6.6 months. Uno presented 20 patients in whom percutaneous endoscopic caecostomy was performed. This series included 15 patients with neurological constipation in whom an "introducer technique" was used. Here, the caecum was identified by transillumination. Under endoscopic visualisation, the caecum was pierced by a

double needle suturing device. The caecum was secured to the abdominal wall by three retention sutures arranged in a triangular formation. In the centre of this the caecum was pierced by an introducer that allowed the stoma to be formed. This was kept patent by a plasticised catheter. In 9 of these, conversion to a low profile Chait Trapdoor Caecostomy Catheter (CTCC) [217] was performed. These patients were reported as having improvement of their constipation with a mean follow up of 8.8 months. Uno reported lower rates of infection in patients with CTCC inserted by the "introducer technique" compared to the 5 in whom caecostomy was fashioned using the "pull through" technique [222].

Both Rivera and Depeppo have used the "pull through" technique for insertion of percutaneous endoscopic caecostomy in children with defecatory difficulties with good results [224 225].

11.13 Complications of Percutaneous Endoscopic Colostomy

Overall, the literature suggests that PEC is a low risk procedure with few serious complications reported. However, small patient numbers and variable periods of follow up mean that the accurate assessment of complications is limited. Several complications have been reported in the adult and paediatric literature and are summarised in Table 61 and Table 62.

Complications of PEC insertion in the adult population

In the management of RSV, recurrence was observed in those subjects who had PEC removed[213,214]. In the series reported by Daniels, the PEC tube was removed at six weeks in three cases and this led to recurrence. At laparotomy in these patients, no residual fixation of the colon to the abdominal wall was seen. It would appear that in some patients, a period of time (more than six weeks) is required before the colon adequately adheres to the abdominal wall. This process is likely to be incomplete if removal is too early. However in 10 of their patients (including five who had PEC removed at six weeks) no complications or recurrence were reported. Baraza et al found PEC to be effective at controlling RSV but encountered an episode of fatal PEC related peritonitis caused by tube migration and faecal contamination[223].

Brown et al, reported no complications in two patients treated with PEC for acute CPO[208]. One patient however had a relatively short follow-up period of three months and PEC was only in situ for one-month. It would appear that the tube was removed because of resolution of symptoms rather than the onset of complications. The other patient was followed up for 12 months.

With regard to PEC insertion in chronic CPO, Thompson encountered no complications in three patients with a follow up ranging from five weeks to 54 months[210]. In contrast, Baraza et al encountered peritonitis in a patient with CPO that necessitated tube removal and laparotomy, bowel resection and end sigmoid colostomy[223].

Daniels found no complications in a patient with MS, although follow up was limited (one month)[211]. In a larger series of 7 neurological patients, the only problem encountered was a patient who developed pressure sores whilst sitting on the commode when irrigating the PEC. Although the PEC improved symptoms the

patient elected to convert to ileostomy. Infections at the site of insertion were not reported in any of the cases[212].

Faecal leakage from the insertion site was reported at six weeks in a patient with obstructive defecation[209]. This was managed successfully by conversion to a low profile button tube (flat Mic-Key tube, Vygon, UK).

Complications of PEC insertion in the paediatric series

Outcomes and complications associated with the PEC insertion in the paediatric group are summarised in Table 62. Rawat encountered several minor complications[226]. These included granuloma formation at the insertion site, abdominal pain associated with enema and local tract infection. The infections were treated successfully with five days of antibiotics. The number of patients affected was not reported. A major complication occurred in one patient whom sepsis occurred post procedure. This necessitated removal of the tube and colostomy was subsequently performed. In one case, PEC was not possible because of failure to identify an insertion point.

In the series by Rivera et al, several complications were reported. One patient who had previously undergone surgical intervention for Hirschsprung's disease developed enterocolitis nine days after insertion. Pressure necrosis from the external bolster occurred in another. This was due to abdominal distension but was treated successfully by venting the colon via the PEC. Urinary tract infection occurred in one case, seizures in one and fever (with negative blood cultures), abdominal distension and pain in another. Five children in the series developed granulation tissue around the stoma. This was managed with silver nitrate and topical steroid cream. None of these complications led to PEC removal. One patient suffered an unrelated death at nine months because of deterioration of their original illness[224].

Author & institution	Indication	Number	cases	Complication	Outcome	Duration PEC in situ	Follow up
Brown SR[208], 2000Sheffield,UK	Acute Colonic pseudo-obstruction	2		Nil	-	1-3 month	12 months
Thompson RA[210] 2004Chichester, UK	Chronic CPO	3		Nil	-	5 weeks -54months	Max 54 months
Heriot AG[209], 2002 Chichester, UK	Obstructed defecation	1	I case	Faecal leakage at 6 weeks	low profile "button" inserted	6 months	6 months
Daniels IR[214], 2000 Chichester, UK	RSV	14	5 cases	Nil	-	12.6 months	12.6 months
			5 cases	Nil	-	6 weeks	12.6 months
			3 cases	Recurrent volvulus after removal	Not reported	6weeks	6 weeks
			1 case	Accidental removal by patient	Sigmoid resection	24 hours	24 hours
Daniels IR[211] 1999 Chichester, UK	Constipation & faecal incontinence due to MS	1	1 case	Nil	-	1 month	1 month
Davis BQ[212], 2003 Chichester UK	Chronic constipation Faecal incontinence due to neurological disease MS n=6 Other n=3	9	7 cases	Nil	-	20-40 months	20-40 months
			1 case	MI 40 months after PEC	Death	40 months	40 months
			1case	Pressure sores from sitting on commode whilst performing washout	ileostomy requested by patient	Not reported	Not reported
Ramage JI[221], 2003 Mayo clinic, USA	Neurological constipation Acute CPO	5	3 cases	Nil	-	6-12 months	6-12 months
			1 case	Leakage / fever	Resolved with antibiotics	5 months	5 months
			1 case	Bleeding	Anticoagulation stopped	2 months	2 months
Baraza et al[223], 2007 Sheffield UK	RSV, Constipation, chronic CPO	19	3 cases	Faecal peritonitis	1 death	28 days to 29 months	Median follow up for whole group 35 months
			1 case	Tube migration	-		
			6 cases	Site infection	Removal =1 case		
			1 case	Buried bumper	-		

Table 61. Reported complications of adult Percutaneous Endoscopic Colostomy (PEC) in the left colon

Author	Indication	number	cases	Complication	Outcome related to complication	Duration PEC in situ	Follow up
Rivera MT et al[224], 2001 Wisconsin, USA	Constipation and encopresis or encopresis alone	12	1 case	Urinary tract infection	-	Not reported	
			1 case	Seizures	-	Not reported	Not reported
			1 case	Fever, abdominal pain and pain	Resolution after five days	Not reported	
			1 case	Died at 9 months after insertion	Unrelated death	Nine months	9 months
			1 case	Pressure necrosis from external buffer	Resolution with antibiotics	Not reported	Not reported
			5 cases	Granulation tissue around stomas	Resolution Silver nitrate and steroid cream	Not reported	Not reported
Rawat DJ et al[226], 2004 London, UK	Chronic constipation and faecal incontinence	15	1 case	Procedure abandoned due to technical difficulties identifying insertion point	Laparoscopic PEC	-	Not reported
			1 case	Major complication: Sepsis	Surgical colostomy	Not reported	Not reported
			not stated	Minor complications: Granuloma, Local tract infection, Abdominal pain with enema	Not reported	12.5 months	12.5 months

Table 62. Reported complications of paediatric Percutaneous Endoscopic Colostomy (PEC)

Complications related to conscious sedation and colonoscopy

Patients undergoing PEC insertion are at risk of the cardiovascular and respiratory complications associated with conscious sedation. Colonoscopy is integral to insertion and the risk of perforation therefore exists. In cases of acute CPO, the risk of perforation may be higher than that expected in purely diagnostic procedures.

Complications occurring at the site of insertion

The procedure requires the participation of experienced endoscopists because it is essential to confidently identify a safe insertion point. It is critical that the risk of transfixing overlying bowel during insertion is minimised. This can be achieved by using endo luminal landmarks, digital indentation and transillumination through the abdominal wall. Fluroscopic screening with an image intensifier can also be used.

A degree of leakage of bowel contents is to be expected at the time when the colon wall is pierced. Such leakage is likely to cause a localised peritonitis for the first 24-48 hours following insertion. It could be argued that the "introducer" method used for endoscopic caecostomy (as described in section 11.12) reduces this leakage since the loop of bowel already secured by sutures to the inner wall before it is pierced to allow insertion of the tube.

Infection at the site of insertion is a recognised complication. This may be associated with leakage of bowel contents that are not sterile. Infection may occur soon after insertion (days to weeks) or may arise later (months). Data are lacking regarding the long-term incidence of infection whilst PEC is in situ or the effect that these episodes have on prognosis after removal. The culprit organisms are not reported although it can be assumed that gut organisms and skin commensals are likely to be involved. In the paediatric series by Rawat, one case of tract infection was identified. This was classified as a minor complication and antibiotic treatment was successful. In addition, there was another case of significant sepsis that necessitated tube removal. This patient proceeded to colostomy. It is unclear whether this was as a result of the septic episode or whether the decision to proceed was made electively. Baraza et al encountered site infection in 6 patients (although it was not reported whether this was recurrent episodes of infection or merely one episode). In all but one of these patients infection settled with antibiotics. In the remaining subject, tubes were removed as a consequence of infection[223].

Granuloma formation was reported frequently in the paediatric population. The factors that predispose to granulation are unknown but adequate toilet of the insertion site may help prevent this problem. Faecal leakage occurring even after PEC has been established for some time has been reported[209]. Management was achieved by replacing the original tube with a low profile device. The practice of replacing the original tube is reported by several authors but the timing of replacement varies between institutions.

11.14 Current guidelines for the insertion of PEC

The National Institute for Health and Clinical Excellence issued guidance for the use of PEC procedure in March 2006. This includes an overview of the indications, efficacy and safety profile of the technique. The primary indications recognised were treatment of RSV and CPO[256]. The document includes recommendations for patient preparation, the procedure for insertion ("pull through" technique) and immediate after care. The guidance is based on expert opinion and a review of the existing literature.

The available published data is limited to small case series with variable follow up. The patients are heterogeneous and unmatched for age, sex or co-morbidity with a control population. Unpublished data from a multi-centre audit was also used to produce the guidance. It was noted that some of the patients included in the existing literature were also included in the unpublished data.

11.15 Summary

PEC insertion represents an alternative to established invasive surgery that has been used to manage patients with conditions that remain refractory to conservative treatments. The technique is becoming increasingly recognised. However, long term data regarding efficacy, outcome, complications and the effect insertion has on prognosis are lacking.

12 USE OF PERCUTANEOUS ENDOSCOPIC COLOSTOMY (PEC) IN THE LEFT COLON FOR THE TREATMENT OF LOWER GASTROINTESTINAL DISORDERS: A CASE SERIES OF 27 PATIENTS FROM A SINGLE UNIT.

12.1 Abstract

Background: Percutaneous Endoscopic Colostomy (PEC) in the left colon is a minimally invasive endoscopic technique increasingly used to treat lower gastrointestinal conditions.

Aim: To evaluate efficacy and safety of PEC insertion at a single unit.

Methods: Retrospective data collection.

Results: Between 2001 and 2005, 31 patients attended for PEC. Insertion was possible in 27. Indications included functional constipation n=8, recurrent sigmoid volvulus n=8, colonic pseudo-obstruction n=5, neurological constipation n=6. In 22 patients (81%), symptoms were significantly improved after insertion. Sigmoid volvulus did not recur with PEC in situ. Mean duration with tubes in place was 9.5 (sd 8.4) months. Tubes were removed in 13 patients due to complications. Only 2 patients still have PEC in situ. Infective episodes occurred in 77% of the group necessitating removal in 44% of patients. Other complications included buried internal bolster, faecal leakage and pain. Mortality was high (26%) with 7 deaths; 5 deaths from unrelated causes and 2 deaths from faecal peritonitis.

Conclusion: Symptoms were effectively controlled by PEC and RSV was prevented. Recurrent complications caused significant morbidity. Infection necessitated removal in the majority of patients. Fatal faecal peritonitis occurred in two patients. Indiscriminate use of PEC is not recommended. PEC should only be considered in carefully selected cases.

12.2 Aims

The objectives of this retrospective study were to evaluate the results and complications of PEC insertion in patients with a variety of lower gastrointestinal conditions. A subsidiary aim was identifying case histories that highlight specific issues related to the technique. The results of histological examination of PEC tracts are also discussed. The results of this assessment were to be used to inform the design of a prospective study of the efficacy of PEC in refractory idiopathic constipation.

12.3 Patients and Methods

Thirty-one patients attended for PEC insertion between 2001 and 2005. The group included patients with recurrent sigmoid volvulus (RSV), patients who had colonic pseudo-obstruction (CPO) and patients with neurological constipation (NC). In these latter patients, constipation was attributable to a neurological condition. In the RSV group the diagnosis was made on the basis of characteristic radiological and endoscopic appearances [216]. The patients with idiopathic constipation met Rome II criteria[10] for functional constipation (FC).

12.4 Patient selection for insertion of PEC

PEC was considered in the FC group because symptoms were refractory to conservative treatments (laxatives, enemas, biofeedback training and rectal irrigation) and because quality of life was significantly impaired. These patients were on the waiting list for surgical intervention and were offered PEC as an alternative. Likewise, the patients with NC had not responded to conservative treatments. PEC was considered instead of surgery in RSV patients because of high surgical risk related to co-morbidity and frailty. The patients with chronic CPO had not responded to symptomatic treatments, prokinetic agents, neostigmine infusion or colonoscopic decompression and were offered PEC as an alternative to surgery. PEC was performed for acute CPO in patients deemed high risk for surgery where supportive therapy, neostigmine infusion and colonoscopic decompression had failed. All patients had provided written consent for the procedure and were made aware of the perceived risks, benefits and alternatives to PEC insertion.

12.5 Procedure for PEC tube insertion

Preparation included full bowel clearance 24 hours before insertion. Intravenous cefuroxime, 750mg (Glaxo Smith Kline, Uxbridge UK) and metronidazole, 500mg (Winthrop Pharmaceuticals, Guildford UK), were given before the procedure as prophylaxis against infection. Intravenous midazolam (Roche, Welwyn UK) and pethidine (Martindale, Brentwood, UK) were titrated to achieve conscious sedation with analgesia. Colonoscopy was performed to identify a site for insertion in the left colon. This site was the point of maximal transillumination and indentation of the abdominal wall suitable for placement of the tube. The area was infiltrated with local anaesthetic. An 18-gauge Seldinger needle was passed through the abdominal wall and its entry into the colonic lumen observed endoscopically. A guide wire was passed through the Seldinger needle and grasped by a polypectomy snare. The guide-wire was pulled through the anus by withdrawing the colonoscope. The PEC tube was attached to the guide-wire and pulled through the abdominal wall via the anus ("pull through" technique). Typically, 20 Fr gastrostomy tubes (Merck Pharmaceuticals, UK) or specifically designed 12 Fr PEC tubes (Merk Pharmaceuticals, UK) were used. The colonoscope was reinserted to check the position of the internal bolster. Finally, the tube was attached to the abdominal wall to avoid dislodgement using an external bolster (Merk Pharmaceuticals, UK). After the procedure patients were admitted for observation. Intravenous antibiotic therapy was continued for a further 5 days. The patients were followed up regularly after insertion.

12.6 Data collection

Efficacy was assessed by reviewing the medical records and classifying patients according to an assessment of their symptoms after insertion. The categories included markedly improved, minimally improved, unchanged and symptoms worsened. A subgroup of constipated patients was selected to undergo pre and post insertion colonic transit studies using radio-opaque markers [53]. All complications were recorded irrespective of severity.

12.7 Statistical methods

Incidence density (ID) was used to determine the rate at which complication episodes occurred with PEC in situ. Incidence density is the measure of each complication episode per 100 patient months with PEC in situ and takes into account that the duration with PEC in place is different for each individual. The following equation was used for the calculation:

$$ID = \frac{\text{No of complication events with PEC in situ}}{\text{Total patient-months with PEC in situ}} \times 100$$

Normality of data was assessed by the Kolmogorov-Smirnov test. Normally distributed data were analysed with Student's *t* test for unpaired samples. Non-normally distributed data were analysed with the Mann-Whitney *U* test and the Kruskal-Wallis test. Categorical data were analysed using Fisher's Exact test. A p value of < 0.05 was considered statistically significant and a p value of < 0.01 considered highly significant.

12.8 Results

The characteristics of the 31 patients are summarised in Table 63. There were 11 patients with FC, 8 with RSV, 8 with CPO and 7 patients with NC. In the NC group, one patient had cerebral palsy, two patients spinal cord injury and four had multiple sclerosis (MS). The CPO group contained 2 cases of acute CPO (Ogilvie's syndrome[230]) and 3 cases of chronic CPO. All of the FC patients had slow colonic transit.

The RSV and CPO patients represented an elderly cohort in whom coexisting medical conditions were common. Two thirds of the RSV group had a WHO performance status of 3 or higher (limited self care, resting >50% of daylight hours)[257]. Four CPO patients had a WHO performance status of 4 (minimal or no self care, bed bound). In the cases of chronic CPO the mean duration of the condition was 3.3 years (sd 1.15). Prior to insertion the mean history of RSV was 6.4 months (sd 3.96). All 8 of the RSV patients described symptoms of bloating and distension during this time. Seven also suffered constipation.

None of the 31 patients were taking steroids or immunosuppressant treatments at the time of insertion. Two of the RSV patients had type II diabetes mellitus. The characteristics of each specific patient selected for PEC insertion are summarised in Appendix C, Table 1 through to Appendix C, Table 4.

Condition	Number of patients selected	Details	Age, years Mean (sd)	Symptom duration Mean (sd)	Median WHO performance status (range; IQR)	Median number of coexisting medical conditions (range; IQR)	Number of patients in whom insertion was not possible
Functional constipation	11	M:1 F:10	41 (9.1)	20.6 (14.6) years	0 (0,0)	1 (0-3; 2.5)	3
Recurrent sigmoid volvulus	8	M:5 F:3	80.4 (9.8)	6.4 (3.9) months	3 (2-4; 1.5)	2 (1-3; 1.5)	0
Neurological constipation	7	M:4 F:3	50 (14.7)	16.7 (9.8) years	2 (1-4; 2.0)	1 (0-2; 1.5)	1
Colonic pseudo-obstruction	5	M:2 F:3 3 chronic CPO 2 acute CPO	70.2 (12.9)	3.3 (1.2) years for chronic CPO	4 (2-4; 1.0)	2 (1-3; 1.0)	0

Table 63 : Characteristics of patients selected for PEC.

12.8.1 Insertion

From the 31 patients, there were 4 (13%) in whom a suitable site for insertion could not be identified and the procedure was abandoned. In the remaining 27 patients, a total of 28 PEC tubes were inserted in the left colon. This included one patient who had two tubes, inserted on separate occasions at different sites in the left colon. This patient had a history of chronic CPO and co-existing medical conditions. The first tube, inserted in the mid-descending colon stayed in situ for 6 months. At the patient's request and because of an improvement in her overall condition, the tube was removed. After 8 months, her quality of life was again severely impaired by colonic symptoms. PEC was reinserted in the mid-sigmoid, leading to symptom resolution.

In the whole group, the mean duration of the procedure was 30 minutes (sd 10.8). The commonest point of insertion was the mid sigmoid (40% of insertions). The remaining insertion positions were; distal descending (33% of insertions), mid-descending (15%) and proximal sigmoid (15%). Twenty patients had 20Fr tubes inserted and 8 patients had 12 Fr tubes inserted.

In 9 patients the original PEC was removed and a replacement tube inserted down the existing tract. The majority of these changes were performed because of recurrent complications including episodes of infection and faecal leakage.

12.8.2 Hospital stay

Mean hospital stay for all patients was 15.4 days (sd 10.8). The CPO and RSV group had prolonged stays because their coexisting conditions required on going management.

The FC patients only required in-patient management for the effects of insertion and their length of stay gives a clearer idea of the hospital stay attributable to PEC itself. The mean hospital stay for these patients was 6.9 days (sd 4.5).

12.8.3 Duration with PEC in situ

The mean duration that the PEC tubes remained in situ was 9.5 (sd 8.3) months (range 4 days to 26 months). In 22 of the 27 patients symptoms were deemed to be markedly improved after insertion. In those with RSV, no further episodes of volvulus occurred with PEC in situ. Tubes stayed in place for a mean of 8.8 (sd 6.5) months in the RSV patients.

12.8.4 Assessment of efficacy

In 22 of the 27 patients symptoms were deemed to be markedly improved after insertion. In those with RSV, no further episodes of volvulus occurred with PEC in situ. Figure 39 shows the results of the assessment of efficacy.

Six patients with constipation had transit studies performed pre and post insertion. Delayed transit was demonstrated (mean colonic transit time 69.3 hours (sd 3.3), before insertion. Following the procedure, the tubes were irrigated regularly and transit studies repeated after 3 months. There was a mean reduction in transit time of 35.7 hours (sd 16.6), ($p=0.003$).

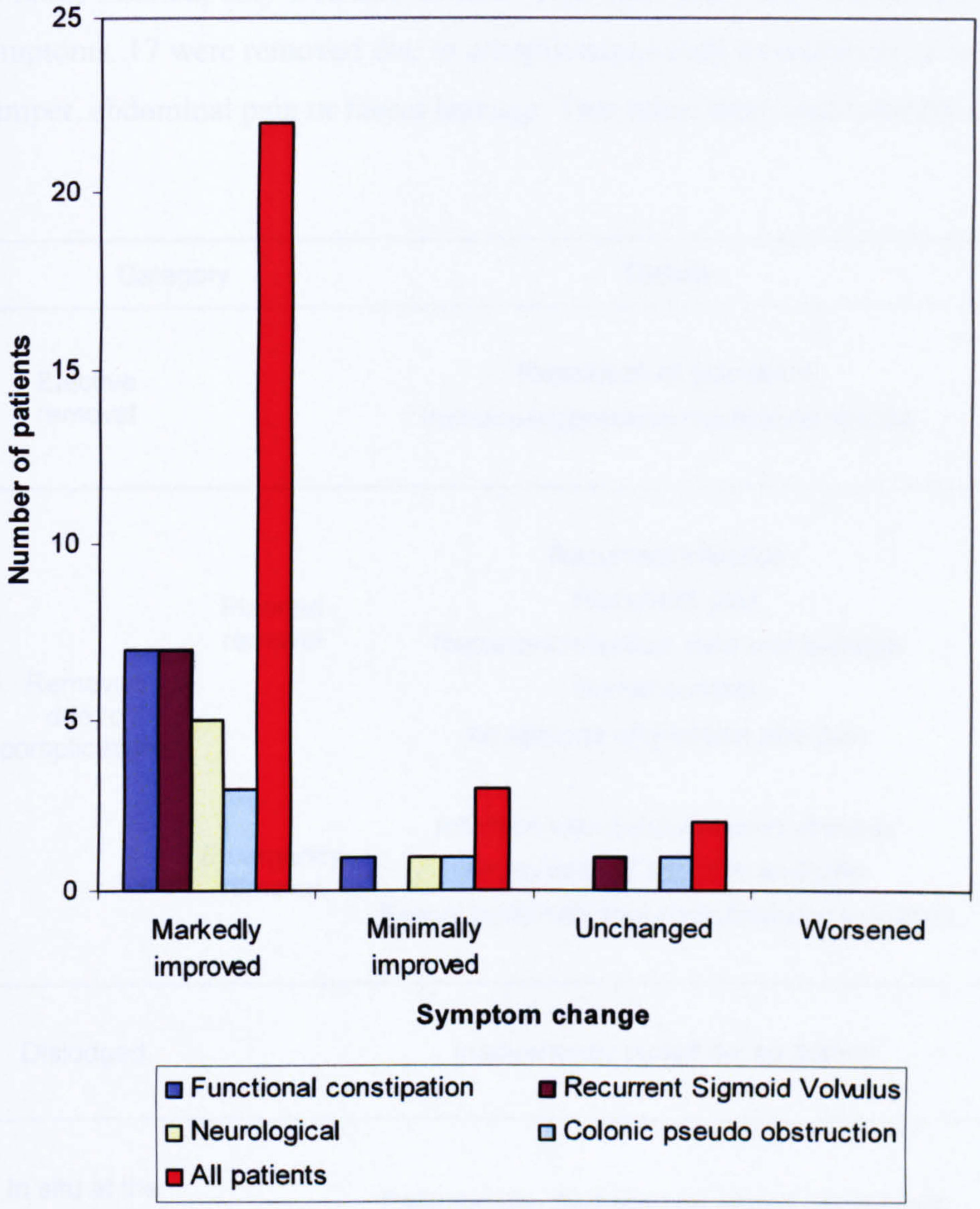


Figure 39. Symptoms after PEC insertion.

12.8.5 PEC tube outcome

PEC tube outcomes for the total group are shown in Table 64 and Figure 40. Of the 28 tubes inserted, only 2 remain in situ. Two were removed because of resolution of symptoms. 17 were removed due to complications such as recurrent infection, buried bumper, abdominal pain or faecal leakage. Two tubes were inadvertently dislodged.

Category		Details	Number of tubes
Elective removal		Resolution of symptoms	2
		Immunosuppressive medication started	1
Removed due to complications	Planned removal	Recurrent infection	7
		Recurrent pain	2
		Recurrent infection, pain and leakage	1
		Buried bumper	1
		An episode of infection and pain	3
	Emergency removal	Infection with subcutaneous abscess	1
		An episode of infection and pain	1
		Faecal peritonitis four days following insertion	1
Dislodged		Inadvertently pulled out by patient	2
In situ at the point of death		Patients who died from unrelated causes with PEC in situ	4
In situ May 06		Two patients who continue in follow up with the PEC tube in situ	2

Table 64: Outcomes for PEC tubes.

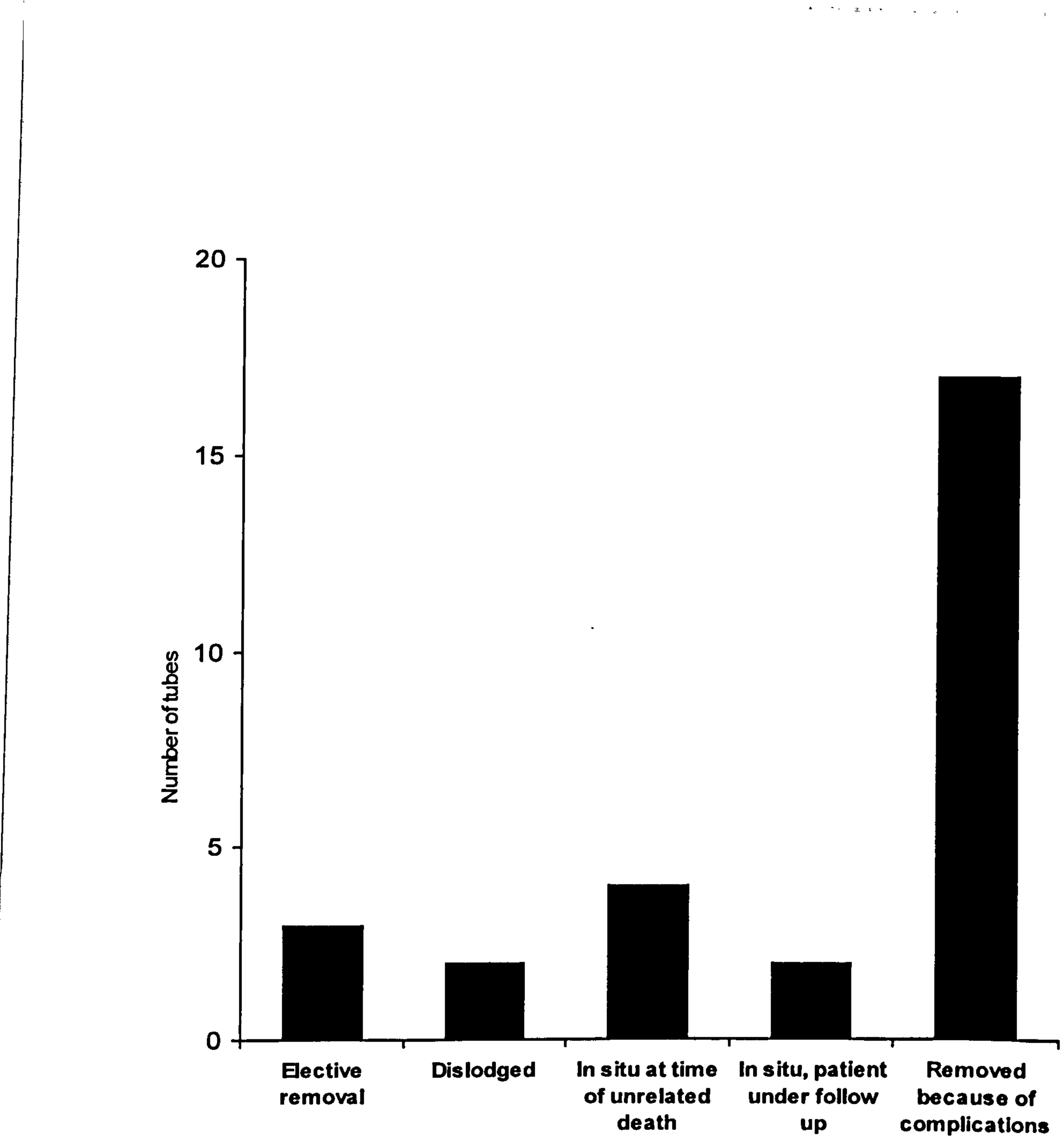


Figure 40: PEC tube outcomes.

12.8.6 Patient outcome

Figure 41 summarises patient outcome. Seven patients from the group of 27 have died. Of these, 5 died from unrelated causes with the tube still in situ (4 cases of pneumonia and 1 patient with lung cancer) at a mean of 8.2 months (sd 6.5) after PEC was inserted. These unrelated deaths all occurred in the RSV patient group. The remaining 2 deaths were caused by faecal peritonitis (patients RSV1 and CPO1). The details of these patients are described as case histories (section 12.9).

In the remaining 20 patients, two still have PEC in place and 18 no longer have tubes in situ. The 2 patients with PEC in place (NC5 and CPO2) have been followed up for 10 and 7 months respectively. Their symptoms are successfully controlled.

The remaining 18 patients have been followed up after their tubes were removed for a mean of 20.4 months (sd 3.5). This group includes: 5 who had tubes removed and recommenced conservative treatment; 2 who remain symptom free requiring no specific treatment after tubes were removed or dislodged and 11 patients who required a definitive surgical procedure following removal. The surgical procedures were performed because of ongoing symptoms relating to the underlying gastrointestinal disorders. All 8 of the FC patients had tubes removed and 6 of these proceeded to surgery; including colectomy and ileorectal anastomosis in 5 (patients FC3, FC4, FC5, FC6, FC7) and Malone Antegrade Colonic Enema procedure [258] performed in 1 case (FC2).

The outcomes for each individual patient are displayed in Appendix C, Table 5 through to Appendix C, Table 8.

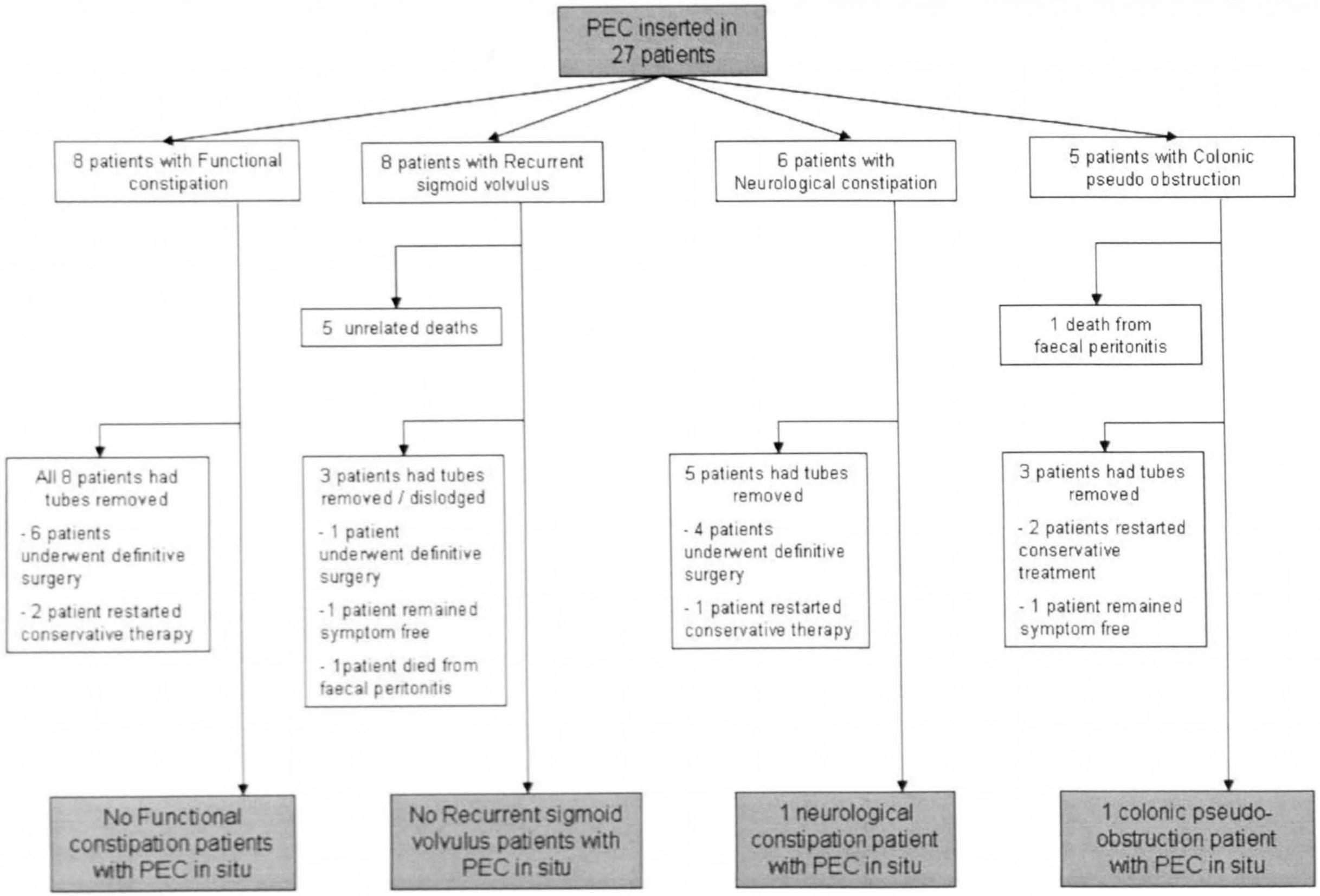


Figure 41: Patient outcomes.

12.8.7 Complications

A variety of complications were recorded. Localised peritonism at the PEC site occurred frequently in the period immediately after insertion, being present in 18 of the 27 patients. The mean duration of peritonism in affected patients was 1.5 days (sd 1.4). When 20 Fr tubes were used, peritonism occurred on 11 occasions after insertion. When 12 Fr tubes were used, there were 4 episodes when peritonism occurred immediately after insertion. There was no difference in the incidence of the episodes of peritonism between groups defined by PEC tube diameter (Table 65).

The mean duration of peritonism after insertion in patients with a 20 Fr tube and those with a 12 Fr tube was not significantly different; mean duration 1.5 days (sd 1.4) and mean 1.7 days (sd 1.6) respectively, ($p = 0.78$). Furthermore, the duration of peritonism immediately after insertion did not differ significantly between the conditions ($p = 0.12$), (Table 66).

In the absence of haemodynamic compromise, localised peritonism universally responded to conservative treatment and analgesia. However, the presence of haemodynamic compromise was a poor prognostic marker, being present in those patients who went on to develop serious complications in the period immediately after insertion.

The incidence density of other complications encountered is expressed in Figure 42 and Table 67. These complications included granulation tissue formation, buried internal bolster, leakage, painful episodes and infective episodes.

Tube diameter	Number of tubes inserted	Number of episodes where NO peritonism occurred after insertion	Number of episodes where peritonism occurred after insertion
20 Fr	20	9	11 *
12 Fr	8	4	4 *

* p = 1.0 (Fisher's Exact test)

Table 65: Episodes of peritonism immediately after insertion

Condition	Number of PEC insertions	Duration of peritonism immediately after insertion, days mean (sd)	p value
FC	8	2.4 (1.4)	
RSV	8	0.8 (1.0)	0.12 *
NC	6	1.2 (1.6)	
CPO	6	1.7 (1.6)	

* Kruskal-Wallis test

Table 66: Duration of peritonism immediately after insertion

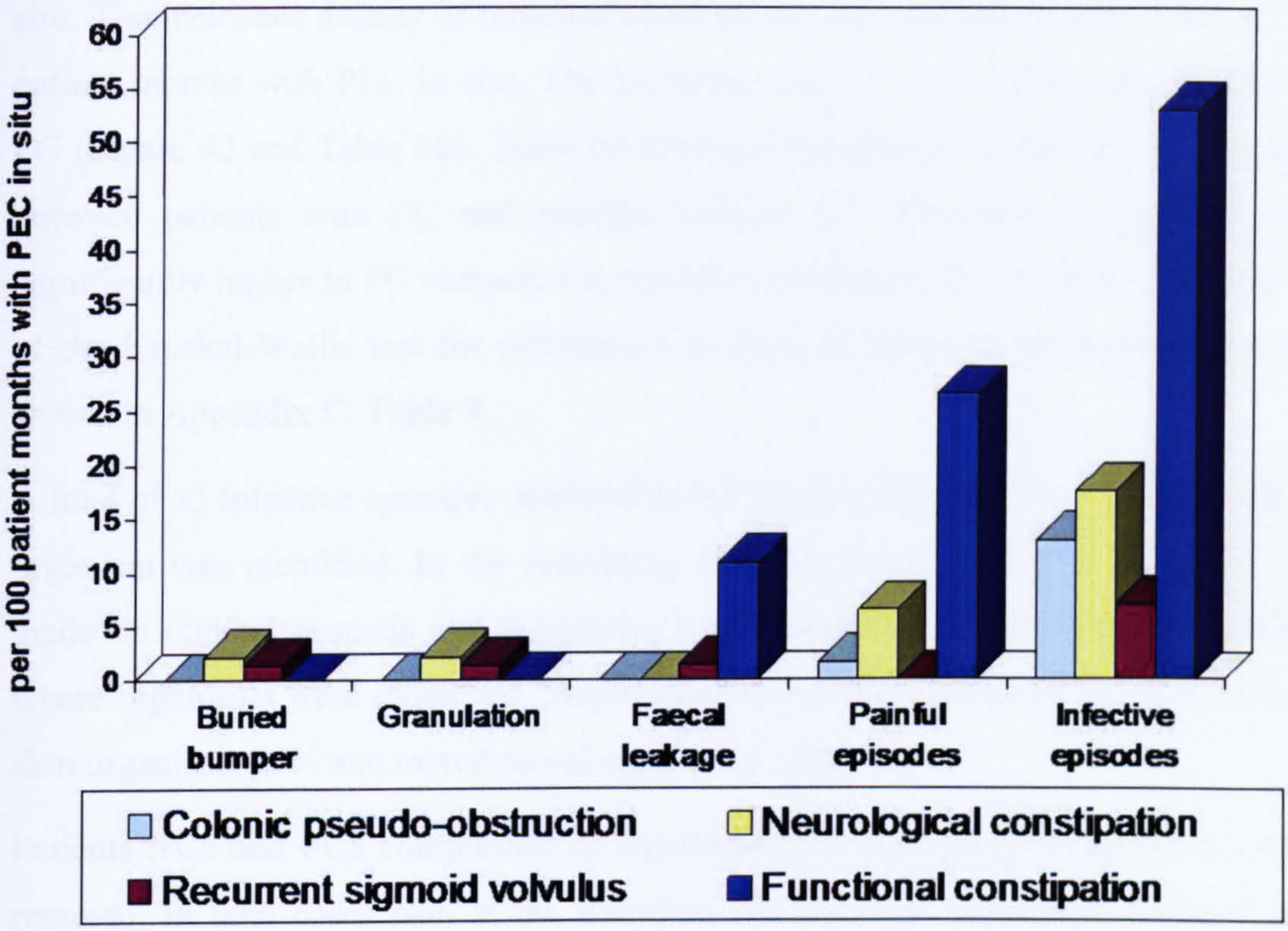


Figure 42: Incidence density of complications

	Incidence density per 100 months with PEC in situ				
	Buried bumper	Granulation tissue	Faecal leakage	Painful episodes	Infective episodes
Functional constipation	0	0	11	26.5	53
Recurrent sigmoid volvulus	1.4	1.4	1.4	0	7.1
Neurological constipation	2.2	2.2	0	6.6	17.6
Colonic pseudo-obstruction	0	0	0	1.6	13.1
Total group	0.7	1.1	0.7	15.1	19.8

Table 67: Incidence density of complications

Twenty of the patients suffered one or more episodes of infection whilst PEC was in situ. The incidence density of infective episodes for the total group was 19.8 per 100 patient months with PEC in situ. The incidence density of infection was greatest in FC (Figure 42 and Table 68). Table 69 shows a comparison of the rate of infection between patients with FC and patients without FC. The rate of infection was significantly higher in FC compared to the other conditions ($p = 0.0004$). The results of the Kruskal-Wallis test for differences in rates of infection between groups are shown in Appendix C, Table 9.

A total of 53 infective episodes occurred in the whole group. In 50 of these, a culprit organism was identified. In the remaining episodes the diagnosis of infection was made on clinical grounds and antibiotics were prescribed empirically. In episodes where organisms were identified, Staphylococcus aureus accounted for 26%, mixed skin organisms 26% and mixed faecal organisms 26%.

Patients NC6 and FC8 complained of significant recurrent pain that prompted tube removal. In both cases pain at the insertion site persisted even after removal and closure of the stoma. The symptom was refractory to simple analgesia but responded to Gabapentin (non-proprietary) suggesting a neuropathic or functional element to the pain.

	Number of patients	Mean Number of infective episodes	sd	Mean duration with PEC in situ months	sd	Incidence density Per 100 patient months with PEC in situ
Functional constipation	8	3	1.51	5.65	6.29	53
Recurrent sigmoid volvulus	8	0.63	0.92	8.75	6.49	7.1
Neurological Constipation	6	2.67	1.2	15.16	9.64	17.6
Colonic pseudo-obstruction	5	1.33	1.50	10.18	10.08	13.1

Table 68: Incidence density of infection

Patients with FC		Patients without FC (RSV, NC, CPO)		Mann Whitney U statistic	p value
n= 8		n = 20			
Mean rate of infection *	sd	Mean rate of infection *	sd		
1.23	1.27	0.16	0.24	10.0	0.0004

* Infective episodes / month

Table 69: Rate of infection in FC and non FC patients

12.8.8 Patients in whom insertion was unsuccessful

In 4 patients from the original 31, it was not possible to insert a PEC (patients NC7, FC9, FC10, and FC11). These patients have been followed up for a mean of 24.6 months (sd 7.27) following these unsuccessful attempts. Two patients underwent surgery and at two years, reported symptom improvement, no complications and no episodes of infection. The other two patients declined surgery, preferring to continue with conservative therapy even though symptoms of constipation persisted.

12.9 Case histories

12.9.1 Fatal faecal peritonitis occurring one year after PEC insertion

Patient RSV1, an 85-year-old lady with advanced dementia and a WHO functional status of 4 had PEC inserted for RSV because surgery was deemed high risk due to her frailty. Over the next 12 months she enjoyed a good quality of life in a nursing home with no further admissions with volvulus. Both she and the staff coped well with the tube. The tube was vented regularly and if constipation developed the PEC was irrigated. After one year the patient inadvertently pulled the tube out. She was admitted with peritonitis and declined rapidly and unfortunately died. Post mortem examination demonstrated a perforation of the sigmoid colon adjacent to the site of the PEC tract. Figure 43 shows the sigmoid to be grossly distended (25cm diameter) with the site of perforation marked with a probe. Proximal to this point the colonic diameter was normal having been decompressed by the PEC tube. Distal to this point the colon and rectum were obstructed with impacted faeces.

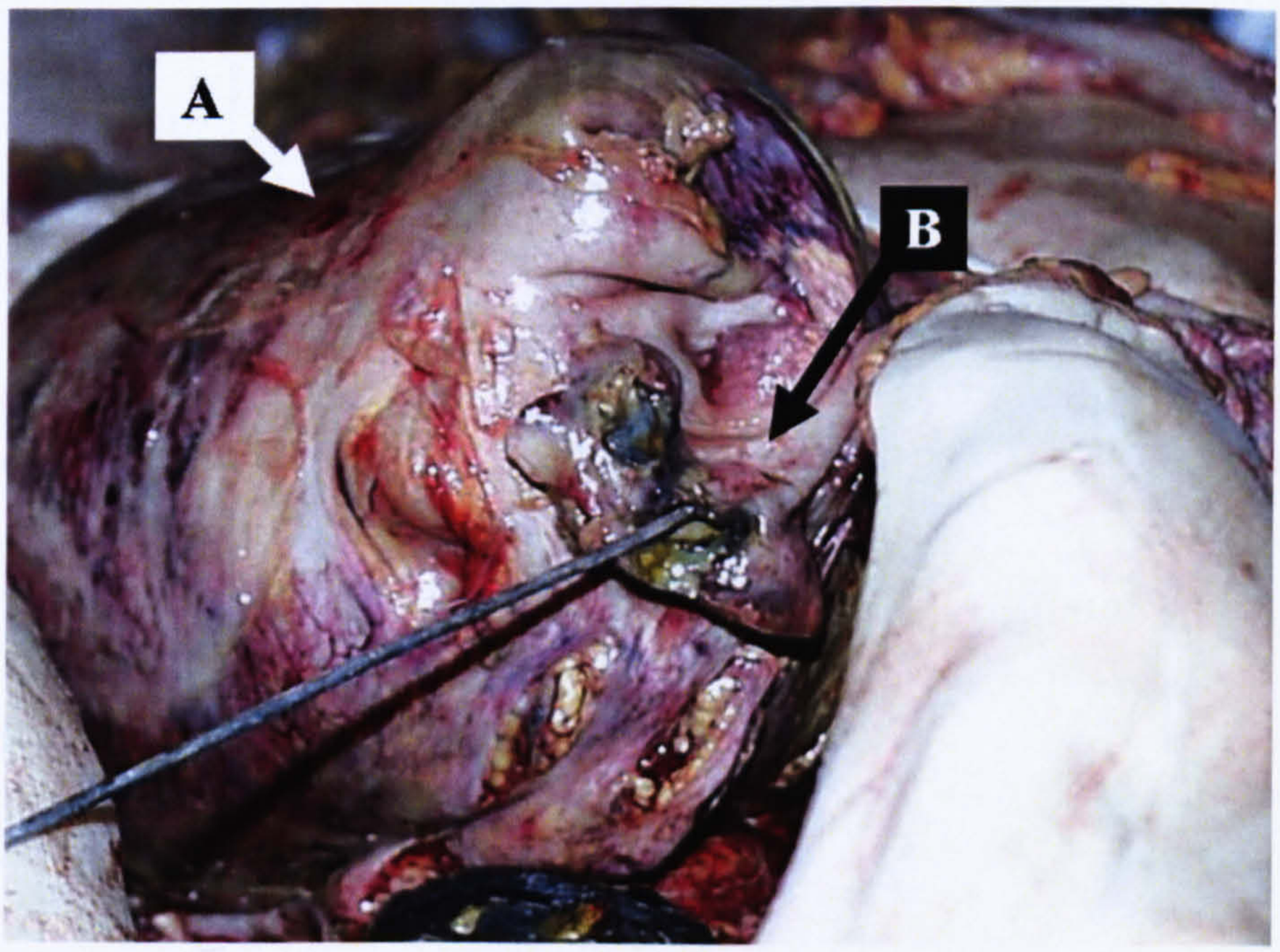


Figure 43: Post mortem appearances in patient RSV1.
Following inadvertent traumatic removal of PEC tube; the sigmoid colon (A) is distended. The surgical probe marks the site of sigmoid perforation (B).

Under normal circumstances this would have presented as abdominal distension with dilation of the proximal colon. Venting the PEC tube prevented the proximal dilation and masked the problem. It is likely that the combination of obstruction, stercoral ulceration and traumatic removal of the tube caused perforation and fatal faecal peritonitis. The case illustrates the dangers of inadvertent traumatic removal of PEC. This danger can exist even in cases where enough time has elapsed for a mature tract to develop. The risk of inadvertent removal may be increased in demented patients. It is important that faecal impaction in the colon distal to the insertion point is prevented. Should this occur, the usual signs of obstruction (proximal dilation) will not be present.

12.9.2 Fatal faecal peritonitis occurring 48 hours after PEC insertion

The case concerns an 85-year-old man (CPO1) with a five-year history of chronic CPO complicated by constipation and overflow incontinence. His quality of life was significantly reduced. PEC was inserted without incident into the sigmoid colon. 48 hours after insertion he complained of abdominal swelling with pain in association with haemodynamic compromise. Plain abdominal radiography demonstrated pneumoperitoneum (Figure 44). Although free gas is not unexpected following PEC insertion, the degree of pneumoperitoneum was excessive. Fluoroscopic imaging demonstrated that the loop of colon was no longer closely opposed to the interior surface of the abdominal wall. A contrast study via the tube failed to show leakage of contrast into the peritoneal cavity.

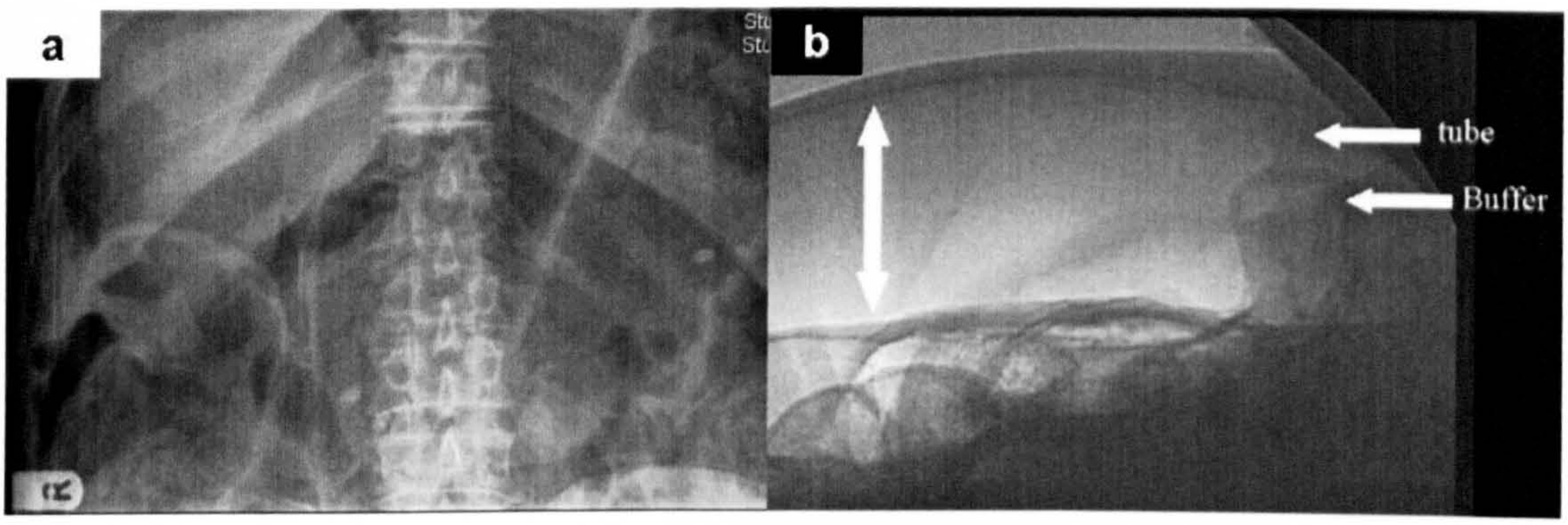


Figure 44. Radiological appearances in patient CPO1
a) Plain abdominal radiograph with pneumoperitoneum. b) Fluoroscopic image showing significant pneumoperitoneum. The PEC tube and internal bolster are indicated by arrows. The loop of sigmoid colon is no longer opposed to the inner surface of the abdomen.

However, due to the clinical suspicion of peritonitis emergency laparotomy was undertaken. Faecal leakage was apparent from the point where the tube entered the colonic lumen. The edges of the puncture site were inflamed and the margins did not completely grip around the tube. Colectomy was performed and ileostomy created. Despite full support in the post-operative period, he deteriorated and died four days after insertion.

In this case, faeculent material leaked from the puncture site and caused generalised peritonitis. A significant pneumoperitoneum was caused by leakage of colonic gas and passage of air through the tract in the abdominal wall. Had the loop of sigmoid

remained tightly opposed to the inner surface of the abdomen then the degree of leakage and pneumoperitoneum may have been less. Until adherence has occurred between these two surfaces, then traction created by the fixing components of the tube is all that prevents the colon falling away from the inner surface.

12.10 Discussion

In this chapter we report on a four-year experience of the use of PEC. The current evidence base regarding the use of PEC is limited. Data are only available from small retrospective case series with varied indications for insertion. The long-term effectiveness, tolerability or incidence of complications remains unknown.

In this current series, PEC effectively controlled symptoms in patients with refractory FC and constipation caused by neurological disorders. Whilst in situ, PEC prevented RSV in all patients. In subjects with acute CPO (Ogilvie's syndrome[230]), PEC helped to decompress the colon.

If the patients in whom symptoms were deemed to be markedly improved are considered, PEC can be said to be effective in 81% (22 out of 27 patients). From the original group of 27, two patients died from faecal peritonitis and one patient had PEC removed because immunosuppressive medications were started. If these subjects are excluded, it might be hoped that 24 patients would still be receiving the benefits of PEC. However, only 7 patients (26%) had PEC in situ at the point that observation for this report ceased (including 5 patients who died of unrelated causes and 2 patients still under follow up with PEC still in place). This high degree of attrition is due to the significant complication rate that led to removal of the tubes in approximately three quarters of patients.

In RSV patients, whilst PEC was in place there was good control of symptoms and more importantly volvulus was prevented. When PEC was removed either inadvertently or electively RSV reoccurred. This observation has also been reported by other authors[214]. In our series recurrence happened in the short term (3 days) or in the medium term (7 months) after removal. It is believed that PEC prevents RSV by anchoring the sigmoid colon to the abdominal wall. Immediately following insertion the loop of bowel is anchored by the traction created by the fastening components of the tube. After a period of time adhesion occurs between the colon and the inner surface of the abdominal wall (an appearance reported at laparotomy). Daniels et al reported on patients who had PEC removed at six weeks and then suffered further volvulus[214]. At laparotomy in these patients there was no residual adherence of the colon to the abdominal wall. Laparotomies performed in our unit suggest that even after 3 months adhesion may not be complete.

The mean duration of PEC tubes in situ for RSV was approximately 8.8 months. Little is known about the longer term effects of PEC in RSV. The longest reported follow up in the literature is a mean of 12.6 months [214]. In our cohort there were five deaths from unrelated causes at 8.2 months after insertion. It is interesting to speculate whether the PEC tubes would have kept these patients volvulus free in the longer term, had they not died of unrelated causes.

Regarding patients with CPO; insertion in the two patients with acute CPO produced clinical and radiological evidence of decompression. Ponec et al[235] have demonstrated the effectiveness of intravenous neostigmine in acute CPO. However, there are a small proportion of patients who do not respond to infusions or colonoscopic decompression. It is recognised that persistent colonic dilation can lead to perforation. Traditionally, urgent surgical intervention would be required[238]. In these circumstances, PEC offers a less invasive and reversible method of decompression[208].

There were 3 patients suffering chronic CPO in our series. In two of these the degree of decompression was minimal after insertion. This is in contrast to the spectacular decompression encountered in the acute CPO cases. This is possibly because different underlying pathological processes exist in these two conditions[232,259]. Although abdominal distension was not improved, troublesome symptoms of constipation, soiling and overflow diarrhoea were improved.

In this series 77% of patients suffered one or more episodes of infection, a figure higher then previously reported. This result is also significantly higher then that quoted in recent PEC guidance, in which unpublished audit data suggested an infection rate of 12%[256].

The explanation for this is difference is unclear. Immuno-compromise in the cohort does not seem to be a factor since only two patients had diabetes mellitus and no subjects were taking steroids. It is not known whether previous studies have underestimated infection because the criteria for reporting infection or the intensity of follow up have been different. Patient selection may also contribute. Infection appears to be more common in FC patients and in this study these patients accounted for almost a third of the total group. Previously published series have included smaller proportions of FC patients. If we accept the theory that infection risk is lower

in non-FC, this may explain why overall infection rates were less in previous reports. However, this argument is negated somewhat because infection rates in our non-FC patients were still higher than previously quoted.

It is not known why infection is more common in FC. The frequency of tube irrigation and the volumes used tended to be higher in this group. These patients were also generally more mobile and active. It is possible that greater mobility and frequent, large volume irrigations traumatise and contaminate the tract to greater extent than in other patient groups, resulting in more infective episodes.

Other factors that might predispose to infection when enteral conduits are formed include the use of the "pull through" method (as opposed to the "introducer method")[260], the effect of pressure damage caused by tension between the internal and external bolster of the PEC tube[261] and the patients' innate wound healing abilities. Further study is necessary to assess these factors.

Infection was the most frequent and important complication necessitating removal. Imaging with isotope labelled leucocyte scans and Magnetic Resonance Imaging suggests that infection occurs not only along the tract but also within the planes of the abdominal wall (Figure 45 and Figure 46).

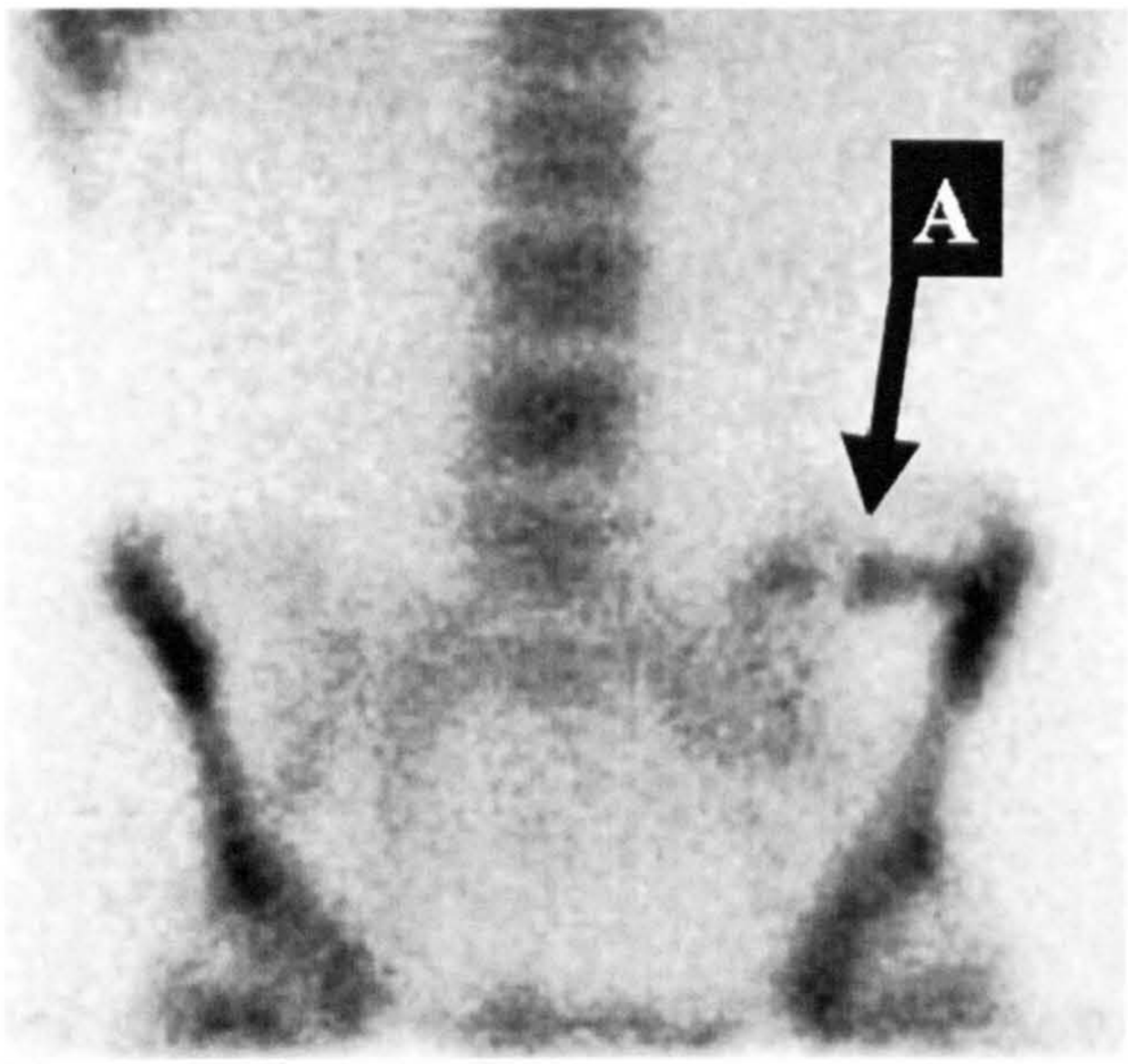


Figure 45. Labelled leucocyte scan image of PEC tube tract infection
An abnormal collection of white cells is present running along the tract (A).

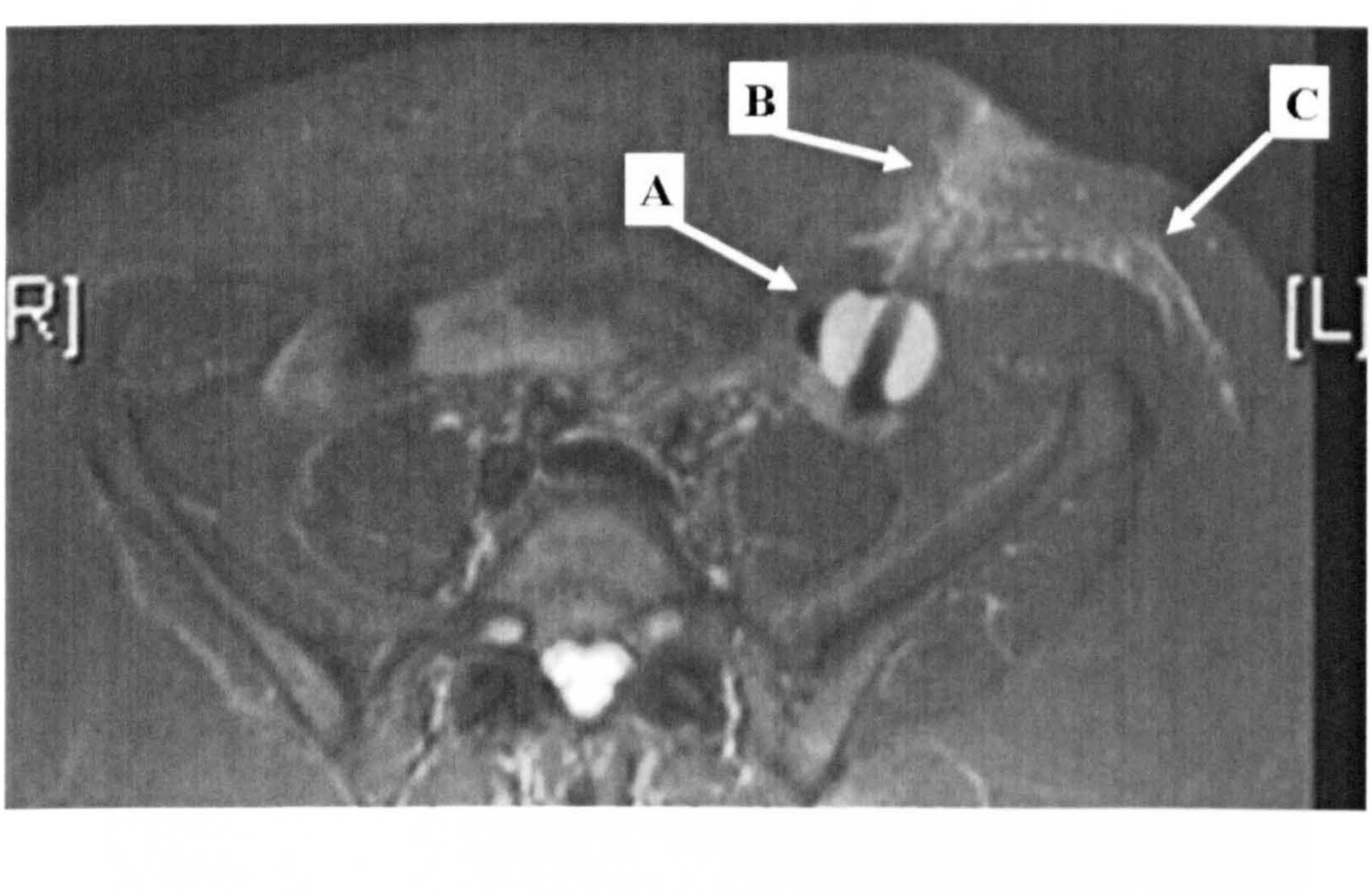


Figure 46. MRI images of patient with PEC tube tract infection
(A) internal bolster of tube. (B) inflammatory changes along the tract. (C) inflammatory changes spreading within the abdominal wall.

Patient NC2 illustrates this concept. After 21 months she was admitted with a tender mass adjacent to the PEC site. Ultrasonography identified a subcutaneous abscess. At laparotomy a fistula was discovered that connected the abscess to the PEC tract. The fistula and abscess were situated between the layers of fascia in the abdominal wall (Figure 47 and Figure 48). Treatment involved removing the PEC, laying open the abscess and performing sigmoid colectomy.

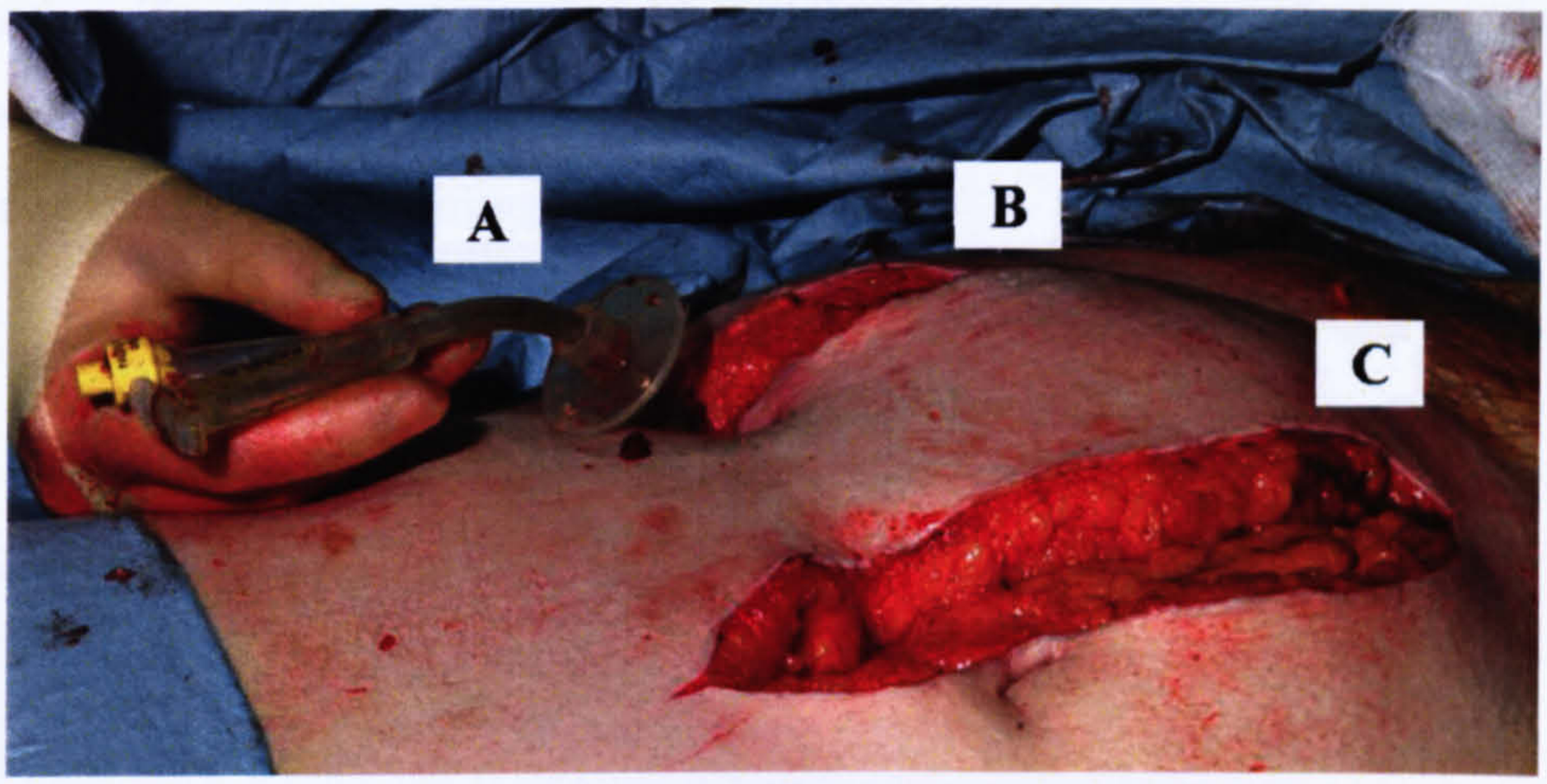


Figure 47. Laparotomy images.
The PEC tube (A) passes through the tract in the abdominal wall into the lumen of the colon. The subcutaneous abscess cavity (B) arises from the tract and has been laid open. The midline Laparotomy incision (C) is shown.

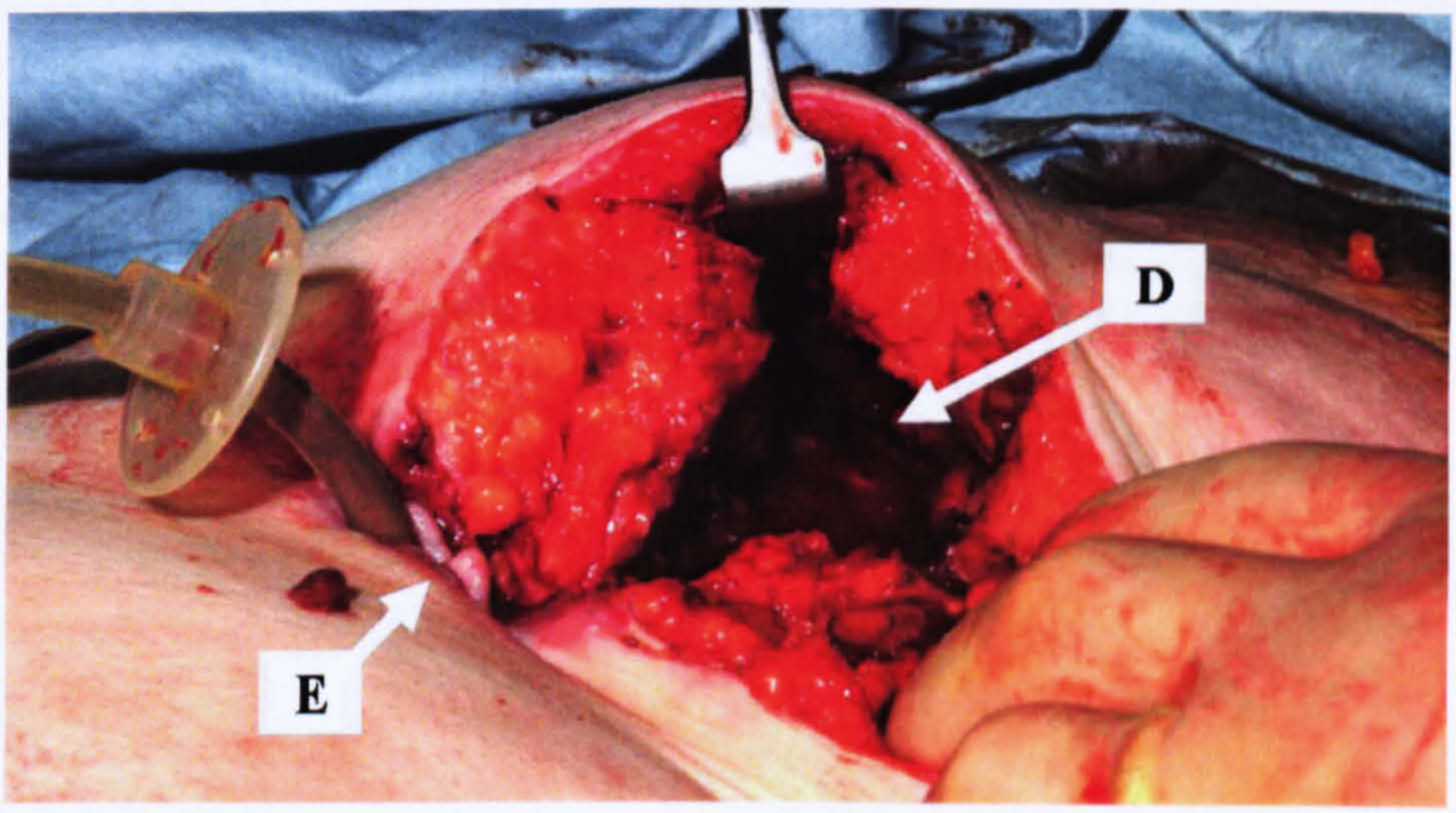


Figure 48. Laparotomy images
The abscess cavity (D) sits in the subcutaneous tissues of the abdominal wall and is contiguous with the PEC tube tract (E).

The high rate of infection in PEC patients is in contrast to that in patients who have had a "Malone" procedure to administer antegrade colonic enemas (ACE). In the archetypal procedure[258], an appendicocaecostomy was fashioned through which catheterisation and irrigation could be performed. An immediate epithelial lining to the tract is created at the time of surgery and infection rates as low as 2.9% have been reported[94]. In contrast, histological examination of PEC tracts shows limited epithelisation. Tract 1 in Figure 49 was excised at 12 months because of an episode of infection. Tract 2 was excised at 16 months for elective non-infective reasons. In both cases there is predominately granulation tissue and inflammatory material rather then a complete epithelial lining.

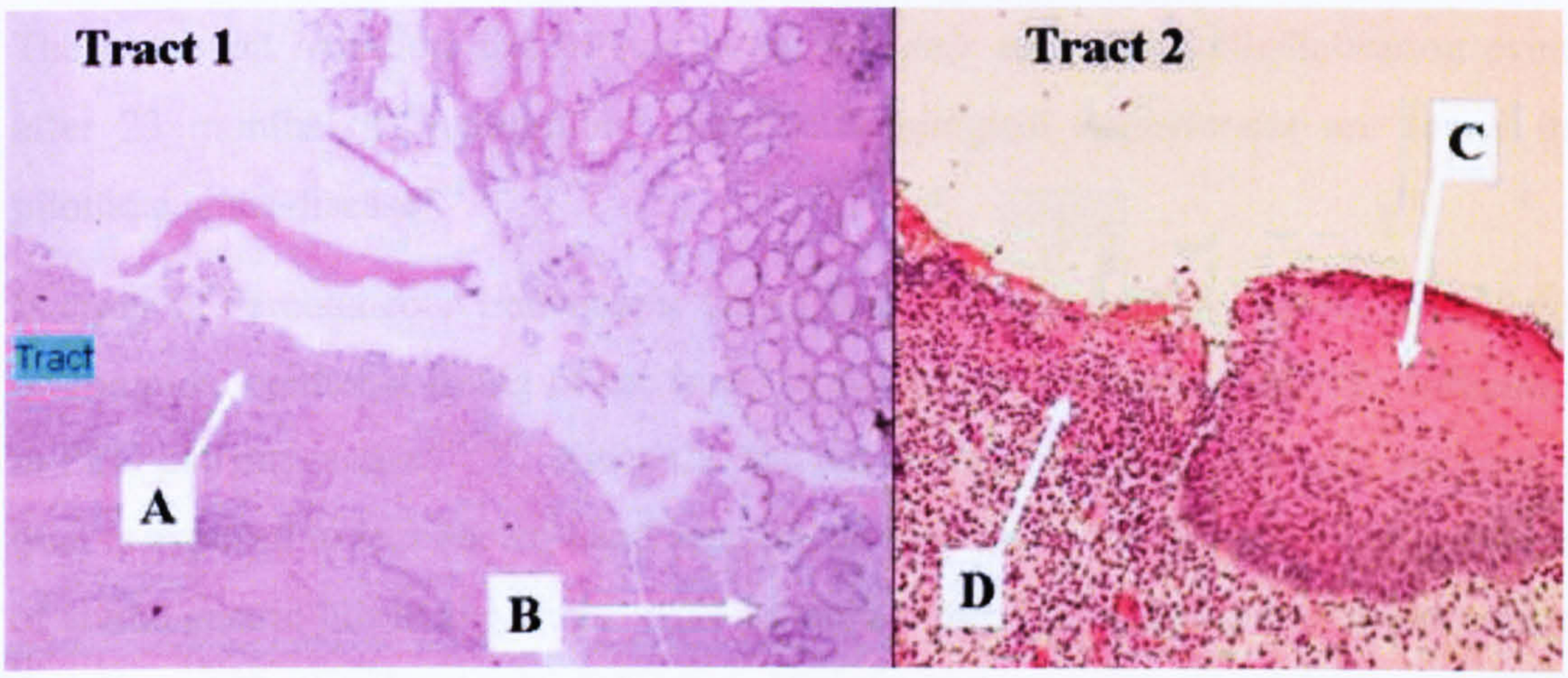
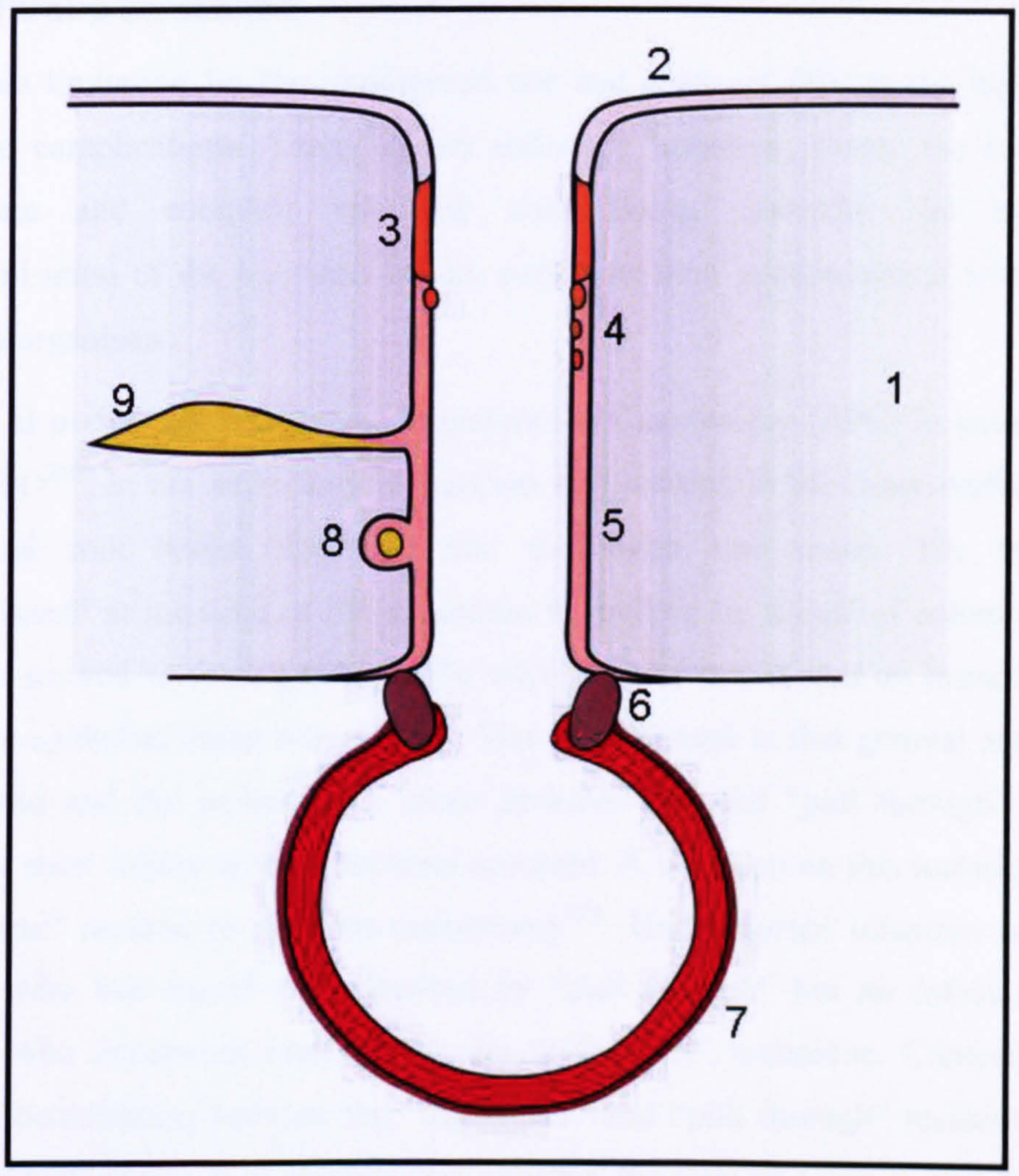


Figure 49. Histological images of PEC tracts
(A) Granulation tissue. (B) Regenerating bowel epithelium. (C) Isolated island of squamous epithelium. (D) Granulation tissue and inflammatory reaction.

A theoretical model of the tracts (based on histology and laparotomy findings) can be proposed (Figure 50). Immediately after insertion, there is a raw surface lined by acute granulation tissue associated with inflammatory infiltrate. As months pass the tract organises. Squamous epithelium from the skin surface migrates downwards and isolated islands of metaplastic squamous epithelium are seen replacing the granulation tissue. In the lower portions of the tract, the lining is loose granulation tissue characterised by inflammatory infiltrate, micro-abscesses and reaction to foreign body material (faeces). Infection can develop from the micro-abscesses and spread between the fascial planes. At the deepest part of the tract, the colon is connected to the inner surface of the abdominal wall by a cuff of fibrous tissue. A degree of epithelialisation with metaplastic glandular epithelium can be seen in this region. Although the cuff prevents leakage into the peritoneal cavity, faeculent material and colonic organisms contaminate the intra abdominal portion of the tract. The persistent irritation and inflammation prevents adequate epithelialisation even after 23 months of "maturation". Similar histological appearances are found in pilonidal sinus disease[262].

In cases of Percutaneous Endoscopic Gastrostomy (PEG), there is also no immediate or complete epithelial lining of the tract. However, in comparison to PEC, infection in PEG patients is rare[263,264]. Since the content of the stomach is generally sterile the tract is exposed to less bacteria and infection is less likely. Furthermore, the presence of acidic gastric juices may cause fibrosis, enhancing the formation of a mature tract that is an effective barrier to infection. Histological comparison of PEC and PEG tracts is required to confirm these theories.

Limitations of this series exist. Collectively the number of patients included is comparable to that of other series, however, the numbers for each specific condition are small. A prospective assessment of PEC would be preferable. However the complications encountered mean that PEC is being inserted less frequently at our unit and the possibility of a prospective study is unlikely.



(1) Abdominal wall

(2) Normal squamous epithelium (skin surface)

(3) Metaplastic squamous epithelium

(4) Islands of metapalstic squamous epithelium

(5) Granulation tissue

(6) Fibrous cuff.

(7) Loop of colon

(8) Micro abscess and inflammatory reaction to faeces

(9) Subcutaneous infection and abscess formation

Figure 50. Histological model of PEC tracts

12.11 Future Directions

The main limitation for the widespread use and study of PEC is the high rate of infective complications. Three factors influence infection; firstly the lack of an immediate and complete epithelial tract lining; secondly the inadequate epithelialisation of the tract and thirdly persistent tract contamination with colonic and skin organisms.

Salm et al performed Endoscopic Percutaneous Caecostomy (EPC) in patients with acute CPO[219]. In the technique the caecum was sutured to the inner surface of the abdominal wall before the tract into the colon was made. The tract was "epitheliased" at the time of the procedure by pulling up a cuff of colonic mucosa that was sutured to form a stoma. The advantage of this is that an immediate and complete epithelial lining was created. The disadvantage is that general anaesthesia is required and the technique is more invasive then the "pull through" method. During a short follow up no infections occurred. A variation on this technique is the "introducer" method to perform caecostomy[222]. Uno reported infection in 2 of 5 patients who had caecal PEC inserted by "pull through" but no infection in 15 patients who underwent insertion by the "introducer" technique. Comparisons of tract epithelialisation between the "introducer" and "pull through" techniques have not been performed. It is possible that suturing the loop of colon to the abdominal wall gives more opposition and facilitates epithelisation such that infections are less. Further study is required to examine this hypothesis.

Canine animal studies have been performed to assess tract formation in Percutaneous Endoscopic Gastrostomy (PEG)[261]. Animal studies of PEC could be considered to determine whether factors that promote epithelialisation improve tract formation and reduce infection. Possible candidates for study include exogenous epidermal growth factor (EGF) and recombinant human granulocyte macrophage colony stimulating factor (molgramostim). These have been used experimentally to improve dermal and anastomotic wound healing experimentally [265-267].

The properties of the tube material may influence tract epithelialisation. Latex has been used to promote the formation of a fibrotic tract after placement of a T-tube in biliary surgery[268,269]. It is not clear whether promoting PEC tract fibrosis would be beneficial for reducing infection. Furthermore, there are suggestions that latex maybe

detrimental to wound and anastomosis healing[270,271]. Again, animal studies may help investigate these issues. The use of drug eluting stents in the biliary system has been reported. Zhang et al showed in vitro inhibition of bacterial growth on the surface of stents[267]. Undoubtedly, PEC tubes could be designed so that the intra abdominal portion elutes factors that have antibacterial properties or promote epithelialisation. However, the topical application of metronidazole cream (Medlock, Bristol, UK) to infected tracts in some of the patients in the series was ineffective.

Contamination of the tracts by colonic bacteria leads to infection. Bacterial concentrations in the intestine increase aborally. It is interesting to speculate what effect the position of PEC has on infection and whether caecal tracts are exposed to lower concentrations of bacteria compared to tracts in the distal colon. Poorly absorbable antibiotics (such as rifaximin[272]) have been used to selectively decontaminate the gut but their effect in PEC patients has not been studied.

12.12 Conclusions

The overall aim of was to evaluate the efficacy and safety of PEC in the left colon, to treat patients with idiopathic refractory constipation. However, the findings from the retrospective data collection of patients who had undergone PEC at our centre suggested that a prospective study would not be possible.

Although the primary aim was not achieved the experience of inserting PEC in a variety of lower gastrointestinal conditions highlighted several key factors relating to the technique;

Insertion of PEC is straightforward and can be performed in less then 30 minutes. In some patients selecting a site for insertion can be difficult using transillumination alone. Fluoroscopy with an image intensifier improves the chances of success. Immediately after insertion localised peritonism is common and a degree of pneumoperitoneum is to be expected. In the absence of haemodynamic compromise these features tend to resolve with conservative measures. The presence of haemodynamic instability is a poor prognostic sign.

PEC is efficacious for treating functional constipation and constipation caused by neurological disorders. Faecal incontinence associated with neurological disorders can also be improved. Whilst PEC is in situ, recurrent sigmoid volvulus is prevented. PEC effectively decompresses the colon in acute colonic pseudo-obstruction. Insertion does not decompress the colon in chronic colonic pseudo-obstruction. Constipation and overflow diarrhoea associated with chronic colonic obstruction can be treated by PEC.

Infective complications are common and can occur at a rate higher than quoted in current guidance. Infection often necessitates removal and this reduces the long-term usefulness of PEC. Major surgery is sometimes required to deal with severe infection.

Two cases of fatal faecal peritonitis have occurred as a consequence of PEC.

The results bring into question the validity of widespread application of PEC. Our findings contrast with those from previous studies that suggested that PEC is well tolerated with low complication rates. Incomplete tract epithelisation represents a major shortcoming of the "pull through" technique. It is possible that strategies to

deal with this problem could be developed in animal studies. However, it is unlikely that robust, prospective human studies will be performed to assess their effectiveness. Insufficient long-term data have been published to determine whether the "introducer" technique represents a viable option for insertion.

Our findings suggest that PEC is not a meaningful alternative to surgery in refractory FC or NC and that insertion should only be considered for treating selected cases of RSV and acute CPO in patients unfit for surgery.

The results provide new and dramatic evidence regarding the safety of PEC in the left colon. NICE issued guidance on PEC in 2006, before these data were available. It is interesting to speculate whether less supportive guidance would have been issued in the light of our findings.

The NICE document recognises that the recommendations it makes are based on limited data derived from heterogenous retrospective case reports and unpublished data (that possibly included duplication of existing results) [256]. This raises the question of whether a more rigorous assessment of efficacy and safety should have been performed before PEC was endorsed for use in the UK.

The Medicines and Healthcare products Regulatory Agency (MRHA) currently recommends that before any *new* medical device is issued with CE marking it must comply with relevant essential requirements on safety and efficacy [273]. To demonstrate this compliance it is necessary to provide clinical data regarding the device. This can be clinical data complied from relevant literature regarding similar or existing techniques or data and conclusions obtained from specifically designed clinical investigation. For any *existing* device or technique that is modified or applied to a different use than originally intended, clinical investigation may not be needed providing adequate information can be presented from the existing literature to support the new role for the device. Interpretation of these issues is open to subjective judgement but the MRHA does suggests that where an existing device is modified or applied to a different use, if the modification *"might significantly affect the clinical performance and/or safety of the device"*, a clinical investigation *is* required to assess efficacy and safety [273].

PEC was originally evaluated in 2003 by SERNIP (Safety and Efficacy Register of New Interventional Procedures). It was further evaluated in 2005 under the auspices

of NICE where advice was sought from the Association of Coloproctology of Great Britain and Ireland and the Association of Endoscopic Surgeons of Great Britain and Ireland. The outcomes of the evaluations in 2003 and 2005 were to endorse the use of the technique (whilst recognising that emerging evidence could change that recommendation) [256]. In both instances an assumption was made that the safety data for Percutaneous Endoscopic Gastrostomy (PEG), e.g. an existing similar technology, could be applied in the evaluation of the new technique. In retrospect it could be argued that instead of making this assumption in the initial stages of evaluation, it would have been prudent to undertake a rigorous UK based prospective efficacy and safety assessment rather than assume that the experience of PEG was transferable to PEC.

Such a move may have meant that the guidance subsequently released in 2006 would not have been reliant on data from retrospective series, case reports (which by their very nature maybe biased and report on patients of particular interest rather than those typically selected to undergo PEC) or indeed unpublished data. These issues highlight the fact that in an era where new endoscopic and minimally invasive techniques develop rapidly, it is necessary to perform robust evaluation of efficacy and safety using adequate and appropriate data perhaps in keeping with the rigorous evaluation processes used for new pharmaceuticals [273].

13 FINAL DISCUSSION

The overall aims of this thesis were to examine three main themes in reference to constipation.

The first aim was to identify factors that can predict disease-specific quality of life in refractory idiopathic constipation. The second aim was to examine the observation that patients with constipation can be separated into distinct groups based on their urge to defecate. The objective here was to determine whether this was due to distinct pathophysiological processes in the two groups. The third aim was to evaluate prospectively the efficacy of a novel therapy that was potentially an alternative to invasive surgery.

The first aim was achieved and predictors for disease-specific quality of life were identified. The results could be used as the basis for future hypothesis driven research regarding QOL in constipation. A limitation of the study is the fact that a convenience sample of patients was examined. Subjects were recruited from the constipation clinic and referral bias means that the results are only applicable to a specific group of constipated subjects. The study does not involve constipated patients from the general population and the findings relate to female patients only.

Future directions include studying the relationship between additional demographics (education, marital and employment status etc) and QOL. Other potential predictor variables could have been studied. For example, a patient's perception of their illness has been shown to be a predictor of QOL in several chronic conditions [274]. This trait could be measured in constipation using the Illness Perception Questionnaire (IPQ)[275] (although modification of the measure maybe required). Previous authors have used the Inventory of Interpersonal Problems (IIP) [276], the Bem Sex Role Inventory (BSRI) [277] and the General Health Questionnaire (GHQ) [278] to demonstrate psychological morbidity in constipated females [40]. The variables evaluated by these measures could conceivably be additional predictors of disease specific QOL. However, it was not practical to include them or other variables in this current study. Our subjects were already completing 3 different measures (PAC-SYM, PAC-QOL and SF-36) and the burden of completing more questionnaires would have been too great.

Our study also demonstrated psychological morbidity in a cohort of patients in whom only a minority had a history of psychiatric illness or depression. The implication of this is that clinicians need to be aware of the problems of psychological wellbeing in constipated patients. Screening strategies need to be considered to identify those who may benefit from psychological or psychiatric input. The results do not support the use of transit study or proctography for the assessment of severity. These investigations did not predict QOL and their use should be reserved for selected patients.

In the process of achieving the first aim, the psychometric properties of PAC-SYM, PAC-QOL and SF-36 were studied. The results provided preliminary psychometric validation of the measures for severe refractory idiopathic constipation. Previous validation studies have not evaluated this particular patient group and have concentrated on subjects with less severe constipation or opiate induced constipation. Confirmation of the psychometric properties provides us with greater confidence to use these measures for future prospective studies in our patients. However, it must be noted that these findings provide preliminary validation and that more extensive psychometric analyses could not be performed because the measures were administered only once. Future research could be performed to confirm test-retest reliability and to further evaluate construct validity, for example through factor analysis. Evaluation of test-retest reliability will require administration on more than one occasion. The predictive validity of the measures, responsiveness and sensitivity to change (eg following treatment) would also require repeated administrations of the measures.

The second aim of this thesis was to test a specific hypothesis; that in idiopathic constipation the frequency of sampling events is less in patients with a reduced rectal urge to defecate compared to patients with a normal rectal urge to defecate. The hypothesis was not proven and no difference in the frequency of sampling reflects was found between the patient groups. To determine whether there are indeed pathophysiological differences between these two groups different techniques will be required for further investigation. The process of testing the hypothesis has provided valuable experience in the use of semi-ambulatory manometry that can form the

basis for future studies with fully ambulatory recordings of the colon for more than 24 hours.

The third aim of the thesis was to study prospectively the efficacy of Percutaneous Endoscopic Colostomy (PEC). Ultimately, this aim was not achieved. In preparation for implementing a prospective study, a detailed retrospective analysis was made of PEC insertion at our institution. The results highlighted significant problems with unacceptably high infection rates, morbidity and mortality. Our findings have had a direct impact on clinical practice. We recommend that PEC is only used in selected patients who are unfit for surgery. Our results do not support the use of PEC as an alternative to surgery in idiopathic constipation. The findings provide valuable additions to the existing literature on PEC which has previously reported good efficacy and minimal complications.

14 APPENDICES

14.1 Appendix A

PAC-QOL ©

PATIENT ASSESSMENT OF CONSTIPATION

The following questions are designed to measure the impact constipation has had on your daily life **during the past 2 weeks**. For each question, please tick one box.

The following questions ask you about the intensity of your symptoms. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
1. have you felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. have you felt heavy because of your constipation?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
3. have you felt any physical discomfort?	☐	☐	☐	☐	☐
4. have you felt the need to open your bowel but not been able to?	☐	☐	☐	☐	☐
5. have you been embarrassed to be with other people?	☐	☐	☐	☐	☐
6. have you been eating less and less because of not being able to have bowel movements?	☐	☐	☐	☐	☐

Appendix A, Table 1. PAC-QOL questionnaire.

The next few questions ask you about the effects of constipation on your <u>daily life</u>. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
7. have you had to be careful about what you eat?	☐	☐	☐	☐	☐
8. have you had a decreased appetite?	☐	☐	☐	☐	☐
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	☐	☐	☐	☐	☐
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	☐	☐	☐	☐	☐
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	☐	☐	☐	☐	☐
12. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	☐	☐	☐	☐	☐

The next few questions ask you about your <u>feelings</u>. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
13. have you felt irritable because of your condition?	☐	☐	☐	☐	☐
14. have you been upset by your condition?	☐	☐	☐	☐	☐
15. have you felt obsessed by your condition?	☐	☐	☐	☐	☐
16. have you felt stressed by your condition?	☐	☐	☐	☐	☐
17. have you been less self-confident because of your condition?	☐	☐	☐	☐	☐
18. have you felt in control of your situation?	☐	☐	☐	☐	☐

Appendix A, Table 1. PAC-QOL questionnaire (continued)

The next questions ask you about your <u>feelings</u>.To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
19. have you been worried about not knowing when you are going to be able to open your bowels?	☐	☐	☐	☐	☐
20. have you been worried about not being able to open your bowels when you needed to?	☐	☐	☐	☐	☐
21. have you been more and more bothered by not being able to open your bowels?	☐	☐	☐	☐	☐

The next questions ask about your <u>life with constipation</u>. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
22. have you been afraid that your condition will get worse?	☐	☐	☐	☐	☐
23. have you felt that your body was not working properly?	☐	☐	☐	☐	☐
24. have you had fewer bowel movements than you would like?	☐	☐	☐	☐	☐

The next questions ask you about <u>how satisfied</u> you are. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
25. have you been satisfied with how often you open your bowels?	☐	☐	☐	☐	☐
26. have you been satisfied with the regularity with which you open your bowels?	☐	☐	☐	☐	☐
27. have you been satisfied with your bowel function?	☐	☐	☐	☐	☐
28. have you been satisfied with your treatment?	☐	☐	☐	☐	☐

Appendix A, Table 1. PAC-QOL questionnaire (continued)

The PAC-QOL contains 28 items within four subscales:

Physical discomfort (4 items)

1. felt bloated to the point of bursting
2. felt heavy because of constipation
3. felt any physical discomfort
4. felt the need to open your bowel but not been able to

Psychosocial discomfort (8 items)

1. been embarrassed to be with other people
2. been eating less and less because of not being able to have bowel movements
3. had to be careful about what you eat
4. had a decreased appetite
5. been worried about not being able to choose what you eat
6. been embarrassed about staying in the toilet for so long when you were away from home
7. been embarrassed about having to go to the toilet so often when you were away from home
8. been worried about having to change your daily routine

Worries and concerns (11 items)

1. felt irritable because of your condition
2. been upset by your condition
3. felt obsessed by your condition
4. felt stressed by your condition
5. felt less self-confident because of your condition
6. felt in control of your situation
7. been worried about not knowing when you are going to be able to open your bowels
8. been worried about not being able to open your bowels when you needed to
9. been more and more bothered by not being able to open your bowels
10. been afraid that your condition will get worse
11. felt that your body was not working properly

Satisfaction (5 items)

1. fewer bowel movements than you would like
2. satisfied with how often you open your bowels
3. satisfied with the regularity with which you open your bowels
4. satisfied with your bowel function
5. satisfied with your treatment

Appendix A, Table 2. PAC-QOL domains.

Items are rated on a 5-point scale:
0=not at all/none of the time 1=a little bit/a little of the time 2=moderately/some of the time 3=quite a bit/most of the time 4=extremely/all of the time
The value will be the numeric score for each item, except for items 18, 25, 26, 27, and 28. The scoring for these items should be reversed: 0→4, 1→3, 2→2, 3→1, and 4→0
Also, define the following parameters: PAC-QOL **overall** score: value = (sum of scores of all non-missing items) / (number of non-missing items) if at least 14 items are non-missing; value is missing if more than 14 items are missing. **Subscale** values are defined as (sum of scores of non-missing included items) divided by (number of non-missing included items) if the missing data handling rule is not met. The value is missing if the missing data handling rule is met. The table below defines the included items and missing data handling rules for each subscale.

Missing data handling rule		
Subscale parameter description	Included items	Missing data handling rule
PAC-QOL Dissatisfaction	24-28	If >2 items are missing, set scale to missing.
PAC-QOL Physical discomfort	1-4	If >2 items are missing, set scale to missing.
PAC-QOL Psychosocial discomfort	5-12	If >4 items are missing, set scale to missing.
PAC-QOL Worries and concerns	13-23	If >5 items are missing, set scale to missing.

Appendix A, Table 3. Scoring algorithm and missing data rule for PAC-QOL.

PAC-SYM ©

PATIENT ASSESSMENT OF CONSTIPATION

This questionnaire asks you about your constipation symptoms in the **past 2 weeks.** Answer each question according to your symptoms, as accurately as possible. There are no right or wrong answers.

For each symptom below, please indicate **how severe** your symptoms have been during the **past 2 weeks.** If you have not had the symptom during the past 2 weeks, tick 0. If the symptom seemed mild, tick 1. If the symptom seemed moderate, tick 2. If the symptom seemed severe, tick 3. If the symptom seemed very severe, tick 4. Please be sure to answer every question.

How severe have each of these symptoms been in the past 2 weeks?	**Absent 0**	**Mild 1**	**Moderate 2**	**Severe 3**	**Very severe 4**
1. discomfort in your stomach	☐	☐	☐	☐	☐
2. pain in your stomach	☐	☐	☐	☐	☐
3. bloating in your stomach	☐	☐	☐	☐	☐
4. stomach cramps	☐	☐	☐	☐	☐
5. painful bowel movements	☐	☐	☐	☐	☐
6. rectal burning during or after a bowel movement	☐	☐	☐	☐	☐
7. rectal bleeding or tearing during or after a bowel movement	☐	☐	☐	☐	☐
8. incomplete bowel movement, as though you didn't "finish"	☐	☐	☐	☐	☐
9. stools that were too hard	☐	☐	☐	☐	☐
10. stools that were too small	☐	☐	☐	☐	☐
11. straining or squeezing to try to pass stools	☐	☐	☐	☐	☐
12. feeling like you had to pass a stool but you couldn't (false alarm)	☐	☐	☐	☐	☐

Appendix A, Table 4. PAC-SYM questionnaire.

The PAC-SYM is a 12-item subject self-administered instrument that measures the severity of constipation-related symptoms. Items are rated on a 5-point Likert scale, where

0=absent
1=mild
2=moderate
3=severe
4=very severe

The PAC-SYM contains the following three subscales:

Subscale parameter description	Included items	Missing data handling rule
PAC-SYM stool symptoms	8-12	If >2 items are missing, set scale to missing.
PAC-SYM abdominal symptoms	1-4	If >2 items are missing, set scale to missing.
PAC-SYM rectal symptoms	5-7	If >1 items are missing, set scale to missing.

Stool symptoms (5 items)
-bowel movements that require straining or squeezing
-bowel movements that are too hard
-bowel movements that are too small
-bowel movements that result in a sensation of incomplete evacuation
-the feeling of having to pass a bowel movement but couldn't (false alarm)
Abdominal symptoms (4 items)
-abdominal discomfort
-abdominal pain
-abdominal cramping
-abdominal bloating
Rectal symptoms (3 items)
-painful bowel movements
-rectal burning
-bleeding or tearing during or after a bowel movements

PAC-SYM **overall** score: value = (sum of scores of all non-missing items) / (number of non-missing items) if at least 6 items are non-missing; value is missing if more than 6 items are missing.
Subscale values are defined as (sum of scores of non-missing included items) divided by (number of non-missing included items) if the missing data handling rule is not met. The value is missing if the missing data handling rule is met. The table below defines the included items and missing data handling rules for each subscale.

Appendix A, Table 5. PAC-SYM domains and data handling rules

Symptom / characteristics	Coding	
Days between defecations with laxative	0	1 day
	1	2 days
	2	3 - 4 days
	3	5-6 days
	4	7-14 days
	5	> 14 days
Laxative use	0	Never
	1	Occasionally
	2	Most days
	3	Every day
Unsuccessful defecatory attempts	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always
Time spent attempting to defecate	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always
Straining during defecation	0	< 5 min
	1	> 5-10min
	2	>10 -20 min
	3	> 20-30 min
	4	>30 min
Painful defecation	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always
Sensation of incomplete evacuation	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always
Digitation to assist defecation	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always
Vaginal pressure to assist defecation	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always

Appendix A, Table 6. Coding details for symptoms / characteristics assessed in cumulative constipation score.

Symptom	Coding	
Abdominal bloating	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always
Abdominal pain	0	Never
	1	Rarely
	2	Some of the time
	3	Usually
	4	Always

Appendix A, Table 6. Coding details for symptoms / characteristics assessed in cumulative constipation score (continued)

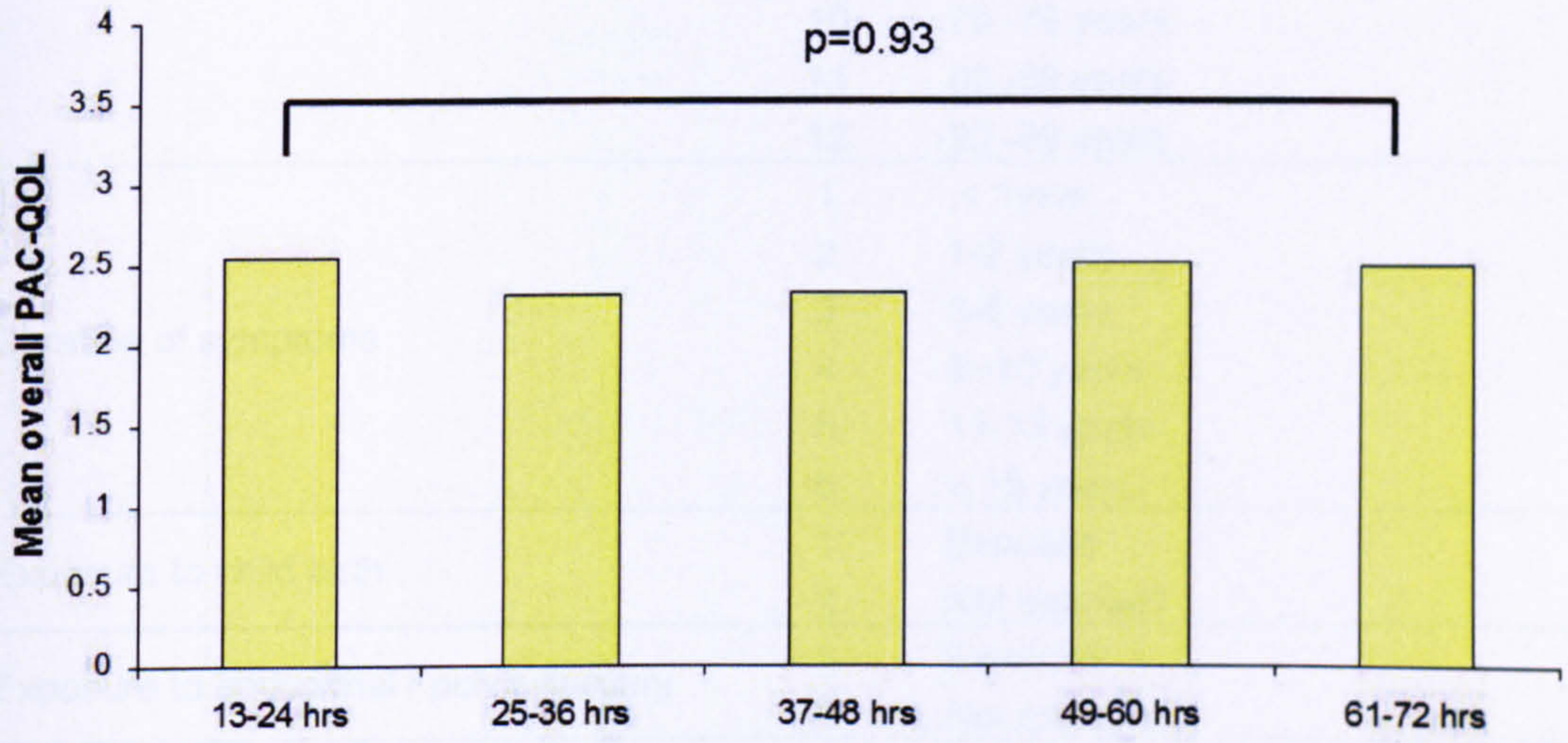
14.2 Appendix B

Subject	Colonic transit (hours) Right	Left	Rectosigmoid	Total	Subject	Colonic transit (hours) Right	Left	Rectosigmoid	Total
1	12	25	2	39	**60**	17	11	40	68
2	26	36	4	66	**61**	67	4	0	71
3	7	20	1	28	**62**	32	25	11	68
4	14	11	39	64	**63**	30	40	1	71
5	48	14	9	71	**64**	9	15	21	45
6	13	18	26	57	**65**	29	30	13	72
7	2	23	43	68	**66**	20	7	29	56
8	36	14	22	72	**67**	18	49	0	67
9	35	18	3	56	**68**	5	62	2	69
10	70	0	0	70	**69**	4	54	0	58
11	17	33	18	68	**70**	4	34	0	38
12	40	23	6	69	**71**	25	37	6	68
13	38	33	0	71	**72**	9	16	25	50
14	39	24	0	63	**73**	24	30	15	69
15	27	7	24	58	**74**	37	21	14	72
16	9	41	8	58	**75**	15	16	20	51
17	6	18	10	34	**76**	**2**	**0**	**0**	**2**
18	0	9	22	31	**77**	18	23	30	71
19	27	33	10	70	**78**	15	24	19	58
20	4	12	28	44	**79**	24	13	18	55
21	12	31	0	43	**80**	23	45	0	68
22	2	10	11	23	**81**	13	20	22	55
23	27	26	1	54	**82**	8	37	21	66
24	14	23	33	70	**83**	7	62	2	71
25	42	24	3	69	**84**	29	28	7	64
26	7	15	50	72	**85**	9	13	19	41
27	16	42	12	70	**86**	35	34	0	69
28	15	25	11	51	**87**	1	44	23	68
29	**6**	**3**	**0**	**9**	**88**	14	40	18	72
30	20	48	3	71	**89**	8	44	16	68
31	18	41	12	71	**90**	25	31	10	66
32	23	21	19	63	**91**	25	30	12	67
33	17	20	8	45	**92**	38	26	0	64
34	1	20	18	39	**93**	13	25	9	47
35	5	12	43	60	**94**	20	15	5	40
36	22	33	13	68	**95**	3	11	40	54
37	12	18	2	32	**96**	2	22	25	49
38	27	10	2	39	**97**	**7**	**1**	**0**	**8**
39	**0**	**4**	**0**	**4**	**98**	28	6	1	35
40	27	15	30	72	**99**	14	40	18	72
41	20	17	5	42	**100**	32	27	13	72
42	37	35	0	72	**101**	51	21	0	72
43	3	11	8	22	**102**	47	13	12	72
44	13	49	10	72	**103**	7	42	21	70
45	29	20	23	72	**104**	35	32	5	72
46	25	24	4	53	**105**	10	37	18	65
47	35	10	3	48	**106**	66	4	0	70
48	14	12	7	33	**107**	**3**	**0**	**5**	**8**
49	12	26	34	72	**108**	22	38	8	68
50	19	34	18	71	**109**	67	3	0	70
51	9	46	9	64	**110**	16	28	9	53
52	51	20	0	71	**111**	42	19	11	72
53	18	41	8	67	**112**	6	32	8	46
54	12	30	28	70	**113**	4	48	18	70
55	10	37	5	52	**114**	31	33	0	64
56	10	1	9	20	**115**	33	15	22	70
57	24	20	20	64	**116**	48	17	3	68
58	5	24	21	50	**117**	25	39	6	70
59	2	22	19	43	**118**	4	5	23	32

Appendix B, Table 1. Colonic transit data for 118 subjects.
Aberrant colonic transit results from subjects 29, 39, 76, 97 and 107 (highlighted).

	Slow transit constipation n=87		Normal transit constipation n=26		p value
	mean	sd	Mean	sd	
Overall PAC-QOL score	2.48	0.68	2.39	0.88	0.57

Appendix B, Table 2. PAC-QOL in slow and normal transit constipation.
Cut off ≥ 50 hours



Appendix B, Figure 1. PAC-QOL according to transit categories.

Transit category	Number of patients	Overall PAC-QOL score Mean	sd
13-24 hours	3	2.55	0.03
25-36 hours	7	2.31	1.08
37-48 hours	15	2.32	0.81
49-60 hours	20	2.51	0.63
61-72 hours	68	2.48	0.70

Kruskal-Wallis Statistic KW = 0.8225 (corrected for ties) p = 0.93

Appendix B, Table 3. PAC-QOL scores according to transit category.
No significant differences in PAC-QOL scores between groups of patients defined by category of colonic transit time (p = 0.93)

Variable	Coding	Details / score
Age of onset	1	Infancy (birth to age three)
	2	Early childhood (ages 4 to 8 years)
	3	Later childhood (ages 9 to 12 years)
	4	Adolescence ages 13 to 19 years)
	5	20 -29 years
	6	30 -39 years
	7	40 - 49 years
	8	50 -59 years
	9	60 -69 years
	10	70 -79 years
	11	80 -89 years
	12	90 -99 years
Duration of symptoms	1	< 1year
	2	1-2 years
	3	3-5 years
	4	6 -10 years
	5	11-15 years
	6	> 15 years
Exposure to child birth	1	Exposed
	2	Not exposed
Exposure to abdominal / pelvic surgery	1	Exposed
	2	Not exposed
Coexisting medical problems	1	Yes
	2	No
Psychiatric History	1	Yes
	2	No
Radiologically significant rectocoele (RSR)	1	Non FRSR or No rectocoele
	2	RSR
Slow Transit Colonic Constipation	1	Slow colonic transit
	2	Normal colonic transit
Cumulative Constipation score		0-44
Evacuation time		Seconds
% Evacuation		%
Rectocoele size		cm
Total colonic transit time		Hours
Physical Component Summary		0-100
Mental Component Summary		0-100
PAC-SYM Stool symptom score		0-4
PAC-SYM Abdominal symptom score		0-4
PAC-SYM Rectal symptom score		0-4
Overall PAC-QOL score		0-4

Appendix B, Table 4. Coding details for predictor variables.

Descriptive Statistics	Score / code		
	Mean	sd	Number
Overall PAC-QOL score	2.49	0.77	97
Age (years)	42.97	14.01	97
Cumulative constipation score	22.69	4.91	97
Age of onset	3.65	2.12	97
Duration of symptoms	4.67	1.77	97
Exposure to child birth	1.31	0.46	97
Exposure to abdominal / pelvic surgery	1.65	0.48	97
Coexisting medical problems	1.60	0.49	97
Psychiatric History	2.87	0.34	97
%Evacuation	70.29	16.79	97
Evacuation time (seconds)	68.29	78.93	97
Rectocoele size (cm)	2.44	1.34	97
Radiologically Significant Rectocoele (RSR)	1.13	0.34	97
Slow Transit Colonic Constipation	0.91	0.29	97
Physical Component Summary	42.75	9.04	97
Mental Component Summary	35.84	14.80	97
PAC-SYM stool symptom score	2.37	0.91	97
PAC-SYM Abdominal symptom score	2.39	0.90	97
PAC-SYM Rectal symptom score	1.41	0.99	97
Total colon transit time (hours)	58.84	14.00	97

Appendix B, Table 5. Descriptive statistics for variables entered into forward, stepwise and backwards regression strategies.

ANOVA Model		Sum of Squares	Degrees of freedom	Mean Square	F statistic	p value
1	Regression	22.42	1	22.42	62.69	<0.01
	Residual	33.98	95	0.36		
	Total	56.40	96			
2	Regression	28.34	2	14.17	47.48	<0.01
	Residual	28.06	94	0.30		
	Total	56.40	96			
3	Regression	31.57	3	10.52	39.42	<0.01
	Residual	24.83	93	0.27		
	Total	56.40	96			

Predictor variables included in each model

model	
1	PAC-SYM Abdominal symptom score
2	PAC-SYM Abdominal symptom score, Mental Component Summary
3	PAC-SYM Abdominal symptom score, Mental Component Summary, PAC-SYM stool symptom score

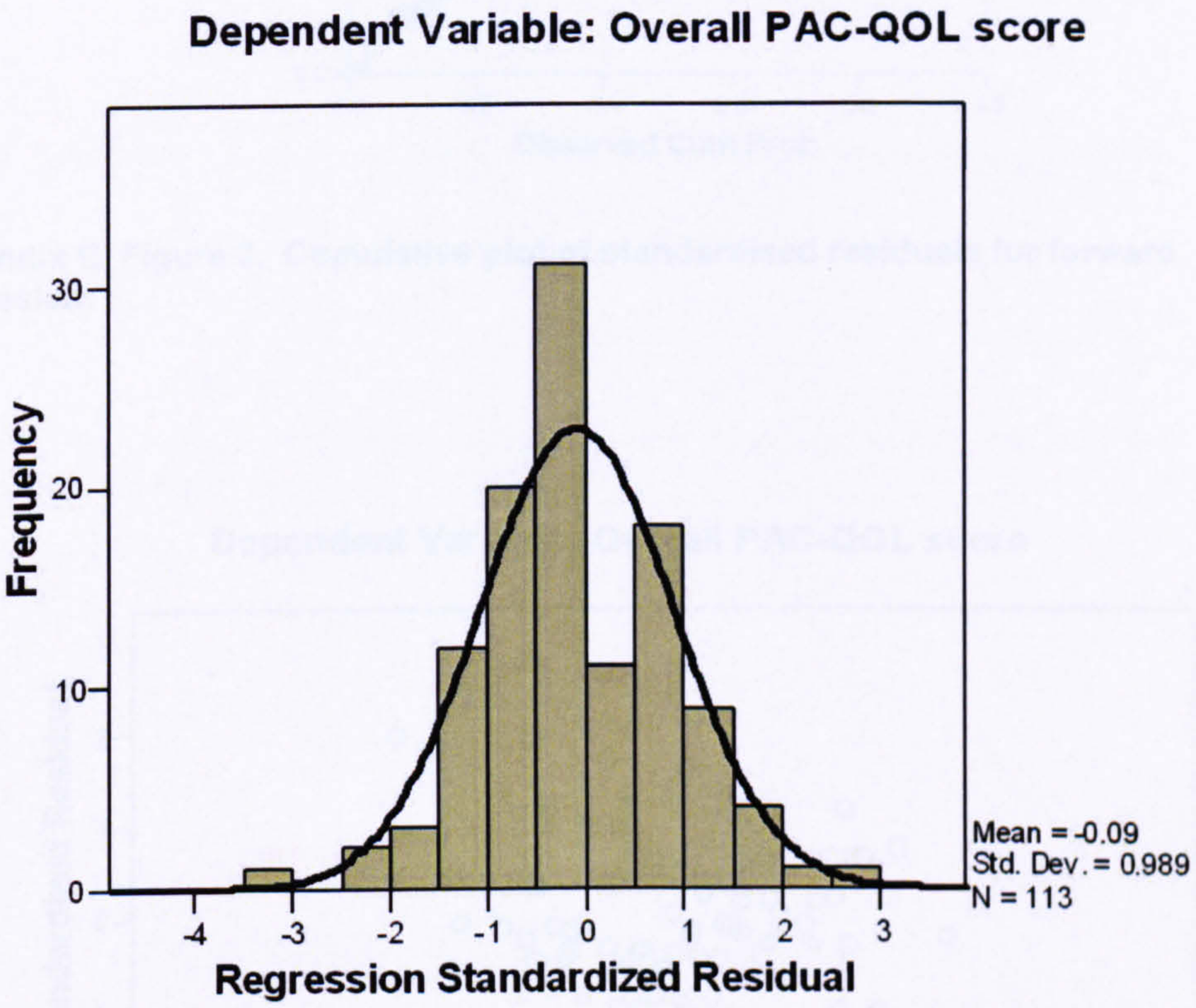
Appendix B, Table 6.Summary of Analysis of Variance (ANOVA) for forward regression strategy

Residuals Statistics(a)

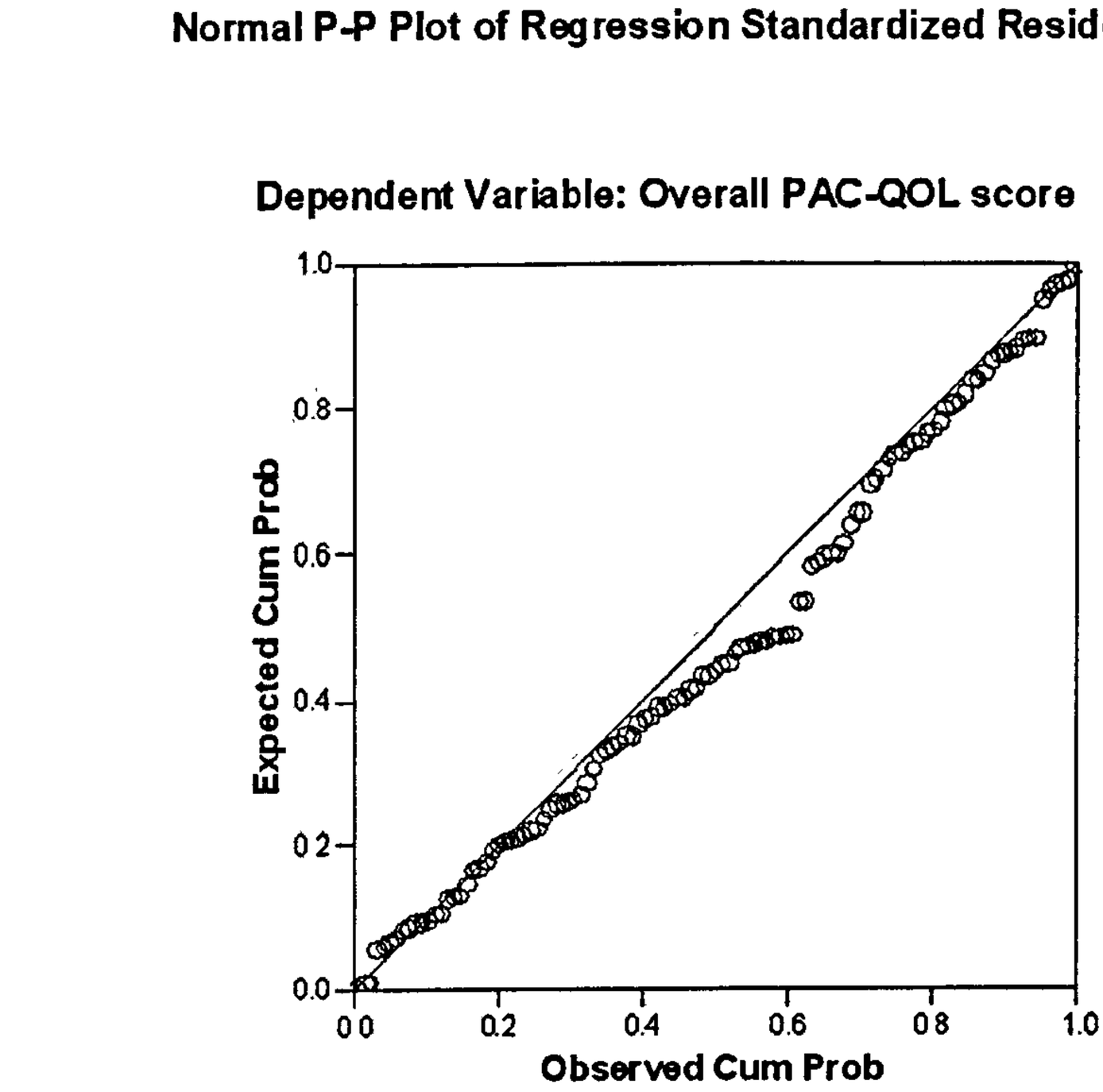
	Minimum	Maximum	Mean	Standard Deviation	Number
Predicted Value	1.13	3.84	2.50	0.56	108
Residual	-1.62	1.46	-0.03	0.51	108
Std. Predicted Value	-2.37	2.36	0.17	0.98	108
Std. Residual	-3.14	2.83	-0.05	0.99	108

a Dependent Variable: Overall PAC-QOL score

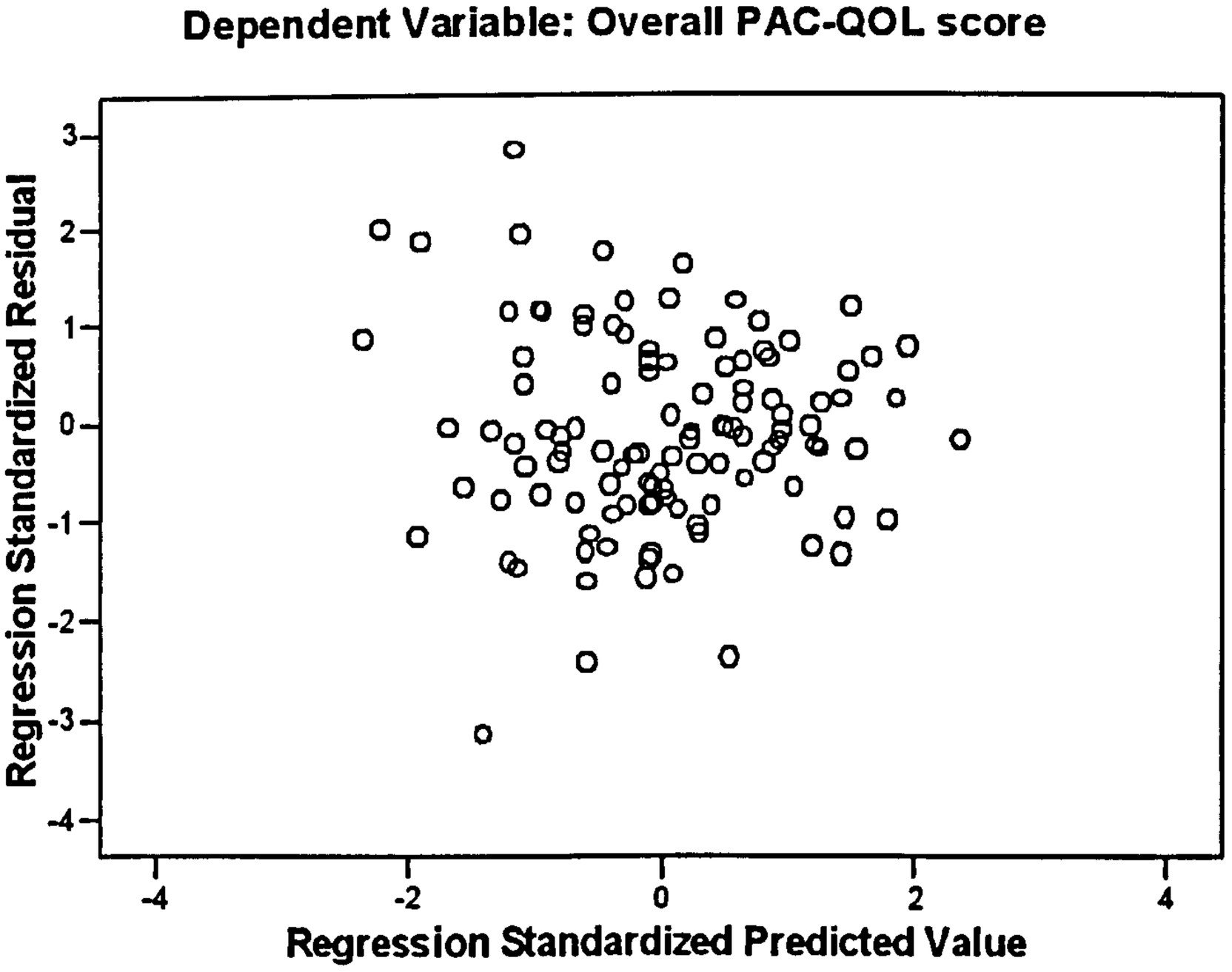
Appendix B, Table 7.Summary of residual statistics for forward regression.



Appendix B, Figure 2. Histogram of the standardised residual for forward regression.



Appendix B, Figure 3. Cumulative plot of standardised residuals for forward regression.



Appendix B, Figure 4. Scatter plot of the predicted scores against residuals for forward regression.

ANOVA Model		Sum of Squares	Degrees of freedom	Mean Square	F statistic	p value
1	Regression	22.42	1	22.42	62.69	<0.01
	Residual	33.98	95	0.36		
	Total	56.40	96			
2	Regression	28.34	2	14.17	47.48	<0.01
	Residual	28.06	94	0.30		
	Total	56.40	96			
3	Regression	31.57	3	10.52	39.42	<0.01
	Residual	24.83	93	0.27		
	Total	56.40	96			

Predictor variables included in each model	
model	
1	PAC-SYM Abdominal symptom score
2	PAC-SYM Abdominal symptom score, Mental Component Summary
3	PAC-SYM Abdominal symptom score, Mental Component Summary, PAC-SYM stool symptom score

Appendix B, Table 8. Summary of Analysis of Variance (ANOVA) for stepwise regression strategy

Model	Dimension	Eigenvalue	Condition Index	Variance Proportions			
				(Constant)	PAC-SYM Abdominal symptom score	Mental Component Summary	PAC-SYM stool symptom score
1	1.00	1.94	1.00	0.03	0.03		
	2.00	0.06	5.50	0.97	0.97		
2	1.00	2.79	1.00	0.01	0.01	0.01	
	2.00	0.18	3.92	0.00	0.28	0.37	
	3.00	0.03	9.48	0.99	0.70	0.62	
3	1.00	3.68	1.00	0.00	0.01	0.01	0.01
	2.00	0.20	4.28	0.00	0.12	0.39	0.07
	3.00	0.09	6.49	0.00	0.48	0.00	0.76
	4.00	0.03	11.58	0.99	0.40	0.60	0.16

Dependent Variable: Overall PAC-QOL score

Appendix B, Table 9. Summary of collinearity diagnostics for stepwise regression.

Residuals Statistics(a)					
	Minimum	Maximum	Mean	Standard Deviation	Number
Predicted Value	1.13	3.84	2.50	0.56	108
Residual	-1.62	1.46	-0.03	0.51	108
Std. Predicted Value	-2.37	2.36	0.17	0.98	108
Std. Residual	-3.14	2.83	-0.05	0.99	108
a	Dependent Variable: Overall PAC-QOL score				

Appendix B, Table 10. Summary of residual statistics for stepwise regression.

Collinearity Diagnostics(a)							
Model	Dimension	Eigenvalue	Condition Index	Variance Proportions			
				(Constant)	Mental Component Summary	PAC-SYM stool symptom score	PAC-SYM Abdominal symptom score
17	1	3.68	1.00	0.00	0.01	0.01	0.01
	2	0.20	4.28	0.00	0.39	0.07	0.12
	3	0.09	6.49	0.00	0.00	0.76	0.48
	4	0.03	11.58	0.99	0.60	0.16	0.40

a Dependent Variable: Overall PAC-QOL score

Appendix B, Table 11. Collinearity diagnostics for backwards regression model 17.

	Minimum	Maximum	Mean	Standard Deviation	Number
Predicted Value	1.13	3.84	2.50	0.56	108
Residual	-1.62	1.46	-0.03	0.51	108
Std. Predicted Value	-2.37	2.36	0.17	0.98	108
Std. Residual	-3.14	2.83	-0.05	0.99	108

a Dependent Variable: Overall PAC-QOL score

Appendix B, Table 12. Summary of residual statistics for backwards regression.

14.3 Appendix C

Condition	Patient	Age	Sex	Duration of symptoms (years)	Co existing medical conditions	WHO performance status
Functional constipation	FC1	36	F	18	-	0
	FC2	43	F	16	GORD	0
	FC3	52	F	40	Asthma Hypertension GORD	0
	FC4	37	F	5	-	0
	FC5	42	F	20	-	0
	FC6	62	F	43	Hypertension IHD	0
	FC7	32	F	25	-	0
	FC8	34	F	8	Hyperthyroid NUD	0
	FC9	38	F	6	NUD	0
	FC10	44	F	40	NUD	0
	FC11	33	F	6	eczema	0

GORD; Gastro oesophageal Reflux Disease IHD; Ischaemic Heart Disease NUD; Non Ulcer Dyspepsia

Appendix C, Table 1. Characteristics of patients with FC selected for PEC

Condition	Patient	Age	Sex	Duration of symptoms (years)	Co existing medical conditions	WHO performance status
Colonic pseudo-obstruction	CPO1	83	M	5	CVD IHD	2
	CPO2	70	F	3	CVD Hypothyroid	4
	CPO3	49	F	3	CVD	4
	CPO4*	74	M	20 days	IHD CVD	4
	CPO5**	77	F	5 days	IHD CVD hypertension	3

*CPO4 suffered acute CPO after fracture neck of femur
** CPO5 suffered acute CPO after skin graft under GA

CVD, Cerebrovascular Disease

IHD, Ischaemic Heart Disease

Appendix C, Table 2. Characteristics of patients with CPO selected for PEC

Condition	Case	Age	Sex	Symptom duration (years)	Co existing medical conditions	WHO performance status
Neurological constipation	NC1	56	M	10	-	2
	NC2	44	F	20	-	4
	NC3	61	F	5	Hypertension	1
	NC4	34	F	34	Menorrhagia	1
	NC5	74	M	24	Hypertension, IHD	4
	NC6	41	M	14	Hypertension	2
	NC7	40	F	12	-	1

IHD, Ischaemic Heart Disease

Appendix C, Table 3. Characteristics of patients with NC selected for PEC

Condition	Case	Age	Sex	Symptom duration (years)	Co existing medical conditions	WHO performance status
Recurrent Sigmoid Volvulus	RSV1	83	F	3	Dementia IHD	4
	RSV2	68	M	1	Lung cancer	2
	RSV3	90	M	10	Hypertension CCF	3
	RSV4	72	M	12	Hypertension Diabetes IHD	3
	RSV5	80	M	6	CCF Diabetes	2
	RSV6	72	F	5	RA PVD hypertension	4
	RSV7	81	F	6	Hypertension	3
	RSV8	97	M	1	Hypertension CVD IHD	2

CCF, Congestive cardiac failure CVD, Cerebrovascular Disease PVD, Peripheral vascular disease

IHD, Ischaemic Heart Disease RA, Rheumatoid arthritis

Appendix C, Table 4. Characteristics of patients with RSV selected for PEC.

Condition	Case	Duration PEC in situ (months)	Effect on symptoms	Number of infective episodes	PEC tube outcome	Reason for removal	Patient outcome
Functional constipation	FC1	20	Much improved	4	Elective removal	Recurrent infection	Recommenced conservative treatment
	FC2	8	Much improved	2	Elective removal	Recurrent infection	Recommenced conservative treatment
	FC3	6	Much improved	3	Elective removal	Recurrent infection	Colectomy & IRA
	FC4	2	No change	1	Elective removal	Infection and pain	Colectomy & IRA
	FC5	3	Much improved	2	Elective removal	Recurrent infection, leakage and pain	Colectomy & IRA
	FC6	10 days	Much improved	1	Emergency removal	Infection and pain	Colectomy & IRA
	FC7	4	Much improved	4	Elective removal	Recurrent infection and pain	Colectomy & IRA
	FC8	2	Much improved	3	Elective removal	Recurrent pain	ACE procedure

Appendix C, Table 5. Outcomes for patients who had PEC inserted for FC

Condition	Case	Duration PEC in situ (months)	Effect on symptoms	Number of infective episodes	PEC tube outcome	Reason for removal	Patient outcome
Colonic pseudo-obstruction	CPO1	4 days	-	0	Emergency removal	Faecal peritonitis	Colectomy, post operative death
	CPO2	7	Much improved	0	In situ	-	Remains in follow up
	CPO3	26	Minimally improved	3	Elective removal	Recurrent infection	Recommenced conservative treatment
	CPO4*	3	No change	3	Elective removal	Resolution of CPO	Resolution of symptoms CPO after 3 months
	CPO5**	19	Much improved	3	Elective removal	Recurrent infection	Remains symptom free in follow up

*CPO4 suffered acute CPO after fracture neck of femur
** CPO5 suffered acute CPO after skin graft under GA

Appendix C, Table 6. Outcomes for patients with CPO who had PEC.

Condition	Case	Duration PEC in situ (months)	Effect on symptoms	Number of infective episodes	PEC tube outcome	Reason for removal	Patient outcome
Neurological constipation	NC1	24	Minimally improved	4	Elective removal	Immuno-suppressive medication	Colectomy & ileostomy
	NC2	21	Much improved	1	Emergency removal	Subcutaneous abscess	Sigmoid colectomy
	NC3	6	Much improved	2	Elective removal	Recurrent infection	Recommenced conservative treatment
	NC4	26	Much improved	4	Elective removal	Recurrent infection	ACE procedure
	NC5	10	Much improved	1	In situ	-	Symptoms controlled
	NC6	4	Much improved	2	Elective removal	Recurrent pain	Colectomy & ileostomy

Appendix C, Table 7. Outcomes for patients with NC who had PEC.

Condition	Case	Duration PEC in situ (months)	Effect on symptoms	Number of infective episodes	PEC tube outcome	Reason for removal	Patient outcome
Recurrent Sigmoid volvulus	RSV1	12	No further RSV with PEC in situ	0	Dislodged	-	Fatal faecal peritonitis
	RSV2	8	No further RSV with PEC in situ	0	In situ at point of death	-	Death due to lung cancer
	RSV3	12	No further RSV with PEC in situ	2	Elective removal	Buried bumper	Recurrent volvulus & colectomy. Post operative death
	RSV4	3	No further RSV with PEC in situ	1	Elective removal	Infection and pain	Recurrence & colectomy. Remains in follow up
	RSV5	16	No further RSV with PEC in situ	0	Dislodged	-	No further episodes of RSV
	RSV6	17	No further RSV with PEC in situ	2	In situ at point of death	-	Fatal pneumonia
	RSV7	1	No further RSV with PEC in situ	0	In situ at point of death	-	Fatal pneumonia
	RSV8	1	No further RSV with PEC in situ	0	In situ at point of death	-	Fatal pneumonia

Appendix C, Table 8. Outcomes for RSV patients with PEC

Group definition	Number	Sum of ranks	Mean of Ranks
Rate of infection in FC	8	186	23.25
Rate of infection in NC	6	68.5	15.33
Rate of infection in RSV	8	92	8.50
Rate of infection in CPO	6	59.0	10.00

Kruskal - Wallis statistic 15.26
p = 0.0014

Dunn's Multiple Comparisons Test

Comparison	Mean rank difference	p value
Rate of infection FC v Rate of infection RSV	14.688	<0.01
Rate of infection FC v Rate of infection NC	7.917	>0.05
Rate of infection FC v Rate of infection CPO	13.333	<0.05
Rate of infection RSV v Rate of infection NC	-6.771	>0.05
Rate of infection RSV v Rate of infection CPO	-1.354	>0.05
Rate of infection NC v Rate of infection CPO	5.417	>0.05

Appendix C, Table 9. Rate of infection in different conditions

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