Optimising the outcome of neuromodulation for faecal incontinence and constipation

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Declaration of originality

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Abstract

This thesis begins with a summary of the general management of faecal incontinence and constipation. This is followed by a review of the literature to support the use of neuromodulation for these conditions. The first study reports the effect of alteration of pulse width and frequency on sacral nerve stimulation for constipation. The next study investigates the outcome of transcutaneous stimulation of the sacrum for faecal incontinence. The outcome of pudendal nerve stimulation is reported for those who have failed to improve with sacral nerve stimulation. Lastly the effect of unilateral transcutaneous posterior tibial nerve stimulation is studied and applied to bilateral stimulation.

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Publications and Presentations arising from the thesis

Review articles

Chapter 2

Advances in the Surgical Treatment of Faecal Incontinence

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Chapter 3

A Review of Posterior Tibial Nerve Stimulation for Faecal Incontinence.

G P Thomas, T C Dudding, G Rahbour, R J Nicholls, C J Vaizey.

Colorectal Disease. 2013 May;15(5):519-26

Chapter 4

Sacral Nerve Stimulation for Constipation.

G P Thomas, T C Dudding, G Rahbour, R J Nicholls, C J Vaizey.

British Journal of Surgery, 2013 vol. 100 (2) 174-81

Original Articles

Chapter 6

A pilot study of transcutaneous sacral nerve stimulation for faecal incontinence.

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Sacral transcutaneous stimulation for faecal incontinence may have a different mechanism of action to sacral nerve stimulation.

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Chapter 7

A pilot study of chronic pudendal nerve stimulation for faecal incontinence for those who have failed sacral nerve stimulation

GP Thomas, AT George, TC Dudding, RJ Nicholls, CJ Vaizey

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Chapter 8

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Pudendal nerve stimulation in the treatment of faecal incontinence.

GP Thomas, AT George, TC Dudding, RJ Nicholls, CJ Vaizey

Colorectal Disease. Vol 15 (suppl 1), 1-65, 2013

Presentations

Development of an optimum treatment regimen for transcutaneous posterior tibial nerve stimulation for faecal incontinence
G P Thomas, T C Dudding, E Bradshaw, R J Nicholls, C J Vaizey
Oral presentation at the Royal Society of Medicine 2013.

Development of an optimum treatment regimen for transcutaneous posterior tibial nerve stimulation for faecal incontinence
G P Thomas, T C Dudding, E Bradshaw, R J Nicholls, C J Vaizey
Oral presentation at the Association of Coloproctology of Great Britain and Ireland 2013.

Development of an optimum treatment regimen for transcutaneous posterior tibial nerve stimulation for faecal incontinence
G P Thomas, T C Dudding, E Bradshaw, R J Nicholls, C J Vaizey
Poster presentation at the British Society of Gastroenterology 2013.

Development of an optimum treatment regimen for transcutaneous posterior tibial nerve stimulation for faecal incontinence
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Transcutaneous sacral nerve stimulation for faecal incontinence
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Pudendal nerve stimulation in the treatment of faecal incontinence
GP Thomas, AT George, TC Dudding, RJ Nicholls, CJ Vaizey
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Factors predictive of success of transcutaneous posterior tibial nerve stimulation for faecal incontinence.
GP Thomas, TC Dudding, RJ Nicholls, CJ Vaizey
Poster presentation at the European Society of Coloproctology, Belgrade, 2013.

CHAPTER 1

Overall aims and outline of thesis

This thesis aims to investigate different methods of optimising existing neuromodulatory treatments for faecal incontinence and constipation. The three forms used most widely have been sacral nerve stimulation, posterior tibial nerve stimulation and pudendal nerve stimulation. The research on sacral nerve stimulation is described in chapters five and six, pudendal nerve stimulation is described in chapter seven and posterior tibial nerve stimulation is described in chapter eight. The aims for each chapter are summarised below.

CHAPTER 2

2.1 Overview of the treatment of faecal incontinence

2.2 Overview of the treatment of constipation

This chapter provides an overview of the treatment of faecal incontinence and constipation. It describes the current position of neuromodulation in the treatment pathway for these conditions.

CHAPTER 3

Neuromodulation for faecal incontinence

2.1 Sacral nerve stimulation

2.2 Posterior tibial nerve stimulation

2.3 Pudendal nerve stimulation

This chapter reviews the scientific literature on neuromodulation for faecal incontinence. It includes a systematic review on the use of posterior tibial nerve stimulation for this condition.

CHAPTER 4

Neuromodulation for constipation

3.1 Sacral nerve stimulation

3.2 Posterior tibial nerve stimulation

3.3 Pudendal nerve stimulation

This chapter reviews the literature on neuromodulation for constipation. It includes a systematic review of the use of sacral nerve stimulation for this condition.

CHAPTER 5

Double blind randomised controlled multicentre study to compare the effect of stimulation parameter changes on sacral nerve stimulation for constipation.

Sacral nerve stimulation (SNS) is typically delivered using a fixed pulse width and frequency. The amplitude and lead electrode position are variable. These settings are based on historical data derived from studies in patients with bladder dysfunction. SNS can be an effective treatment for constipation, but even when successful, improvement is usually partial rather than complete. The effect of altered pulse width and frequency on SNS for faecal incontinence has been reported. An improvement in symptoms was seen when a higher frequency was used. The aim of this study was to see if the efficacy of SNS for constipation can be improved by altering these stimulation parameters.

CHAPTER 6

Studies into transcutaneous stimulation over the sacrum for faecal incontinence

Until recently, only one study has reported transcutaneous SNS for faecal incontinence. This described unilateral stimulation of the area over the third sacral foramen for two hours a day over three months. Encouraging results were seen. Transcutaneous SNS is cheaper and safer than SNS by direct electrode stimulation of the anterior nerve root.

The aim of the first study was to see if a more intensive treatment regimen, using bilateral stimulation over the entire sacrum, could achieve a significant therapeutic effect.

The next study attempted to see if transcutaneous SNS had a similar mechanism of action to SNS. Stimulation of the third sacral nerve root using a SNS electrode causes contraction of the external anal sphincter. The aim of the next study was to see if transcutaneous SNS had a similar effect on the sphincter. It is unlikely that transcutaneous SNS has a similar mechanism of action to SNS. It may be that it is only providing cutaneous stimulation. The final study in this chapter aimed to see whether cutaneous electrical stimulation of another area of the body can achieve a similar therapeutic effect.

CHAPTER 7

Pudendal nerve stimulation for faecal incontinence

This chapter describes a pilot study of the medium term outcome of pudendal nerve stimulation for faecal incontinence. There are several reports of its use for bladder dysfunction, but except two cases reports, this technique has not been reported for faecal incontinence.

CHAPTER 8

Studies of transcutaneous posterior tibial nerve stimulation for faecal incontinence

Posterior tibial nerve stimulation (PTNS) has been reported to be effective for faecal incontinence. Many different techniques have been reported. The first study carried out aimed to compare a more intensive treatment regimen with the less intensive regimen of unilateral transcutaneous PTNS. The second study investigated bilateral transcutaneous PTNS, using the optimal stimulation regimen determined from the first study. Bilateral transcutaneous PTNS has not been reported previously. The final study used the data from the earlier two studies to see which factors might affect the outcome of transcutaneous PTNS.

CHAPTER 2

2.1 Overview of the treatment of faecal incontinence

Introduction

Faecal incontinence (FI) is common. It occurs in 2% to 20% of the adult population in the western world [1-4]. It is under reported and most commonly affects women over 65 years of age [2]. It causes considerable morbidity and reduces quality of life. It may be caused by increased forced of expulsion of faeces or by an impaired ability to retain them. The former may be due to inflammation causing irritability of the rectum or to loss of rectal or neorectal capacity. Failure to retain faeces may be due to motor or sensory impairment of the anorectal sphincter mechanism. In many patients both factors are present. The main causes are summarised in Table 1.

Treatment strategy

Conservative treatment should be offered initially. This includes anti-diarrhoeal medication, the use of a pad or anal plug, pelvic floor physiotherapy and biofeedback [5]. A recent Cochrane review of biofeedback for FI, found little good quality evidence for its effectiveness. However, the authors concluded that biofeedback was probably superior to pelvic floor exercise alone [6]. Retrograde rectal irrigation may be effective in up two thirds of patients [7]. More invasive treatment is reserved for those who fail conservative therapy. Neuromodulatory therapies are described in Chapter 2. An overview of the treatment pathway is shown in Figure 1. A full thickness external rectal prolapse should be surgically corrected before any other treatment.

a. Injectable anal bulking agents

The first report of an injectable bulking agent to treat faecal incontinence was published in 1993 [8]. This used a Teflon-like material. Since then many different materials have been studied. The results have generally been disappointing, mostly due to poor efficacy and safety [9]. The short term results of a new bulking agent, the Anal Gatekeeper, have recently been reported [10]. This consisted of an implantable cylinder of polyacrylonitrile, injected into the intersphincteric space. Episodes of passive incontinence improved from 7.1 (7.4) per week at baseline to 0.4 (0.6) per week at 33.5 (12.4) months mean follow up. Clinical improvement correlated with improved quality of life. No adverse effects were reported, but the study was small (n=14). Larger studies are currently under way.

a. Radiofrequency ablation (SECCA)

The SECCA system (Curon Medical Inc, Sunnyvale, CA, USA) works by delivering radiofrequency energy to the internal anal sphincter to induce fibrosis to cause anal canal closure by contraction of collagen. It is used for passive FI in which internal sphincter weakness predominates. It is a day case procedure and can be performed under local anaesthesia with sedation. In 2002 Takahsahi et al [11] reported its use in ten patients with idiopathic FI. At six months a significant improvement in the Wexner FI score was seen (13.5 to 5). Less impressive improvements in the Wexner FI score were reported by Efron in 2003 [12], Lefebure in 2008 [13] and Ruiz in 2010 [14] (14.5 to 11.1, 14.07 to 12.33 and 15.6 to 12.9 respectively). Most patients remained moderately incontinent after treatment and it appears that SECCA gives only a marginal benefit.

b. Anal Sphincteroplasty

Overlapping sphincter repair is the operation of choice for most patients with an external anal sphincter defect. In a recent systematic review of the long term outcome of 900 patients at five or more years [15], the authors found marked differences in the criteria adopted among the studies to define incontinence. There was however an initial improvement in most studies followed by a gradual deterioration over time. This deterioration did not however, correlate with quality of life or patient satisfaction. No consistent predictive factors for failure were identified.

c. Artificial Anal Sphincter prostheses

AMS 800 and Acticon Neosphincter

The use of an artificial anal sphincter for FI was first reported in 1987 [16]. This utilized the AMS 800 device, which had originally been devised for urinary incontinence. Many reports have further described its efficacy [17-23] and subsequently the device being applied to the anus was renamed the Acticon neosphincter. The device consists of an inflated cuff which encircles the sphincter complex. This is connected to a hydraulic system whereby deflation of the cuff is effected by a pump located in the labia majora or scrotum when defecation is desired. A systematic review [24] of 14 reports found a very high incidence of device removal mostly due to erosion, infection or mechanical failure. Few reports analysed the data on an intention to treat basis, but patients who continued to have a functioning implant experienced a significant improvement in symptoms. These results were reflected by a recent report describing 52 patients, who had been implanted with the Acticon device over a 14 year period [25]. At a mean follow up of 64.3 ±46.5 months, 26% had had the device removed owing to infection in most cases and 24% underwent revision due to device failure. Of the patients left with a

functioning device, 67.3% had a significant improvement in the Wexner faecal incontinence score and in quality of life.

The Prosthetic Anal Sphincter

The prosthetic anal sphincter (PAS), was reported in 2004 [26]. This expandable device is placed at the anorectal junction, and acts to accentuate the effect of puborectalis, by narrowing the angle between the rectum and anus. The PAS can be controlled by the patient, to allow the anorectal angle to straighten when defecation is desired. In a report of 12 patients at a median follow up of 59 (30-72) months, ten became continent. The Wexner faecal incontinence score improved from 16 (7-20) at baseline to 3 (0-7). Two devices were removed due to infection following revisional surgery. Despite this, the reported improvement in symptoms is encouraging.

The Magnetic Anal Sphincter

The magnetic anal sphincter is a recent development. It includes a flexible ring of magnetic titanium beads which is inserted around the anal canal in a similar manner to its use for gastro-oesophageal reflux. The beads come together by magnetism to close the anus and the pressure exerted by voluntary defecation separates them to allow defecation. In a preliminary report of 14 patients [27], three had the device removed and at a median follow up of six months, five of the remaining patients had a significant reduction in incontinent episodes from 7.2 at baseline to 0.7 with a significant improvement in quality of life.

A small non-randomised study indirectly compared the outcome of the magnetic anal sphincter (n=10) with the Acticon device (n=10)[28]. Four of the latter were revised and two were removed owing to infection. One of the former spontaneously eroded. Overall a significant reduction in the Wexner faecal incontinence score was seen in both groups. Sacral nerve stimulation was compared with the magnetic anal sphincter in a similar fashion [29]. Both therapies achieved a significant reduction in episodes of incontinence and improvements in quality of life. In both studies, it is likely that multiple reporting of the same patients had taken place. These studies were non-randomised and small, therefore it is difficult to draw any firm conclusions. Larger, truly prospective randomised trials are needed to determine the efficacy and safety of the magnetic anal sphincter.

d. Graciloplasty

Non-stimulated graciloplasty was first described in 1952 [30]. The gracilis muscle derives its blood supply proximally, so can be divided distally without compromising viability. The muscle is mobilised to encircle the anus. The results were disappointing initially. Stimulation of the nerve supplying the gracilis muscle, dynamic graciloplasty, was described in 1988 [31]. High frequency

stimulation by an implantable pulse generator, converts the fast twitch fibres of the gracilis to fatigue resistant slow twitch activity. This has lead to an improved outcome, with up to 60% of patients reported to have improved function in some studies [32], although others have been less successful [33] The procedure is associated with high complication and reoperation rates with the former occurring in up to two thirds of patients [34].

e. Antegrade colonic enema

First reported by Malone in 1990 [35], this utilised a Mitrofanoff valve to produce a catheterisable continent colonic stoma to permit antegrade colonic irrigation. Worsoe and colleagues [36] reported 80 patients who had undergone an antegrade colonic enema, 69 of whom used an appendicostomy. At a median follow up of 75 months, 38% had had complications related to the appendicostomy and success was reported in 51 (74%). Chereau et al [37] reported a similar outcome. Seventy five patients underwent this procedure, 68 of whom had an appendicostomy. Complications occurred in 16 (21%). At a median follow up of 48 months, 64 were still using the stoma, and of these 55 (86%) had a satisfactory outcome with a fall in the Wexner score from 14.3 (±2.9) to 3.4 (±2.4).

f. Stoma

When other treatments fail, a stoma may be the best means of management. It can bring relief with improved quality of life to a patient for whom other treatments are not adequate. Faecal diversion can be either by ileostomy or colostomy. Patients who have a stoma after more conservative failed attempts to improve incontinence may be very satisfied with the result [38] . Anal leakage of mucus from the rectum may continue to be troublesome however and occasionally it may be necessary to perform rectal excision after a stoma for incontinence. Stoma related complications including herniation, prolapse and retraction are common particularly in an elderly patient.

2.2 Overview of the treatment of constipation

Introduction

It has been estimated that, worldwide, around 14% of adults suffer from constipation. The incidence is higher in older patients, in females and in those of lower socioeconomic status [39]. Constipation has been defined by various consensus groups, such as the Rome Foundation which developed the Rome III criteria. According to these, two of six symptoms must be present for 6 months or more. The symptoms include straining at stool, passing hard stools, sensation of incomplete emptying, sensation

of anorectal obstruction, self digitation and a defecation frequency of less than three times per week. [40]. These diagnostic criteria reflect the variety of symptoms that can be present with constipation, along with abdominal pain, bloating and frequent laxative and enema use.

The pathogenesis of constipation can be broadly subdivided into disorders of colonic motility and evacuatory dysfunction, with a degree of overlap in many patients [41]. Various factors may be responsible for delayed colonic motility, these include immobility, age, medication, endocrine, psychological, aganglionosis and pseudo-obstruction. Evacuatory dysfunction may be due to a mechanical cause, such as rectal intusussception, rectal prolapse, rectocele or enterocele. It may also be due to functional causes such as anismus or dyssynergia, descending perineum syndrome or spinal injury. In many patients, both mechanical and functional elements will co-exist.

Treatment

Medical treatment includes dietary advice, drug treatment (laxatives, enemas, suppositories) and biofeedback. Chiotakakou-Faliakou and colleagues reported the outcome of 100 patients who had undergone biofeedback for constipation. This group included equal proportions of those with slow colonic transit and impaired pelvic floor co-ordination. At a median follow up of 23 (12-44) months 57% felt that their symptoms had improved significantly [42]. A flow diagram of the treatment for constipation is shown in Figure 2. Neuromodulation is usually offered if a patient fails to improve following conservative measures. This is discussed in more detail in chapter four. It is helpful in about 50% of patients selected for this treatment and in these the abdominal symptoms of distension and discomfort may also be relieved.

Surgery has a role in a few carefully selected cases if conservative treatment, including neuromodulation, fails and the patient is still severely symptomatic. In those with slow transit constipation, an antegrade continence enema procedure (ACE) or colectomy with or without stoma formation has been advocated [41]. While often successful in childhood, the ACE procedure in adults is associated with a high complication rate, up to 88% re-operation rate and a 48 - 59% failure rate through dropouts in the medium term. Colectomy often improves defecation frequency but symptoms of abdominal pain persist in 41% of patients, this perhaps reflects the pan-enteric motility disorder that exists in many subjects. Following colectomy, 14% of patients develop diarrhoea and/or faecal incontinence and 18% adhesional small bowel obstruction [43].

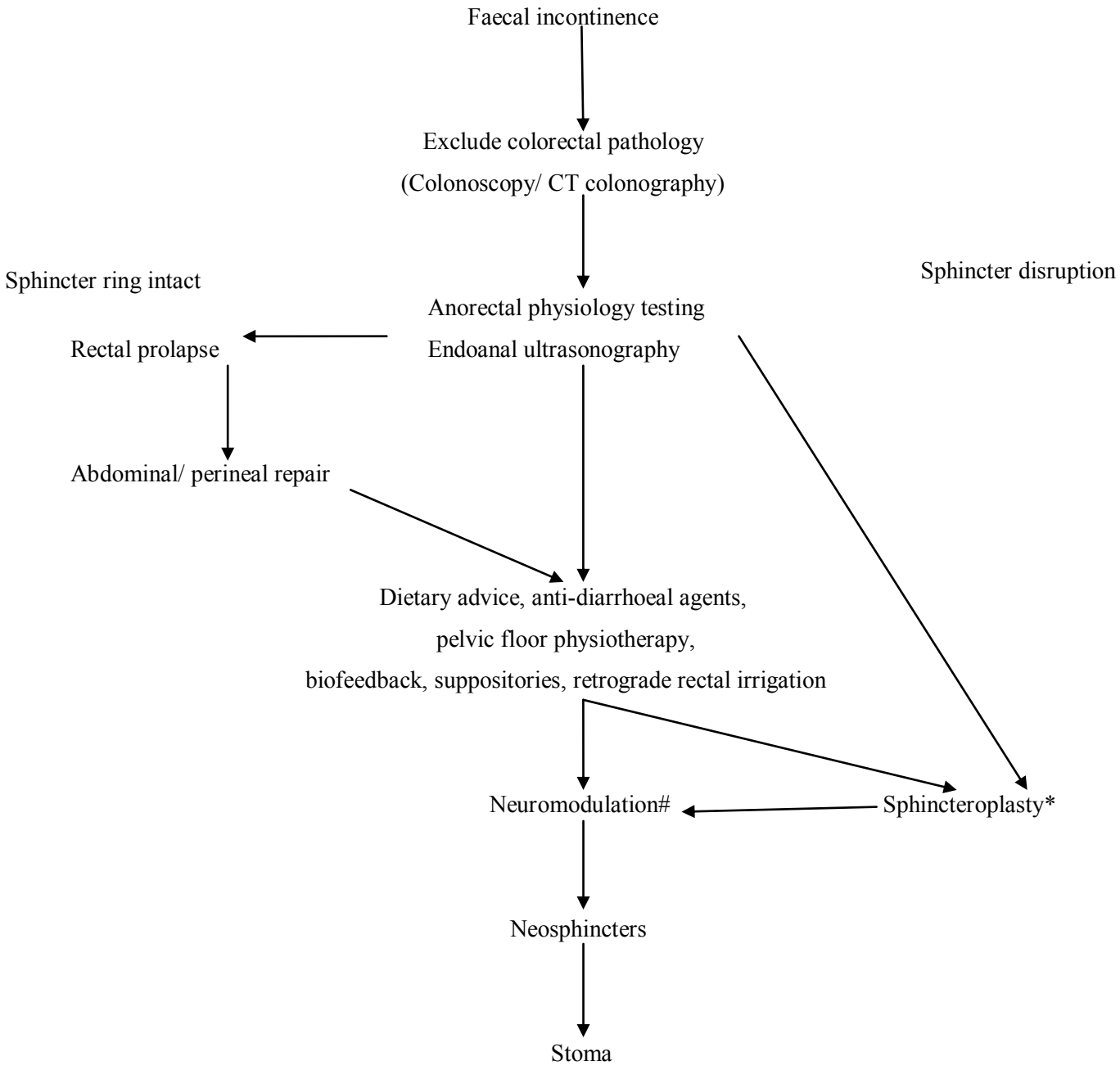
For patients with solely rectal hyposensitivity or pelvic floor dyssynergia, abdominal or perineal surgery is not an option. In those with mechanical dysfunction, operations can be divided into “hitching” procedures (e.g. rectopexy) or “excision” procedures (e.g. stapled transanal rectal

resection). It should be noted that functional and mechanical deficiencies may often coexist to varying degrees. In such patients, correction of the pelvic floor and rectal anatomy may not always improve symptoms. The literature in this area is complicated by the heterogenicity in the groups of patients studied. Rectal intussusception and rectocele are often observed in patients with normal evacuation and the relevance of finding these abnormalities on proctography remains unclear. Reports of worsened constipation with posterior rectopexy have swung current treatment algorithms towards ventral mesh in rectopexy which is often coupled with colpopexy in women with inadequate support of the vaginal vault. STARR remains an alternative treatment option, however there are concerns about its potentially significant complications. A defunctioning colostomy is an alternative for these patients. A proposed treatment algorithm is shown in figure 2.

Table 1. Summary of the main causes of faecal incontinence

Colorectal disease	**Anal sphincter weakness**
Inflammatory (enteritis, colitis, proctitis)	Intact sphincter Functional weakness age, neurological disorder, myopathy, radiotherapy
Irritable bowel syndrome	Ruptured sphincter obstetric, anal surgery, trauma
Reduced rectal capacity (post rectal resection, radiotherapy)	Rectal fistula to vagina or perineum
Congenital anomaly	Physiological activation of the anorectal inhibitory reflex in faecal impaction

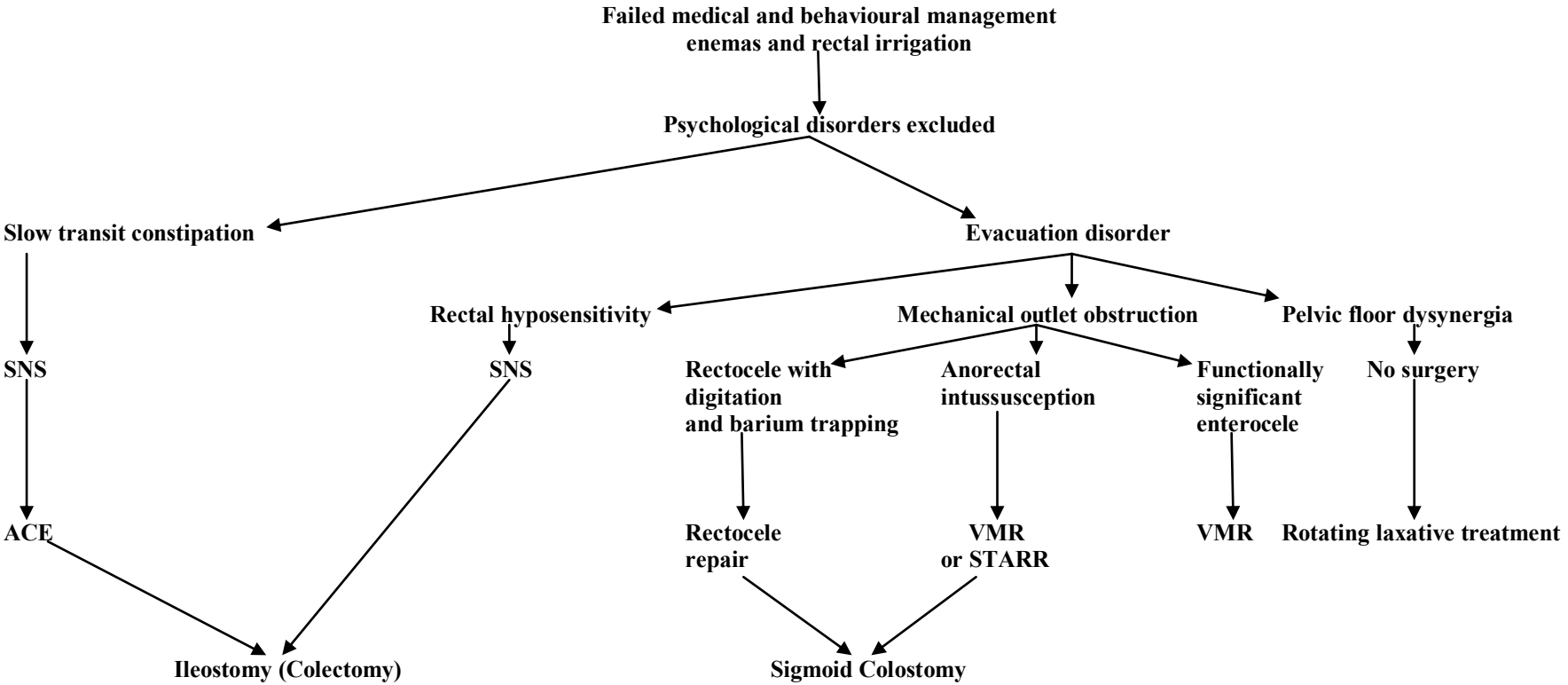
Figure 1. Flow Diagram of the treatment pathway for faecal incontinence



#at present it is uncertain whether sacral nerve stimulation or posterior tibial nerve stimulation should be offered first. Pudendal nerve stimulation is not available outside a research setting.

* only applicable to selected patients. Typically younger patients, with a full length external anal sphincter defect and a good level of residual muscle function.

Figure 2. Proposed treatment algorithm for the treatment of constipation



This algorithm applies to those patients in whom Hirschsprung's disease and megabowel have been excluded.
SNS= sacral nerve stimulation; ACE= antegrade colonic enema; STARR= stapled transanal rectal resection; VMR= ventral mesh rectopexy.

Chapter 3

Neuromodulation for faecal incontinence

3.1 Sacral nerve stimulation for faecal incontinence

Introduction

Sacral nerve stimulation (SNS) is achieved by direct stimulation of the third sacral nerve root, or, less commonly the second or fourth root. It was first developed for bladder dysfunction in 1982 [44]and was applied to faecal incontinence (FI) in 1995 [45]. The effect of SNS was reported in three patients with faecal incontinence with encouraging results. SNS has become increasingly popular and is now considered by many to be the first line treatment for patients who have failed to improve with conservative treatment.

Method

A review was carried out of publications on sacral nerve stimulation for faecal incontinence. Medline, Pubmed and Embase databases were searched electronically using the keywords and/ or MeSH "sacral", "faecal incontinence", "neuromodulation", "stimulation". Further relevant studies were identified by cross referencing from relevant articles and abstracts. Only studies that reported the clinical outcome of SNS for faecal incontinence in the English language were reviewed.

Description of use

a. Test stimulation

Prior to chronic stimulation, the patient must undergo a period of test stimulation. This is typically two to three weeks in duration and is known as peripheral nerve evaluation, or PNE. At the end of this period the patient's response to PNE is evaluated. An objective measure of this can be gained by a prospectively kept bowel diary. If the patient has achieved a successful response, they may then be offered chronic stimulation. A successful response has been judged arbitrarily to be a 50% or more improvement in the frequency of incontinent episodes, incontinent days or in the ability to defer defecation.

PNE may be performed under local or general anaesthesia. The patient is positioned in the prone position. Antibiotics are administered. The buttocks are strapped apart, and the lower back and anal area are prepared. Using surface anatomy, a hollow PNE foramen needle is placed percutaneously

into the third posterior sacral foramen. It is then connected to an external stimulation device (Test stimulator 3692, Medtronic Inc, Minnesota, USA). Correct needle positioning is confirmed by either a sensory response in the anal area, or by contraction of the external anal sphincter and in some instances flexion of the ipsilateral hallux. Once the needle is positioned correctly, the PNE lead is fed down it, and the needle in the foramen is removed. The PNE lead is secured with adhesive tape and connected to the black socket of another lead. The red plug of this lead is connected to a ground pad, which is placed on the upper ipsilateral buttock. Further adhesive dressings are placed over the lower back so as to cover this area. The lead is connected to the external stimulation device (Test stimulator 3692, Medtronic Inc, Minnesota, USA). The frequency is set to 14Hz and the pulse width to 210μsecs. The amplitude is set at level just perceived by the patient or to a level just below this point. The patient should experience a tingling sensation in the perianal or natal cleft area at sensory threshold. Stimulation is provided continuously throughout the test period. At the end of this time, the lead can be removed without the need for anaesthesia.

b. Chronic stimulation

This may be performed under local or general anaesthesia. The patient is positioned prone. The third sacral foramen is entered using a needle electrode in the same manner as during PNE. Once in place, a guide wire is inserted down the needle and the electrode is then removed. The skin at the point of puncture is opened a little by a number 11 scalpel, and an introducer sheath is passed over the guide wire. This is then advanced under X-ray guidance so that its tip comes to be at the level with the cortex of the anterior sacral bone. Under radiological control the permanent lead is placed down the introducer (Medtronic model 3093).

Satisfactory insertion is achieved if one or two proximal electrodes lie within the third sacral foramen. Each electrode is tested to ensure that contraction of the external anal sphincter is achieved, if this is performed under local anaesthesia then a sensory response should be sought. The sheath is then withdrawn and as it comes out, the barbs of the electrode lead are deployed thereby fixing it in the tissues. The pulse generator (Medtronic model 3058) is implanted in a subcutaneous pocket in the ipsilateral buttock, at a point away from any pressure area. A site just below belt line is ideal. The electrode is tunnelled subcutaneously to the pulse generator and is connected. The wounds are closed with sutures. The device is activated once the patient has fully recovered from the anaesthesia. The settings can be adjusted by the clinician using a remote control device (Medtronic N'Vision 8840) or by the patient (Medtronic iCon 3037).

Outcome of SNS for FI

The early reports of SNS for FI all described significant improvements in the frequency of incontinent episodes and in the ability to defer defecation. Improvements in quality of life measures were also observed [46-50]. The follow up in these studies was no longer than a median 24 months. The success rate of PNE ranged from 80 to 100%. Most reported the outcome of SNS in those with structurally intact anal sphincters. The effects of SNS on those with a sphincter lesion are discussed below. A systematic review by Jarrett and colleagues in 2004 summarised the early evidence [51]. They reported the outcome of 266 patients in six published series, including 11 to 116 patients. The follow up ranged from one to 99 months. The PNE success rate was between 55 to 80%. Seventy five to 100% of those with a permanent implant experienced a 50% or more improvement in the frequency of incontinent episodes and 41-75% achieved complete continence. There were also significant improvements in symptom severity scores and in quality of life measures.

Larger prospective series have confirmed the effectiveness of SNS. Melenhorst and colleagues [52] reported on 134 patients who underwent PNE, of these 100 (74.6%) went onto chronic stimulation. The mean number of incontinent episodes per week fell from 31.3 to 4.4 (p=0.0001) at a mean follow up of 25.5 (2.5-63.2) months. Michelsen [53] reported the outcome of 177 patients, of whom 142 (80%) had a good response to PNE. The median Wexner incontinence score [54] improved from 16 (6-20) to 10 (0-20) (p=0.0001) at a median follow up of 24 (3-72) months. In 2010, Wexner and colleagues [55] described 133 patients who had undergone PNE. 120 had a satisfactory response and underwent chronic stimulation. At a follow up of 24 months, 85% had experienced a greater than 50% improvement in their symptoms.

The efficacy of SNS over the longer term has now been described. George and colleagues summarised the results of SNS over a 10 year period in 2012[56]. Twenty three patients had undergone chronic stimulation, of these 12 (52%) had maintained complete continence at a median follow up of 114 (96-164) months. Two of the 23 had lost efficacy at 48 and 60 months respectively. Hull [57] reported the outcome of 76 patients at a minimum of five year follow up. Sixty four (89%) achieved a greater than 50% reduction in incontinent symptoms, and 26 (30%) achieved complete continence. Five patients experienced a loss of efficacy by year five.

Comparison against control and other treatments

Two studies have attempted to compare SNS to placebo. Both utilised a double blinded cross over design. The first was by Vaizey and colleagues in 2000 [58]. This was a double blinded cross over study. Two patients with passive faecal incontinence had undergone nine months of SNS. Each was exposed

to a trial period of two two-week periods, with the stimulator turned on for two weeks and off for two weeks. There was a large improvement in incontinent episodes per week during the on period when compared to the off period with rates of 0 and 2 per week and four and 20 per week, in the on and off groups. The second study was by Leroi and colleagues [59]. Twenty seven patients were randomised to one month periods with the stimulator switched on or off. There was a significant improvement in the frequency of incontinent episodes per week, in the ability to defer defecation, a disease specific quality of life score and in the Wexner score in the on compared with the off group. A recent abstract from Giannini and colleagues [60] has, however, suggested that simply switching the device off may not be an adequate placebo. They reported 18 patients, with faecal and urinary incontinence, who had successfully undergone SNS for at least one year. The implants were deactivated and patients were followed up to see when the symptoms began to deteriorate. They did so in 10 patients by four months and in the remaining eight by 12 months.

Only one study has attempted prospectively to compare SNS with another established treatment. Tjandra [61] compared SNS to medical treatment in two randomised matched groups of 60 patients. Medical treatment included pelvic floor physiotherapy, stool bulking agents and dietary manipulation. They reported no improvement in the control group. However, significant improvements in the frequency of incontinent episodes per week, ability to defer defecation and in the Rockwood QOL score were seen in the SNS group. Several studies have sought to compare SNS indirectly with other treatments, including sphincteroplasty [62], the magnetic anal artificial sphincter [29] and the artificial bowel sphincter [Acticon] [63]. All have suggested equivalence or superiority of SNS. However, given the design of these studies, their conclusions must be viewed with caution. As yet, no published work has directly compared SNS to any of these alternative treatments.

Sphincter defect

Leroi and colleagues first reported the effect of SNS in patients with an anal sphincter lesion [64]. A systematic review by Ratto and colleagues [65] evaluated the available data concerning SNS for those with an anal sphincter defect. All were non-comparative series. They found a further nine studies which had reported 119 patients, with a heterogenous mixture of internal and external sphincter defects. Following PNE, 89% progressed onto chronic stimulation. Significant improvements in the frequency of incontinent episodes per week from 12.1 to 2.3, and in the Wexner incontinence score [54], of 16.5 to 3.8 were seen when the data were analysed together. Improvements in the ability to defer defecation and in the many quality of life measures were also seen.

Systemic sclerosis

SNS was studied in a group of five female patients with systemic sclerosis and faecal incontinence [66]. Four had a successful response to PNE and underwent chronic stimulation. At a median follow up of 24 months the median frequency of incontinent episodes per week had fallen from 15 (7-25) to zero, all patients became continent with an improvement in the ability to defer defecation.

Inflammatory bowel disease

In 2008 Vitton [67] reported five patients with faecal incontinence secondary to sphincter disruption related to Crohn's disease, although none had active Crohn's disease at the time of SNS. All underwent PNE followed by chronic stimulation. At a median follow up of 14 (3-36) months all had a significant improvements in the Wexner score (median 15 to 6 [$p<0.05$]), frequency of defecation per 24 hours (7 to 2 [$p<0.05$] and in frequency of incontinent episodes per 24 hours ($p<0.05$).

In 2012 Lehur and colleagues [68], reported the effect of bilateral SNS on porcine rectal mucosa. They described a reduction in rectal paracellular permeability, reduction in mucosal thickness and an increase in mucus on surface epithelium when compared with a control group. They speculated that SNS acted to reinforce the rectal mucosal barrier and may be effective for gastrointestinal pathologies in which this function is reduced.

After rectal surgery (prolapse repair and rectal resection)

Two reports have described SNS following rectal prolapse repair. The first, by Jarrett in 2005, [69] reported the outcome of four women who had undergone a perineal repair of rectal prolapse. The frequency of incontinent episodes per week fell from 11, 24.7, 5 and 8 to zero, 1.5. 5.5 and 1 in the four patients with improvement in the quality of life. Robert-Yap [70] and colleagues assessed the response to SNS of 11 women following prolapse repair. Nine achieved a good response during PNE and underwent chronic stimulation. At a median follow up of 36 (12-75) months, there was a statistically significant improvement in the frequency of incontinent episodes per week from 15 (13-20) to five (3-7) ($p<0.01$).

Six studies have reported the effect of SNS in patients following rectal resection. The first was by Matzel and colleagues in 2002 [71] of a 48 year old male who underwent bilateral stimulation of the fourth sacral nerve roots using a dual channelled IPG. At latest follow up, complete continence was achieved and there was a reduction in the Wexner incontinence score from 17 to two. The remaining

studies have all reported on the use of unilateral S3 stimulation. All have shown SNS to be an effective treatment for these patients [72-76].

Congenital sphincter defect

Thomas and colleagues [77] reported the outcome of two patients, both born with an imperforate anus, who had undergone SNS. One failed to improve with PNE. The other had a successful response to PNE and underwent chronic stimulation. He improved from daily incontinence to complete continence and an improvement in the ability to defer defecation from two to 15 minutes. This was maintained in the short term.

Spinal pathology

A few studies have examined the effect of SNS in those with spinal pathology. The first was a report by Jarrett in 2005[78]. Thirteen patients, with a heterogenous mixture of partial spinal injuries underwent PNE. Twelve had a successful response and underwent chronic stimulation. At a median follow up of 12 (6-24) months, there was a significant improvement in the frequency of incontinent episodes, from 9.33 (7.64) to 2.39 (3.69) (p=0.012) and in the ability to defer defecation from 0-1 minutes to 5-15 minutes (p=0.022). Gstaltner [79] reported its use for those with complete cauda equina syndrome. Eight out of 11 achieved a good response to PNE, five underwent chronic stimulation. All achieved a significant improvement in their symptoms. Lansen-Koch and colleagues [80] reported an improvement in incontinent symptoms in three patients with spinal bifida and mixed urinary and bowel incontinence.

Cost effectiveness

SNS is expensive. Its current cost in the NHS is around £10500. A replacement battery costs around £7000. This will need to be replaced at approximately six years. Follow up of these patients requires a specialist medical practitioner to reprogram the device when required. Several cost benefit analyses have been performed [81-85]. All have shown SNS to be cost effective, when compared to the alternative treatment. This would be colostomy or continued use of pads and anti diarrhoeal agents. Nonetheless, the initial cost of SNS and the benign nature of faecal incontinence, means that it should be offered only to those with severe disease who have failed to improve with conservative treatment.

Bilateral SNS

Bilateral SNS was first reported by Matzel and colleagues in 2002 [71]. Sievert reported its use for bladder dysfunction in early complete spinal cord injury[86]. Assuming that SNS works by the

activation of multiple ascending sensory neural pathways, then simultaneous stimulation of both third sacral nerve roots should activate more of these pathways. It is not unreasonable to speculate that this may lead to an improved therapeutic effect. However, this would require two leads and possibly two pulse generators. This significant increase in cost would need to be taken into account.

Transcutaneous SNS

Chew and colleagues [87] first reported the use of transcutaneous SNS for faecal incontinence in 2011. They stimulated the area over S3 unilaterally using five millimetre squared electrode pads. This was performed for two hours a day over a three month period. They reported modest, but statistically significant, improvements in the Wexner faecal incontinence score. A similar technique was employed by Leung in 2013 [88]. They described unilateral S3 stimulation for up to eight hours a day over a median period of 10 months. The mean Wexner score improved from 7.9 (4.2) to 4 (3.1) and the St Mark's score [89] improved from 12.7 (5.7) to 5.8 (5.6).

Proposed mechanisms of action

The mechanism of action is currently uncertain. A review of the available literature by Gourcerol and colleagues in 2011[90] proposed three possible mechanisms. The first was a neuromodulatory effect on somato-visceral reflexes, the second a modulation of the perception of afferent information and lastly an effect on external anal sphincter activity.

Many studies have attempted to report changes in anorectal sensory and motor function as a result of SNS. There does not appear to be a consistent pattern to these changes in the literature[91]. SNS is also effective in those with both acquired and congenital sphincter defects. These issues appear to contradict the theory that SNS solely acts upon the sphincter complex. The effect on rectal sensation is also uncertain. However, Knowles in 2012 [92], reported a normalisation of rectal sensory function in 13 patients with evacuatory dysfunction and rectal hyposensitivity. Despite this, it is unlikely that the rectum is the sole target organ for SNS, since it is effective in those who have undergone a rectal resection. The effect of SNS upon colonic motility was examined by Michelsen in 2008 [93]. They assessed segmental colonic transit times in 20 patients over three weeks. A reduction in overall colonic transit time was seen. Patton [94] reported a similar outcome in 2013. Using a double blind cross-over study design, 11 patients were exposed to suprasensory stimulation and to a period of no stimulation, to act as a control. There was significant increase in retrograde colonic propagating sequences during stimulation when compared to control ($p=0.014$). This is in contradiction to the findings of Kamm [95], who reported an increase in colonic time in those successfully treated for slow

transit constipation, and those of Dinning [96] in which there was a significant increase in antegrade colonic propagating sequences during stimulation when compared to baseline (p=0.01). In 2012, further work by Dinning and colleagues [97] compared suprasensory stimulation to subsensory stimulation and to no stimulation in those with slow transit constipation. They reported a significant increase in pancolonic antegrade propagating sequences during suprasensory stimulation. Currently, SNS is delivered using subsensory stimulation. The results of suprasensory stimulation described above have potentially significant implications for the clinical use of SNS.

Several authors have examined the effect of SNS on cortical activity. Giani and colleagues [98] demonstrated an increase in the latency of cerebral somatosensory evoked potentials in patients with faecal incontinence and constipation undergoing SNS. Griffin and co-workers [99] examined the effects of posterior tibial nerve stimulation and SNS on the somatosensory cortex in an animal model. An increase in amplitude of primary cortical evoked potentials was seen during stimulation. These findings suggest that SNS may alter the representation of the lower gastrointestinal tract in the sensory cortex. Lundby and colleagues [100] used positron emission tomography to examine brain activity during two weeks of SNS. They reported an increase in areas of the frontal cortex associated with attention, followed by activation of parts of the caudate nucleus associated with learning and reward processing.

The stimulation parameters used for SNS are typically set at a constant pulse width of 210 μsecs and a frequency of 14Hz. The lead electrode position and amplitude are variable. The pulse width and frequency settings were described by Matzel in 1995 [45], and are based on the those used for urinary disorders [101] in early work by Tanagho in the 1980s. A recent double blinded randomised study by Duelund-Jakobsen and colleagues in 2012 [102] examined the effect of altered frequency and pulse width in 15 patients with FI. They found that an increased frequency conferred a greater therapeutic effect. This echoes earlier work by Dudding [103] in which rectal compliance was used a surrogate marker of success for 12 patients. They found that an increased frequency and reduced pulse width brought an increase in rectal compliance.

Complications

The most common complications of SNS are infection, adverse stimulation and loss or lack of efficacy. Infection rates in the larger series vary from 1.6% in 142 patients [53] to 10.8% in 120 patients [104]. In 2011 a meta-analysis of the available literature, found an overall infection rate of 2% in the 995 patients who underwent PNE and 3% in the 665 who underwent permanent stimulation[105]. Maeda and colleagues [106] reviewed the prospectively collected data of 176 patients who had undergone SNS. At a median follow up of 11 (4-26) months there were 212 episodes of loss of efficacy in 87 patients. 186

events of loss of efficacy in 68 patients were found and pain or discomfort occurred 126 times in 67 patients. Many of these problems were successfully treated by device reprogramming. At 33 (20-52) months 31 patients (17.6%) had had their device explanted or treatment discontinued. The large prospective series by Hull in 2013[57], reported that of 76 patients at 5 years, 27 (35.5%) had required device revision, removal or replacement.

Discussion

SNS appears to be an effective treatment for faecal incontinence in both the short and longer term. This is supported by reported significant improvements in both measures of disease symptoms such as frequency of incontinent episodes and incontinence score, and perhaps more importantly, in quality of life measures. SNS is reserved for those who have failed to improve with conservative treatment. This view is upheld by the guidance from the National Institute for Clinical Excellence in relation to SNS. The two main reasons for this are the cost of SNS provision and the potential complications that a patient may face.

The absence of studies which directly compare SNS to other treatments is disappointing. This may be explained partly by the lack of other comparative effective treatments which are available. For those with a sphincter defect, the obvious alternative treatment is sphincteroplasty. A review of the long term outcome of sphincteroplasty was performed by Glasgow and colleagues [15]. They reported initial success rates of between 40-85%, which declined over the following five years. However despite the worsening symptoms, patient satisfaction and quality of life measures remained high. It remains to be seen how sphincteroplasty compares to SNS.

Despite the reported success of those undergoing chronic stimulation, there are a significant number of patients who do not benefit from SNS. When SNS, including those undergoing PNE, is analysed on an intention to treat basis, around 60% will benefit. This was emphasised by a prospective report of 50 patients who had undergone PNE, over a follow up of 17 (2-55) months[107]. The authors reported that 13 (26%) failed to achieve a greater than 50% improvement in symptoms during PNE. Of those who underwent chronic stimulation, 10 (20%) failed to achieve at least a 50% improvement. Of the initial 50 patients, 27 (54%) achieved at least a 50% improvement, of these, 13 (26%) achieved complete continence. That left 23 (46%) patients who had failed to benefit from SNS. Of those who had obtained benefit from SNS, there may be a loss of efficacy in the longer term. Further treatment for these patients is difficult. Improved patient selection is needed to determine which patients are likely to benefit most from SNS at an earlier stage. A better understanding of how SNS works may aid this.

The outcome measures that are commonly used for SNS must be questioned. To classify a reduction of 50% or more of frequency of incontinent as a successful response is misleading. To those with mild to moderate disease this may represent a complete cure. However this will not be the case for those with severe disease. The effect upon the ability to defer defecation must also be taken into consideration. Patients with severe urgency may not experience a significant number of incontinent episodes, since they would have made considerable changes to their daily lifestyle in order to accommodate this symptom. Symptom scores, such as the St Mark's score [89], go some way to addressing these issues by including the effect of urgency and impact upon daily life. Given that faecal incontinence is a benign disease and that a complete resolution of symptoms is difficult to achieve, it may be that quality of life measures should be used rather than symptom assessment.

Transcutaneous SNS is interesting. It is cheaper and safer than percutaneous SNS. The two published reports [87, 88] suggest that it has promise as a treatment for faecal incontinence. Its mechanism of action is uncertain. It is difficult to believe that the applied electrical stimulation has any effect upon the third sacral nerve root, given the depth of skin, fat and bone that it must traverse first. This implies a different mechanism of action to percutaneous SNS. However, the data for this technique are small and far from conclusive, and any placebo effect cannot be discounted at this stage. Larger studies are needed to investigate this further, and a direct comparison to alternative therapies should be made.

3.2 Posterior tibial nerve stimulation for faecal incontinence

Introduction

Posterior tibial nerve stimulation (PTNS) was first used for urinary incontinence by Nakamura et al in 1983 [108] and McGuire et al in 1983 [109]. It was first described for faecal incontinence by Shafik in 2003, who used percutaneous stimulation [110]. This was followed by the less invasive transcutaneous stimulation introduced by Queralto et al [111]. Since then 12 further studies have investigated its effectiveness for faecal incontinence. We have reviewed the results of PTNS by a formal search of the literature. Transcutaneous PTNS is performed using an adhesive electrode pad placed over the posterior tibial nerve, in a position posterior and superior to the medial malleolus. Percutaneous PTNS utilises an electrode needle instead. For both techniques a ground pad is placed nearby.

Method

A review was performed of all the evidence published on posterior tibial nerve stimulation for faecal incontinence. An electronic search was performed of the Medline, Pubmed and Embase databases using the keywords and/ or MeSH "tibial", "faecal incontinence", "neuromodulation", "stimulation". Further relevant studies were identified by cross referencing from relevant articles and abstracts. Only studies that reported the clinical outcome of PTNS for faecal incontinence in the English language were included (see table 1).

Results

Table 1 summarises the study type, study population, modality of PTNS used, regimen of PTNS used and the level of evidence for each study. Table 2 summarises the different outcome measures used for each study.

Percutaneous PTNS

Shafik, in 2003 [110] described thirty two patients, all with idiopathic faecal incontinence, who had received percutaneous PTNS. All had an intact sphincter, and had failed biofeedback and other conservative treatment. They received 30 minutes of stimulation on alternate days for a period of four weeks. This group was compared with 20 untreated control patients. The primary endpoint was >50% improvement in a faecal incontinence score, similar to the Wexner FI Score [112]. A > 50% improvement in the continence score occurred in 27 (84%) of patients treated, nine (29%) of whom experienced a relapse during a mean period of 22.3 ± 4.6 [SD] months. Six of these patients benefitted from further "top-up" therapy. It is unclear whether randomisation or matching of the two groups were attempted, or how the control group was managed or how they compared with the treatment group. The follow up period ranged from 16 to 30 months.

De la Portilla [113] described 16 subjects treated by PTNS for 30 minutes once a week for three months. All had failed conservative therapy, and all had an intact sphincter. A statistically significant reduction in the Wexner faecal incontinence score was seen immediately after treatment, which was maintained at a 3 month assessment. The reduction in the number of incontinent episodes was, however, not statistically significant. Maximal anal canal squeeze pressure was significantly increased.

In a prospective multicentre study 22 patients received twice weekly 30 minute PTNS for six weeks [114]. All had failed conservative treatment and none had a significant sphincter defect. Treatment was continued weekly, then biweekly and finally monthly. At six weeks 14 (63%) had a greater than 50%

reduction in incontinent episodes, but this was not statistically significant. If symptoms reappeared or worsened, then treatment reverted to the last effective treatment schedule and was continued for one year. At one year assessment, there was a significant reduction in incontinence episodes in the 14 patients, who remained in the study. There was a statistically significant reduction in the Wexner faecal incontinence score at six weeks, three months and one year after PTNS. A significant improvement in the SF-36 health related quality of life score at one year was also seen. Anorectal physiological parameters were not assessed.

In a retrospective report of 13 patients, [115] PTNS was given weekly for 30 minutes for three months. Using prospectively collected data, a statistically significant reduction in incontinent episodes was demonstrated. This improvement was maintained at one month follow up.

Three prospective studies of percutaneous PTNS were reported from the same institution [116-118]. The largest of these [118] included 100 patients having twelve 30 minute sessions either twice weekly over six weeks or once weekly over 12 weeks. The patients were divided into groups according to the type of incontinence, whether passive or urge. In patients with passive incontinence there was no significant difference in the Wexner score (11.5±4.1 before; 9.41 ±4.3 after), urgency (5 minutes before; 12 minutes after) and the number of incontinent episodes (median 4/week before; 3/week after). There was a significant improvement in the depression and lifestyle domains of the Rockwell faecal incontinence quality of life score (2.85+/-0.79 to 3.23+/-0.87, and 2.96+/-1.1 to 3.14+/-1.06 respectively). In the urge incontinence group there was a statistically significant improvement in the Wexner FI score (11± 4.1 before; 8.3 ± 4.8 after), urgency (1 minute before; 5 minutes after) and in the number of incontinent episodes per week (median 4 before; 0 after). There were significant improvements in the coping and depression domains of the quality of life score (1.43+/-0.36 to 1.92+/-0.73, and 2.36+/-0.63 to 2.88+/-0.79 respectively). In patients with both passive and urge incontinence, there was a significant difference in the Wexner FI score (12.8 ± 3.7 before; 9.1 ±4.4 after), urgency (1 minute before; 5 minutes after) and the number of incontinent episodes per week (median 5 before; 1 after). All domains of the quality of life score improved significantly (Lifestyle: 2.4+/- to 2.9+/-0.93, Coping: 1.74+/-0.61 to2.36+/-0.77, Depression: 2.89+/-0.91 to 3.27+/-0.77, Embarrassment: 2.03+/-0.89 to 2.6+/-0.89).

Transcutaneous PTNS

In a prospective uncontrolled study [111], ten patients received daily treatment for 20 minutes for four weeks. All had an intact sphincter and had failed biofeedback. A statistically significant improvement of more than 60% in the Wexner FI score was reported, which was maintained at a 12 week

assessment. It is unclear whether this was statistically significant. There was no statistically significant change in anal canal pressures.

Twenty four patients [119] received 20 minute daily sessions for three months. All had failed conservative therapy, but no data on the integrity of the anal sphincter were given. There was no statistically significant difference in the Wexner FI score before and after treatment. Those with evidence of improvement were offered further treatment. On assessment at a mean of 15 months, this improvement was maintained. Anorectal manometry was not performed.

Another study included 32 patients treated twice daily for one month [120]. The primary endpoint was a visual analogue score simply to assess overall benefit. Secondary endpoints included the Wexner FI score and a faecal incontinence quality of life score [121]. Twenty (62.5%) recorded a greater than 10% improvement in the visual analogue score. There was also a statistically significant improvement in the mean Wexner faecal incontinence score (14.5 to 11), which was maintained at three and six months, following further top-up treatment.

Percutaneous compared with Transcutaneous PTNS

Percutaneous and transcutaneous PTNS has been compared in only one study[122]. Patients were randomised to three groups, percutaneous (n=11), transcutaneous (n=11) and a sham transcutaneous stimulation group (n=8) acting as a placebo. All groups had twice weekly 30 minute treatment sessions for six weeks. Nine of the percutaneous group reported a greater than 50% reduction in incontinent episodes, compared with five in the transcutaneous group. A statistically significant improvement in soiling episodes was seen in the percutaneous group and not in the transcutaneous group. A statistically significant reduction in the St. Mark's FI score [89] was seen in the percutaneous (19 before; 12.7 after) and transcutaneous (18.5 before; 14.7 after) groups. No improvement was seen in the sham group. The percutaneous group showed a statistically significant improvement in the ability to defer defecation (1.9 minutes to 6.7 minutes). No improvement in deferral time was seen in the transcutaneous or sham groups. There were no significant changes in anal canal pressures.

Transcutaneous PTNS compared to sham stimulation

Leroi and colleagues compared unilateral transcutaneous PTNS with sham stimulation in 2012 [123]. In this study, 144 were randomised to receive three months of treatment or sham, the study was double-blinded. The treatment group received 20 minutes of therapy twice daily for three months, with the amplitude set at sensory level. The sham group received the same frequency of treatment using a

dummy box which did not deliver a current. The frequency of incontinent episodes per week fell significantly in the treatment group from 1.7 (0-23) to 1 (0-14.3) (p=0.004). There was a non-significant reduction in the sham group from 2.9 (0-25) to 1.6 (0-23.6) (p=0.06). The Wexner FI score fell significantly in both groups. However, 47% of the treatment group achieved a ≥30% reduction in the Wexner score compared to only 27% of the sham group (p=0.02). However, on intergroup analysis, there was no significant difference found between the two groups. This suggested that unilateral transcutaneous PTNS may be no more effective than placebo.

PTNS and Spinal Injury

A case series by Mentes in 2007 [124] described the use of percutaneous PTNS in two incontinent patients with partial spinal cord injury. PTNS was given several years following the injury. Both received 30 minutes of PTNS on alternate days for four weeks. There was an improvement in the Wexner score, Rockwood faecal incontinence quality of life score, anal resting and squeeze pressures and rectal sensory thresholds.

PTNS and Inflammatory Bowel Disease

Twelve patients with inflammatory bowel disease of mixed aetiology underwent self-administered transcutaneous PTNS [125] for three months. The primary endpoints included change in the Wexner score and in a visual analogue scale (0-5) to assess subjectively improvements in bowel function and quality of life. PTNS failed to improve the Wexner score and in patients with Crohn's there was no improvement in the Harvey-Bradshaw index [126]. Subjective improvement in symptoms was recorded in 42% and in quality of life in 50%. No statistical tests were applied.

Discussion

It is uncertain how PTNS works. It is thought to neuromodulate the sacral nerve plexus remotely via the posterior tibial nerve; so ultimately having a similar action to SNS. The exact mechanism of action of SNS is uncertain. It is likely to be the result of multiple different physiological effects [90, 127], such as alteration of local somato-visceral reflexes leading to changes in colonic motility and anal sphincter activity, and also modulation of higher perception of afferent information [98, 99]. There are no anorectal physiological changes consistently observed from PTNS, this is also the case with SNS [91]. The acupuncture point ''sanyinjiao'' or ''spleen-6", overlies the posterior tibial nerve near the ankle. Chang and colleagues [128] reported the effects of acupuncture stimulation of this point in patients with lower urinary tract dysfunction. An improvement was seen in the majority of the patients. A small

study by Scaglia and colleagues [129], reported improvement in faecal continence using acupuncture. One of the acupuncture points used here corresponded to the position of the posterior tibial nerve. No work published to date has directly compared acupuncture with PTNS.

PTNS is usually delivered unilaterally, at the nerve's most superficial position above and behind the medial malleolus. It does not matter which leg is used. There has been no suggestion of any dominance of the left or right tibial nerve, although work has been done in relation to dominance of the pudendal nerve and its effect on anal sphincter activity [130]. A frequency of 10-20 Hz and a pulse width of 200 μsecs are usually used for PTNS, these are similar to the settings used for SNS. It has been [103] suggested that a shorter pulse width and a higher frequency may improve faecal incontinence in patients receiving SNS. There is no published work investigating the effect of altering these parameters in PTNS. The optimum duration and frequency of treatment have yet to be determined. The published literature describes a diverse range of treatment schedules (table 1). The therapeutic effects of SNS are short-lived once treatment has stopped. Much of the literature suggests that there is a residual therapeutic effect after PTNS treatment finished. It is unclear how long this can last for, and how this is related to the initial treatment regimen and modality of PTNS used. Govaert [114] described a reduced frequency of "top-up" treatments to maintain efficacy once the initial treatment had been completed. The frequency of treatment could then be increased if the patient's symptoms relapsed. Hotouras employed a similar top-up therapy regimen, although did not report the outcome of this.

PTNS is an attractive treatment option because of the ease with which it can be administered, and its apparent low cost. A reusable PTNS stimulator device costs £800 and a box of single use percutaneous needle electrodes costs £380 [117]. The transcutaneous electrode pads can be reused for each patient, and cost approximately one pound each. In comparison, SNS costs in excess of £9000 for equipment alone [84] and requires an operating theatre. It may be that the effect of repeat PTNS administration will cause this difference to narrow in the longer term. No analyses were found assessing the cost effectiveness of PTNS for FI. SNS carries with it the risk of potentially significant complications [106, 131], none of which have been reported from PTNS.

Govaert and colleagues [114] reported 60% of their patients had achieved a 50% or more reduction in incontinent episodes. George and colleagues [122] reported 82% of the percutaneous arm of their study achieved a 50% or more reduction in incontinent episodes. These short term outcomes compare favourably with those seen from SNS. It is uncertain how SNS and PTNS compare in the longer term. The longest reported follow up for PTNS is 30 months [110]. Unfortunately a composite FI score was used in this study, rather than change in frequency of incontinent episodes. Govaert's work described a follow up of 12 months, during which a statistically significant reduction in incontinent episodes had been maintained. Disappointingly, six studies did not use the change in incontinent episodes as an

outcome measure at all. Instead, a FI score was used as a primary endpoint. Two studies even used a visual analogue score to measure outcome. The effect of PTNS on defecatory urgency is under reported. Only four studies described the effect of PTNS on the ability to defer defecation. Because of these differences in outcome reporting (see table 2), comparisons between the studies are difficult to make.

George and colleagues [122]attempted to compare transcutaneous PTNS with percutaneous PTNS. When the treatment modalities were compared individually, a significant improvement in soiling was only seen from percutaneous PTNS. However, statistically, it is not clear if this equated to superiority of percutaneous PTNS over transcutaneous PTNS. This study was likely to have been limited by the number of patients used, with only 11 in each treatment group. It is worth noting also, that transcutaneous PTNS was administered twice weekly in this study. This is in contrast to the treatment regimens described by Queralto [111], Vitton [119, 125] and Eleouet [120], in which transcutaneous PTNS was administered on at least a daily basis.

SNS can be an effective treatment for patients with FI secondary to partial spinal cord injury [78]. The case series by Mentes reported PTNS in patients with FI and partial spinal cord injuries, this suggested some promise. However, this is a very small series, and it is difficult to draw any firm conclusions. The use of PTNS in this patient group deserves to be investigated further. The results of PTNS in patients with inflammatory bowel disease are disappointing. This contrasts to previous work from the same group, in which SNS was reported to have improved FI in patients with Crohn's and co-existing sphincter defects [67].

Hotouras is the only author to report the differing outcome for each FI sub-group. This work suggested that those with passive incontinence did not benefit as much as those with urge or combined FI. However, the passive FI group was small (n=15) compared to the urge FI and combined FI groups (n=25 and n=60 respectively). It is uncertain if this poor outcome would still be evident if larger patient numbers are used.

The 14 studies published so far contain many defects of design including retrospective collection of data, small numbers and absence of a comparative group. There is also a wide variation in the outcome measures used. Two randomised controlled trials and one non-randomised controlled trial were identified. The remaining studies were non-comparative case series. The quality of evidence has been graded in table 1 [132]. Overall, the quality of evidence is poor and there is marked heterogeneity of treatment technique and outcome measures employed. Because of this, at present it would not be possible to perform any summative analysis, such as meta-analysis, of the evidence base.

There is evidence that PTNS is an effective treatment for faecal incontinence in some patients and that a response is maintained over several months, and can be improved by top up treatment if efficacy declines with time. Further work is needed to compare PTNS to more established treatment modalities using large randomised controlled trials, and to investigate how its efficacy can be improved. More consistent and robust reporting of outcome is needed. The efficacy of PTNS in the longer term needs to be investigated too.

3.3 Pudendal nerve stimulation for faecal incontinence

Introduction

In recent years, neuromodulation, in the form of sacral nerve stimulation (SNS), has become the first-line surgical treatment when non-operative methods fail [45]. The short and long-term effects of SNS have been widely reported [133, 134]. When SNS is evaluated on an intention to treat basis, around 60% of patients will experience a ≥50% reduction of incontinent episodes, and around 30% will become fully continent [55]. Approximately one-third of patients will not improve significantly with chronic stimulation in the short term. There will also be those patients who lose efficacy over the longer term. Further treatment of these patients is difficult, many may progress to a defunctioning colostomy.

SNS is believed to work, in part, by the activation of ascending afferent fibres in the sacral nerve roots [135]. Stimulation leads to modulation of local reflex pathways at the spinal cord level, which are integral to colonic, rectal and pelvic floor function [90]. Central effects on the sensory cortex and cerebral evoked potentials have also been described [98, 99]. One limitation of sacral nerve stimulation is that usually only one nerve root is stimulated. The afferent outflow from the pelvic floor, distal bowel and anal sphincter is predominantly found in the S2 and S3 roots and in some patients may be asymmetric or at a single level [130, 136]. Sacral nerve stimulation is most frequently performed at the level of the S3 root as direct S2 root stimulation can lead to adverse effects with pain experienced in the buttock, leg or foot. Absence of afferent outflow at the S3 level may explain why sacral nerve stimulation fails to benefit some patients. The pudendal nerve is derived from three sacral nerve roots, S2-S4. In theory, greater afferent stimulation can be achieved by stimulation of this nerve than by stimulation of a single sacral nerve root. In some patients this may translate to an improved therapeutic effect. In addition as the pudendal nerve is an isolated structure at the level of the ischial spine there is less risk of unwanted stimulation of adjacent nerve roots. PNS has been used in a small number of patients with urinary voiding dysfunction and interstitial cystitis, including patients that have failed to benefit from SNS [137, 138].

Methods

A review was performed of all the evidence published on pudendal nerve stimulation (PNS) for faecal incontinence. An electronic search was performed of the Medline, Pubmed and Embase databases using the keywords and/ or MeSH "pudendal", "faecal incontinence", "neuromodulation", "stimulation". Further relevant studies were identified by cross referencing from relevant articles and abstracts. Only studies that reported the clinical outcome of pudendal nerve stimulation for faecal incontinence in the English language were included.

Technique for PNS

PNS requires a period of test stimulation. This can vary from one to three weeks in duration. This is to predict the likely outcome to chronic PNS. A successful response can be defined as a ≥50% improvement in symptoms of faecal incontinence, in a similar fashion to that used for SNS. This response can be measured in frequency of incontinent episodes, or incontinent days. Pudendal nerve stimulation is delivered using a Medtronic model 3093 lead (Medtronic Inc, Minnesota, USA) inserted percutaneously under general anaesthesia. This can be performed using a transgluteal approach [139], in which the lead insertion point is at the intersection of a horizontal line from the greater trochanter of the hip and a vertical line from the ischial tuberosity. Correct lead placement is confirmed by contraction of the external anal sphincter. This can be assessed by electromyographic analysis, or by placing a finger in the anus. The alternative technique is an infra-gluteal approach [138]. Here, the lead insertion point is at the midpoint of a line between the ischial spine and the anus. Correct lead placement is best confirmed by electromyographic analysis. The PNS lead is connected to an external stimulator via a percutaneous extension (Test stimulator 3692, Medtronic Inc, Minnesota, USA). Test stimulation is performed at a sub-sensory level for a three-week period. During this period all the patients keep a bowel habit diary to record the response of the therapy on their symptoms. If an unsuccessful response is experienced, then the lead is removed at three weeks. If a successful response has been experienced, then the lead is connected to an implantable pulse generator (IPG) placed in the ipsilateral buttock (model 3023 or model 3058, Medtronic Inc, Minnesota, USA). Stimulation is set to the parameters traditionally used for sacral nerve stimulation at a pulse width of 210μsec and pulse frequency of 14Hz. Electrode configuration was altered so that the sensory stimulus was felt in the perianal area.

Results

Pudendal nerve stimulation for FI was first described by Matzel and colleagues [140] in 2005. They reported the use of a Bion microstimulator (Advanced Bionics Corporation, CA, USA) to stimulate the pudendal nerve, for a patient with bowel and bladder dysfunction following an extensive pelvic fracture. They reported an improvement in frequency of incontinent episodes of eight to two per week, at a follow up of 10 months. Bock et al [141] reported the first use of the Interstim device (Medtronic Inc, Minnesota, USA) for PNS. This was applied to two patients who had failed to improve with SNS. At four months follow up the patients' symptoms improved from four and seven incontinent episodes per day respectively to complete continence.

Discussion

At present, there is a paucity of published data to support the use of PNS for faecal incontinence. PNS requires two operations three weeks apart, after the test period has finished. This is because the PNS lead has to be removed or connected to the IPG at this point. Whichever of these actions is taken, both require an operation. This differs to SNS, in which the test lead can be removed in the outpatient clinic, and chronic stimulation can be arranged at convenient time. It is the author's opinion that PNS is a more difficult procedure to perform than SNS. For these reasons it is unlikely that PNS will supersede SNS, unless PNS is shown to have significantly superior efficacy. No published studies have attempted to directly compare them for FI. Peters and colleagues [142] compared the two for patients with bladder voiding dysfunction. They described 30 patients, who had undergone a single blinded randomised cross-over trial. Symptom relief obtained by PNS was greater than that obtained by SNS in 80% of patients.

PNS may find a role as a second line treatment after SNS. This makes sense, when one considers that increased number of afferent sensory pathways which are stimulated during PNS. Larger studies are needed to examine this further. It is a more attractive treatment option in those who have failed chronic SNS. In such patients, there is no need for a second operation immediately after the test period, since the PNS lead can be connected to the SNS IPG during the first operation.

Table 1- *Table to show the method of PTNS and treatment regime.*

Author, Year	Subject Number	Modality of PTNS	Duration of Therapy	Frequency of Therapy	Study Type	Level of Evidence
Shafik, 2003	32	Percutaneous	4 weeks	Alternate days	Non-randomised controlled trial	IIIB
Queralto, 2006	10	Transcutaneous	4 weeks	Daily	Prospective Uncontrolled	IV
Mentes, 2007	2	Percutaneous	4 weeks	Alternate days	Prospective Uncontrolled	IV
Vitton, 2009	12	Transcutaneous	12 weeks	Daily	Prospective Uncontrolled	IV
De La Portilla, 2010	16	Percutaneous	12 weeks	Weekly	Prospective Uncontrolled	IV
Vitton, 2010	24	Transcutaneous	12 weeks	Daily	Prospective Uncontrolled	IV
Govaert, 2010	22	Percutaneous	6 weeks	Twice weekly	Prospective Uncontrolled	IIB
Boyle, 2010 ●	31	Percutaneous	12 weeks	Weekly	Prospective Uncontrolled	IV
Findlay, 2010	13	Percutaneous	12 weeks	Weekly	Retrospective Uncontrolled	IV
George, 2010-A *	11	Transcutaneous	6 weeks	Twice weekly	Randomised Controlled Trial	IIB
George, 2010-B #	11	Percutaneous	6 weeks	Twice weekly	Randomised Controlled Trial	IIB
Eleouet, 2010	32	Transcutaneous	4 weeks	Twice daily	Prospective Uncontrolled	IV
Allison, 2011 ●	90	Percutaneous	6 or 12 weeks	Twice weekly or Weekly	Prospective Uncontrolled	IV
Hotouras, 2011 ●	100	Percutaneous	6 or 12 weeks	Twice weekly or Weekly	Prospective Uncontrolled	IV
Leroi, 2012	144	Transcutaneous compared to sham	3 months	Twice daily	Randomised Controlled Trial	IIB

*refers to the transcutaneous PTNS arm of the study

#refers to the percutaneous PTNS arm of the study

● same institution with likely duplication of results.

Levels of evidence according to the Oxford Centre for Evidence Based Medicine. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

Table 2- *Table to show the differing treatment outcome measures used ("Yes" indicates inclusion as an outcome measure, "No" indicates non-inclusion as an outcome measure)*

Author, Year	**FI Score Change**	**FI episode change/ week**	**Ability to defer defecation/ mins**	**Patient centred subjective assessment of bowel function**	**SF-36 QOL Change**	**Rockwood FI-QOL Score Change**
Shafik, 2003	Yes- Composite FI score	No	No	No	No	No
Queralto, 2006	Yes- Cleveland Clinic FI score	No	No	No	No	No
Mentes, 2007	Yes- Cleveland Clinic FI score	No	No	No	No	Yes
Vitton, 2009	Yes- Cleveland Clinic FI score	No	No	No	No	No
De La Portilla, 2010	Yes- Cleveland Clinic FI score	Yes	No	Yes	No	Yes
Vitton, 2010	Yes- Cleveland Clinic FI score	No	No	Yes	No	No
Govaert, 2010	Yes- Cleveland Clinic FI score	Yes	No	No	Yes	Yes
Boyle, 2010●	Yes- Cleveland Clinic FI score	Yes	Yes	No	No	No
Findlay, 2010	No	Yes	No	No	No	Yes
George, 2010-A	Yes- St Mark's FI score	Yes	Yes	No	Yes	Yes
George, 2010-B	Yes- St Mark's FI score	Yes	Yes	No	Yes	Yes
Eleouet, 2010	Yes- Cleveland Clinic FI score	No	No	Yes	No	No
Allison, 2011●	Yes- Cleveland Clinic FI score	Yes	Yes	No	No	No
Hotouras, 2011●	Yes- Cleveland Clinic FI score	Yes	Yes	No	No	Yes
Leroi, 2012	Yes- Cleveland Clinic FI score	Yes	Yes	No	No	Yes

● refers to the fact that these studies all originated from the same institution and likely duplicate reporting of patient outcomes has occurred.

Chapter 4

Neuromodulation for constipation

4.1 Sacral Nerve Stimulation for Constipation

Introduction

Sacral nerve stimulation was first reported for bladder dysfunction in 1982 [44] and for faecal incontinence in 1995 [45]. Its use for constipation was first reported in 2001.

Method

A review was carried out of all the evidence published on the use of SNS for chronic constipation. An electronic search was performed using Medline, Pubmed and Embase, with the keywords and/ or MeSH headings of "constipation", "sacral nerve stimulation", and "sacral neuromodulation". Further studies were identified by cross referencing from relevant articles and abstracts. Only studies that reported the clinical outcome of SNS for constipation in the English language were included in this review. The aim of this review was to assess the clinical efficacy of SNS for constipation using the current published literature.

Mechanism of action

The mechanism of action of SNS is unclear. It is likely to involve multiple physiological effects, in particular modulation of afferent and local reflex pathways [90]. The S2 root has the greatest afferent outflow from the sacral plexus [136], however stimulation of this root often leads to activation of sciatic motor fibres that can lead to buttock and leg pain. Therefore stimulation of the S3 root is often the preferable option for therapy providing maximal sacral afferent stimulation in the absence of unwanted side-effects. The proposed mechanisms of action of SNS have been described in chapter two. A few studies have attempted to determine this mechanism of action in relation solely to constipation. Knowles and colleagues reported a double-blinded randomized study to assess the effect of sacral nerve stimulation on rectal sensation in patients with rectal hyposensitivity. They suggested that modulation of afferent pathways may be important as improvement in threshold and maximal tolerated volumes to balloon distension occurs with therapy [92]. The effects of SNS on colonic motility were investigated by Dinning and colleagues in 2007 [96]. They showed that SNS at supra-sensory threshold significantly increased antegrade pan-colonic wave sequence in patients with slow transit constipation. This corresponded to an increase in frequency of defecation and a reduction in laxative use. However, stimulation at sub-sensory threshold, as used routinely in clinical practice, may not have an effect on motility[97]. However Kamm in 2010 [95], showed normalization of whole gut transit time at six months follow-up in one-half of patients undergoing SNS for slow transit constipation

using stimulation at sub-sensory threshold . This corresponded to an increase in frequency of defecation. In contrast, sacral nerve stimulation in patients with faecal incontinence may reduce anterograde colonic transit [93]. The difference in the effect of stimulation with different conditions remains unclear but sacral nerve stimulation may act to normalise transit by modulation of the enteric nervous system or reflex pathways at the spinal cord level.

SNS and constipation

Thirteen published studies were found reporting the use of SNS for constipation (Table 1). Ten referred to adults, two of which were double-blinded cross-over studies, and three were retrospective reviews. Three studies reported the use of SNS in children and adolescents.

Ganio and colleagues in 2001 [48] described 40 patients suffering from a variety of functional anorectal and urinary disturbances, of whom 12 had constipation. These patients were subjected to ten days of PNE. Ten of these patients completed a week's course of stimulation. This group showed no increase in the number of bowel movements per week however there was improvement in initiating evacuation and reduction in the number of unsuccessful visits to the toilet and time required to evacuate.

Malouf and colleagues in 2001 [143] exposed eight patients to three weeks of PNE, all of whom had slow-transit constipation. Two patients demonstrated an increase in the frequency of spontaneous defecation over the test period and an improvement in bowel function as assessed by visual analogue score. The remaining six showed no improvement.

More convincing results were reported by Kenefick in 2002 [144]. Four women with constipation were exposed to PNE and then to permanent SNS. Two patients had slow transit constipation and two had dyssynergia on defecation proctography. An increase in the number of spontaneous defecations and an improvement in abdominal pain and bloating were demonstrated at six month follow-up. Improvements in the Cleveland Clinic constipation score [145] and in a visual analogue score were seen. In a subsequent study, Kenefick and colleagues [146] described a double-blinded placebo controlled crossover study using two of these patients. Improvement in defecatory frequency, abdominal pain, bloating and a visual analogue score was demonstrated when the stimulator was switched on, compared to when it was off.

In 2008, Holzer and colleagues [147] described 19 patients who underwent temporary SNS. 42% of these had slow transit constipation and 47% had evacuatory dysfunction. Only eight patients (42%) were deemed eligible for permanent stimulation defined as improvement of evacuation frequency to achieve two or more defecations per week or defecation without digitation. Clinical benefit was

maintained with chronic stimulation at a median follow-up of 11 months with associated reduction in the Cleveland Clinic constipation scores (median (range) 23 (18-27) at baseline to 8 (4-13) at 12 months) and SF-36 quality of life scores [148].

A retrospective study by Naldini and colleagues in 2010 [149] described the outcome of 15 patients with slow transit constipation who had undergone PNE. Of these, nine (60%) met the study criteria for placement of a permanent implant. The criteria for permanent SNS was defined as disappearance of the need for laxatives or enema use, occurrence of spontaneous defecation or an increase in SF-36 quality of life score. At 6 months follow-up there was a significant increase in the number of bowel movements per week (mean 1.8 at baseline to 3.3 at 6 months) with concurrent reduction in the number of enemas required. The Cleveland Clinic constipation improved from 24 at baseline to 12 at 6 months with improvement in all domains of the SF-36 quality of life score.

The largest prospective study to date was carried out by Kamm and colleagues in 2010 [95]. In this multicentre international study 62 patients underwent test stimulation, 50 (81%) of whom had slow transit constipation. Forty five (73%) progressed to permanent stimulation. The criteria for progression onto permanent SNS included a frequency of evacuation of three or more times per week, a reduction of 50% or more in the number of evacuations associated with straining or a 50% decrease in the sensation of incomplete evacuation. The patients were followed for a median of 28 months. Thirty nine (87%) of those who had undergone permanent stimulation, showed an improvement in symptoms, including frequency of defecation, straining, sensation of incomplete evacuation, abdominal pain and bloating. The Cleveland Clinic constipation score improved from 18 at baseline to 10 at latest follow-up with a visual analogue score that rated overall bowel function increasing from 8 to 66 (where 0 was equal to worst function and 100 equal to best function). Significant improvements were seen in four of the eight domains of the SF-36 health questionnaire. Rectal sensation was altered with stimulation with reduction in the sensory, urge and maximal thresholds to rectal balloon distension. One half of patients with slow gut transit at baseline normalised colonic transit time at six months and this improvement corresponded to an increase in frequency of defaecation.

Sharma and colleagues published a retrospective study in 2011 [150]. Twenty one patients had undergone temporary stimulation, 86% of whom had slow transit constipation. Of these 11 (52%) went on to have a permanent implant. Frequency of defecation increased from a median of one defecation per week at baseline to a median of four per week at 34 months follow-up. Eight of these 11 patients completely stopped laxative medication.

A recent retrospective study by Govaert and colleagues [151] reported 117 patients who had undergone PNE. Of these 68 (58%) proceeded to permanent SNS. Some of the patients were part of the multi-

centre study published by Kamm [95]. There was an initial significant improvement in the Cleveland Clinic constipation score from 17 (3.8) to 10.2 (8.3) at first follow-up. This improvement was maintained at a median follow up of 37 months. Data regarding pathogenesis of constipation were incomplete but both patients with slow transit constipation and evacuatory dysfunction appeared to benefit from treatment.

Carriero and colleagues[152] suggested that psychological assessment may aid the selection of patients. In this study, 68 patients with slow transit constipation were offered psychological assessment using the MMPI-2 (Minnesota Multiphasic Personality Inventory-2) questionnaire [153]. Forty-five completed the questionnaire. Thirteen had a normal score, and underwent PNE. Of these, 11(85%) proceeded to permanent stimulation. Nine of those who had refused the MMPI-2 questionnaire or had an abnormal score also underwent PNE. Of these, only three progressed onto permanent stimulation (33%).

SNS in children with constipation

Two studies reported the effect of SNS in children with severe dysfunctional elimination syndrome. This syndrome includes a broad spectrum of functional disturbances involving the urinary and lower gastrointestinal tract in the absence of any obvious anatomical or neurological deficiency. One of the problems experienced by these children is constipation. The first study[154], described 23 children, of whom 15 were experiencing constipation type symptoms. The patients' age ranged from six to 15 years. After a mean follow up of 13 months, constipation improved in 12 out of the 15 patients treated with permanent SNS. The next study by Roth and colleagues in 2008 [155] described 17 children with constipation type symptoms, in 12 children these symptoms either resolved or improved following SNS. The age range in this study was 8-17 years but it is unclear in both studies how symptoms improved since no objective measurements were described.

Van Wunnik and colleagues described a retrospective study, in which 13 female adolescents underwent PNE for constipation [156]. The age range of these patients was ten to 18 years, and all had failed conservative therapy. Twelve underwent placement of a permanent implant. At a follow up of between six to 12 months, there was an improvement in the number of defecations per week, abdominal pain, straining and in the Cleveland Clinic constipation score. Absence from school was noted in ten of these patients at baseline, however at six months follow up, all were attending school regularly [156].

Adverse events with SNS and constipation

A retrospective review by Maeda and colleagues [157] described the suboptimal outcome and complications observed in an individual unit from SNS for constipation. Thirty eight patients had

undergone permanent stimulation, 22 (58%) of whom had an adverse event specifically related to their treatment. Nearly half of the events resolved with re-programming, however a third needed a further surgical procedure. Kamm and colleagues [95] reported 61 adverse events in 45 permanent implants specifically related to the treatment. Another 40 adverse events were attributed to the underlying constipation or to a new unrelated diagnosis. Two thirds of the SNS related adverse events were self-limiting, and most required re-programming of the device. Although the frequency of these adverse events appears high, it is unclear as to the proportion of subjects affected. These reports would appear to be comparable to those observed from the use of SNS for faecal incontinence. Maeda et al found that 85% of those with a permanent implant for faecal incontinence reported an adverse event, with the majority relating to a loss of efficacy[106]

Discussion

Chronic constipation is common. It should initially be managed by a combination of pharmacological agents, rectal irrigation and/or behavioural treatments. There is a close association between severe constipation and psychological disorders including a past history of physical or sexual abuse. Addressing these problems is mandatory before considering any form of surgical intervention which is complex and requires a sound understanding of the underlying aetiological factors contributing to the patient's symptoms.

SNS appears to be effective treatment for constipation but research to date has been predominantly confined to small low-level evidence studies with most lacking a coherent definition of constipation. While there may to be potential for neuromodulation in slow transit constipation, it is only uncommonly used in current clinical practice. This may be because of the cost of this therapy, leading to reluctance by health care providers to fund the treatment in the absence of more robust data. While patients with evacuatory dysfunction have also benefited from treatment it is unclear which patients are most likely to benefit from the therapy. Given the size of the studies and the inconsistency of the outcome reported to date, it would be difficult to perform any meaningful summative analysis of the data.

Constipation is associated with a wide range of clinical features. This is important to remember when evaluating studies assessing treatment as often multiple outcome measures are recorded. The most common outcome measured in these studies is a change in the frequency of defecation. Few studies describe other clinical features, such as abdominal pain, straining and the sensation of incomplete emptying. Only the paper by Kamm and colleagues [95] sought to address how the majority of these symptoms were affected. It is worth noting that, although many of these symptoms improved significantly, none completely resolved. Because of their complexity, it may be that complete

resolution is impossible to achieve by a single intervention. With this in mind, the aim of any therapeutic intervention for constipation should be to see if the patient can achieve an acceptable bowel function and quality of life. To this end, constipation-related symptom and quality of life scores, and patient based visual analogue scores (assessing overall satisfaction with bowel function) may be better assessments of efficacy.

As with all studies of functional bowel disorders the risk of a placebo effect from those undergoing an operative intervention is high. The two double-blind cross over studies performed by Kenefick [146] and Dinning [96] demonstrate that a true clinical effect from therapy does occur and this is supported by outcome data that report ongoing benefit from SNS in the long-term.

The success rate of PNE for constipation in adults ranges from 42% [147] to 73% [95]. The reported success rates of PNE when used for faecal incontinence are between 74% [107] to 90%[55]. This would suggest that the rate of patients with constipation progressing from PNE to permanent stimulation is lower than that seen with the faecal incontinence group. However, the evidence base of SNS for constipation is considerably smaller than for faecal incontinence. It may be that the two or three week period of temporary SNS, although seemingly suitable in patients with faecal incontinence, may not be sufficient for patients with constipation. Govaert and colleagues [151] suggested that age is a significant predictive factor for successful PNE, in favour of younger patients whilst Carriero and colleagues [152] suggested that psychological assessment may aid the selection of patients.

So far, follow up of these patients has been relatively short. The longest duration of follow-up has been a median of 37 months. It is unclear whether any early improvement of constipation is maintained in the longer term. It is known that there is a gradual loss of efficacy over the long-term in some patients undergoing SNS for faecal incontinence [158] and it could be assumed that this may also occur in the constipation group. In some patients, adjustment of stimulation parameters may restore efficacy.

With the exception of a reduction in rectal sensation urge and maximal threshold volume to balloon rectal distension, there does not appear to be any other consistent anorectal physiologic changes. This is analogous to SNS for faecal incontinence, where there are no consistent changes in physiological parameters [91] [105]. There is limited evidence that other forms of neurostimulation including percutaneous and transcutaneous posterior tibial nerve stimulation and acupuncture are beneficial in treating slow-transit constipation. It may be that the mechanism of action, as with faecal incontinence and urological disorders is mediated predominantly by the stimulation of afferent pathways. Kamm and Dinning have reported an increase in colonic motility in patients with slow transit type constipation. As previously stated, it is not clear from the literature whether slow colonic transit or

evacuatory dysfunction type constipation is likely to respond better to SNS.

All of the studies have been uncontrolled with no direct comparison with any other treatment. Most studies were retrospective case series and can be graded as level IV scientific evidence. The exceptions to this are the double-blind cross-over study by Kenefick and the larger cohort studies of Kamm and Govaert which are level IIb evidence (see Table 1) [132].

All patients had failed conservative measures such as biofeedback and medications. Although not explicitly mentioned, it can be assumed that mechanical causes for constipation were ruled out by the authors. Constipation often has a mixed aetiology and slow transit and evacuatory disorders can be present in the same patient to varying degrees. Surgery should only be considered in patients that have undergone full medical and psychosocial evaluation and conservative measures, including psychiatric treatment where necessary, have been exhausted. Sacral nerve stimulation allows a minimally invasive trial of therapy with low morbidity and in our opinion should be the first line surgical option for those with slow-transit constipation and/or rectal hyposensitivity. Further evidence is required to ascertain whether SNS is truly beneficial in those with pelvic floor dyssynergia.

Based on the evidence of this limited number of studies, SNS appears to be effective treatment for chronic constipation. Larger clinical and cost-effectiveness studies comparing sacral nerve stimulation with alternative treatments are required. Better-defined measures of constipation using improved symptom and constipation specific quality of life scores should be used. Patients often complain of multiple symptoms, and frequency of defecation, although sometimes important, is not the only endpoint.

4.2 Posterior tibial nerve stimulation for constipation

Method

A review was performed of all the evidence published on posterior tibial nerve stimulation for constipation. An electronic search was performed of the Medline, Pubmed and Embase databases using the keywords and/ or MeSH “tibial”, “constipation”, “neuromodulation”, “stimulation”. Further relevant studies were identified by cross referencing from relevant articles and abstracts. Only studies that reported the clinical outcome of PTNS for constipation in the English language were included.

Results

One study was found which described the outcome of PTNS for constipation. Collins and colleagues [159] reported the outcome of 18 patients, who had undergone twelve 30 minute sessions of unilateral percutaneous PTNS. All had slow transit constipation, and had failed conservative therapy. This

included biofeedback, laxative and enema use. Statistically significant improvements were seen in the Wexner score [145] of median 18 (10-24) to 14 (7-22) (p=0.003) and in the global PAC-QOL [160] score of 2.31 (1.36-3.61) to 1.43 (0.39-3.78) (p=0.008). Statistically significant improvements were also seen in the frequency of defecation per week of 9 (2- 48) to 16 (1-35) (p=0.048) and in the use of laxatives. No change in colonic motility was seen.

Discussion

These results are encouraging in a group of patients for whom further treatment is difficult. Its effect upon a larger group of patients, and over a longer period of time, need to be investigated. Its effect upon all symptoms of constipation is uncertain. As has been seen with SNS, at best there may only be an overall improvement rather than a complete resolution of symptoms.

PTNS is significantly cheaper than SNS in the short term. However, the patient will need to attend on repeat occasions for percutaneous PTNS, and it is likely there will still be a need for supplementary laxatives and enemas. These factors may mean that the difference in cost will narrow in the medium to longer term.

Its mechanism of action is uncertain. Collins and colleagues failed to show any improvement in colonic transit time, despite significant improvements in a disease severity score, disease specific quality of life score and in frequency of defecation. This may be explained by the fact, that many of the patients had co-existing evacuatory dysfunction. This may have improved, rather than the rate of anterograde colonic transit. The role of placebo cannot be discounted in this study. Placebo may well be a common confounding factor for many neuromodulatory therapies. Its effect cannot be discounted until large placebo controlled studies are performed. Unfortunately, there are very few of these in the published literature at present.

4.3 Pudendal nerve stimulation for constipation

Method

A review was performed of all the evidence published on pudendal nerve stimulation (PNS) for constipation. An electronic search was performed of the Medline, Pubmed and Embase databases using the keywords and/ or MeSH “pudendal”, “constipation”, “neuromodulation”, “stimulation”. Further relevant studies were identified by cross referencing from relevant articles and abstracts. Only studies that reported the clinical outcome of pudendal nerve stimulation for constipation in the English language were included.

Results

Only one study was found on PNS for constipation, in this case for neurogenic constipation. George and colleagues [161] described eight patients with a complete cauda equina lesion and constipation, who had undergone PNE. After three weeks of temporary stimulation, five achieved a greater than 50% improvement in symptoms and underwent chronic stimulation. One month later there was an improvement in the frequency of defecation from 3 (0.4) to 8 (1) (p=0.11), in the sensation of incomplete emptying from 80% to 0% (p=0.004) and in the Cleveland clinic constipation score [145] of 17 (32) to 9 (18) (p=0.03). This improvement was maintained at a mean follow up of 12 months.

Discussion

Further work is needed to investigate the effect of PNS in patients with constipation, especially in those with non-neurogenic disease. Assuming that PNS works by a similar mechanism of action to SNS, one might speculate that its effect upon constipation will be similar to that of SNS.

Table 1. Results of studies of sacral nerve stimulation (SNS) for constipation.

Study	Study Type	**Level of Evidence #**	Patient group	**Type of Constipation**	PNE No.	Permanent SNS No.	PNE Success Rate %	Follow Up
Ganio 2001	Prospective Uncontrolled	**IV**	Adult	**Idiopathic**	10	n/a	n/a	10 days
Malouf 2002	Prospective Uncontrolled	**IV**	Adult	**Slow colonic transit**	8	n/a	n/a	3 weeks
Kenefick 2002	Prospective Uncontrolled	**IV**	Adult	**Idiopathic**	4	4	100	6 months (mean)
Kenefick 2002	Double-blind Cross-over	**IIb**	Adults	**Idiopathic**	n/a	2	n/a	4 weeks
Humphreys 2006	Prospective Uncontrolled	**IV**	Children	**Idiopathic**	*	15	n/a	13 months (mean)
Holzer 2008	Prospective Uncontrolled	**IV**	Adult	**Slow colonic transit and evacuatory dysfunction**	19	8	42	11 months (median)
Roth 2008	Prospective Uncontrolled	**IV**	Children	**Idiopathic**	*	17	n/a	27 months (median)
Naldini 2010	Retrospective	**IV**	Adult	**Slow colonic transit**	15	9	60	42 months (mean)
Kamm 2010	Prospective Uncontrolled	**IIb**	Adult	**Slow colonic transit and evacuatory dysfunction**	62	45	73	28 months (median)
Sharma 2011	Retrospective	**IV**	Adult	**Slow colonic transit & idiopathic**	21	11	52	34 months (median)
Govaert 2012	Retrospective	**IIb**	Adult	**Slow colonic transit and evacuatory dysfunction**	117	68	58	37 months (median)
Van Wunnik 2012	Retrospective	**IV**	Children	**Slow colonic transit and evacuatory dysfunction**	13	12	92	6- 12 months
Knowles 2012	**Double-blind Cross-over**	**IIb**	**Adult**	**Evacuatory dysfunction**	**13**	**11**	**85**	**19 months (mean)**

* denotes that is unclear how many of these patients underwent PNE

according to the Centre for Evidence Based Medicine, University of Oxford (*Group TOLoEW. The Oxford 2011 Levels of Evidence. The Oxford Centre for Evidence Based Medicine,* http:/wwwcebmnet/indexaspx?o=5653. 2011).

Chapter 5

Double blinded randomised multicentre study to investigate the effect of stimulation parameter changes on sacral nerve stimulation for constipation.

Introduction

SNS can be effective for the treatment of constipation, but at best it can only improvement symptoms rather than abolish them. It is delivered typically with a pulse width of 210 μsec and a frequency of 14 Hz. Only the amplitude and position of the electrode are routinely adjusted. The stimulation parameters used for SNS are those reported by Matzel et al [45]. They are based on settings used in earlier reports of SNS for urinary disorders [101]. There is a need for improvement in the efficacy of SNS for constipation. Maeda et al reported adverse events, including loss of efficacy, in nearly 60% of patients having SNS for constipation[157]. Half of them were corrected by re-programming by re-adjustment of the position of the electrode and by the amplitude of stimulation. Dudding et al [103] reported the outcome of a double blind cross over study into the effects of altered pulse width and frequency in 12 patients. They suggested that a higher frequency (31Hz) and a shorter pulse width (90μsec) may improve the efficacy of SNS for faecal incontinence. In a similar study, Duelund-Jakobsen et al [102] suggested that a higher frequency of 31 Hz may improve the outcome in the same patient group.

The aim of this study was to assess the effect of altered pulse width and frequency in patients with constipation who had failed to have a significant improvement from SNS.

Method

Ethical approval was granted by the local ethics committee (NRES Committee London- Central, ref 11/LO/1345). Patients were recruited according to the inclusion and exclusion criteria shown in Table 1. Failure to achieve a significant improvement in symptoms from SNS was defined as less than a 50% improvement in the Cleveland Clinic constipation score [145] when compared with baseline. In an effort to increase the number of enrolled patients, recruitment was extended to the Royal London Hospital, University College Hospital London and Aarhus University Hospital, Aarhus Denmark. Baseline data were obtained using a three week constipation bowel diary, the Cleveland Clinic constipation score [145], the patient assessment of constipation symptoms questionnaire (PAC-SYM) [162] and patient assessment of constipation quality of life questionnaire (PAC-QOL) [160] . A visual analogue scale rated the patient's response to the question "*how happy are you with the way your*

bowels have been functioning?" on a scale of 1-100 whereby zero indicated maximal happiness and 100 the opposite.

Each patient was exposed to the parameters in each of the five test groups (Table 2). Test group 1 used the standard SNS settings and acted as a control. The other test groups were adjusted by either halving or doubling the pulse width and frequency. They were based on settings used in earlier work [102, 103]. Each patient was randomised to each test group in random order. Randomisation was performed using a sealed opaque envelope, drawn by the patient, which contained a randomly generated order of the five settings. A technician not involved in the assessment of the patient was responsible for adjusting the settings, rendering both patient and investigator blind to the stimulation groups. The amplitude was adjusted to maintain a sub sensory stimulus in the anal area or perineum. The position of the electrode was adjusted only if uncomfortable stimulation occurred. Patients were exposed to each setting for five weeks. During each of the five weeks, the first two were regarded as a "wash-out" period. A bowel diary was kept during the final three weeks and the remaining questionnaires were completed at the end of each five week period.

Once the patient had passed through each of the five settings, she was asked to state which setting was felt to be the most efficacious.

Statistical analysis

Since there had been no previously published studies on the effect of altering these parameter settings in constipation, it was not possible to perform a sample size calculation. This was therefore a feasibility study in which we aimed to recruit up to 15 patients. The results were expressed as mean and standard deviation. A linear regression model was used to compare the outcome from each setting change. The Chi-squared test was used to compare the choice of preferred settings.

Results

Ten patients were recruited, all were female. Their characteristics are shown in Table 3. Patient 6 became pregnant during the study and withdrew after three setting changes. The mean values of the outcome measures for each Test Group are shown in Figure 1 and the results of the multi-level linear regression model are given in Table 4. Of all the end points, only the time spent during one defecation showed a statistically significant difference ($p=0.04$), being shortest for Test Group 3 followed by Test Group 4 and longest for Test Group 1 and Test Group 5. There were differences in the patient satisfaction, Cleveland Clinic and PAC-QOL scores, but these did not achieve statistical significance.

Five patients preferred Test Group 1 and two preferred Test Group 2. There was no statistically significant difference between these choices (p=0.08) (Table 5). No complications were reported.

Discussion

The study suggests that only time spent during defecation changed significantly was related to the Test Groups. It is uncertain if this difference was of clinical significance, but Test Group 1 achieved superior albeit non-significantly different scores for almost all other outcome measures. This may explain why the majority of patients preferred Test Group 1. This study suggests that alteration of the pulse width and frequency has a limited effect on the outcome of SNS for constipation.

The small number of patients studied may have affected the ability to detect significant differences between each setting. We were unable to recruit the desired 15 patients, largely owing to the unwillingness of many of those approached to commit to the time needed to complete the study. Thus it was only possible by collaboration with other institutions. The three week assessment period for each setting was necessary to obtain an accurate representation of the patient's symptoms of which frequency of defaecation per week was already low and given the design, a wash-out period had to be included. The period of two weeks was based on earlier cross-over studies[146]. This meant that for a patient to progress through all settings, required she 25 weeks of data recording. Of the 10 patients who were recruited, none were able to commit themselves to this rigorous regime and in the one patient who could not, the reason was understandable.

Deulund-Jakobsen et al [102] suggested that an increased frequency of stimulation may improve the outcome of SNS for patients with faecal incontinence, but this did not appear to be the case in the present study. This may be due to the small number of patients included but also to the possibly that different disorders respond differently. The variability of symptoms particularly of patients with constipation can make assessment of the outcome very complex to assess. It may also be that the outcome measures used were not sensitive enough to detect a difference. There was indeed evidence of considerable heterogeneity among the patients, for example in prolonged colonic transit time and abnormalities of defecating proctography.

Since the mechanism of action of SNS is uncertain, it is also unclear whether slow transit or evacuatory-predominant constipation may benefit the most from SNS. These uncertainties make improvements in patient selection difficult and are compounded by the difficulty in trying to achieve a homogeneous population for the purposes of study.

Conclusion

This pilot study suggests that alteration of pulse width and frequency did not appear to affect significantly the outcome of SNS for constipation.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Chronic SNS for constipation for at least six months	New colonic or rectal pathology
Willing to complete all assessment forms during study	Surgical intervention for constipation within six months
An improvement of 50% or less of the Cleveland Clinic constipation score from SNS	Previous failure to comply with a trial
	Significant psychological morbidity
	Neurological disease
	Pregnancy

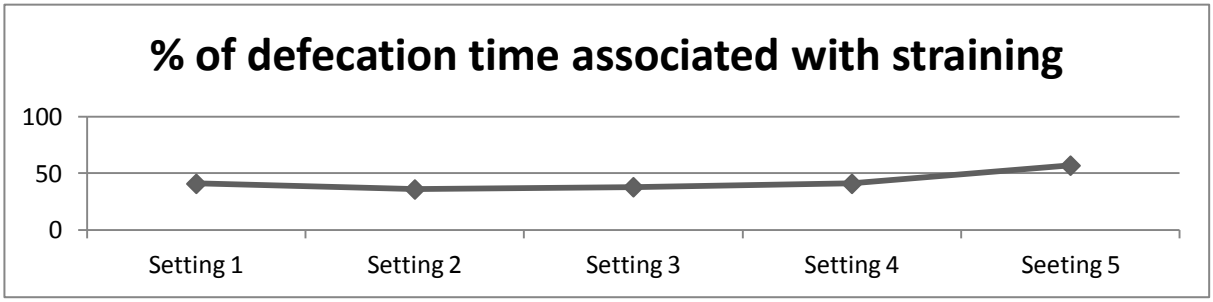
Table 2. Settings in the test groups

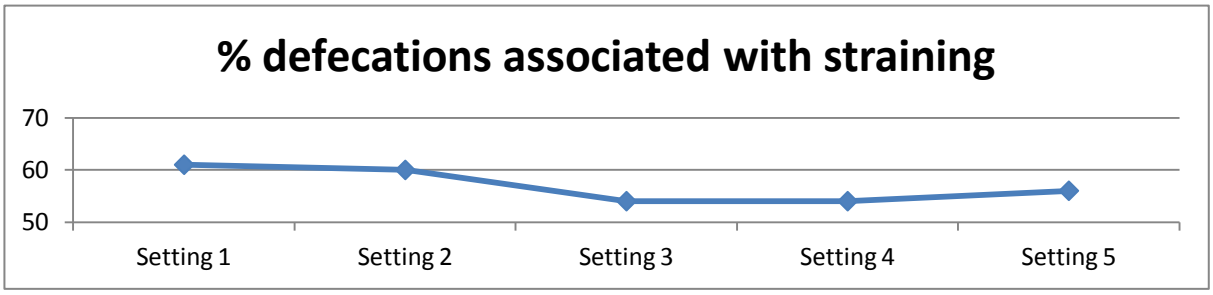
Test Group	**Electrodes**	**Amplitude**	**Frequency**	**Pulse Width**
1	Optimised electrode settings	Sensory Threshold	14	210
2	Optimised electrode settings	Sensory Threshold	6.9	210
3	Optimised electrode settings	Sensory Threshold	31	210
4	Optimised electrode settings	Sensory Threshold	14	90
5	Optimised electrode settings	Sensory Threshold	14	450

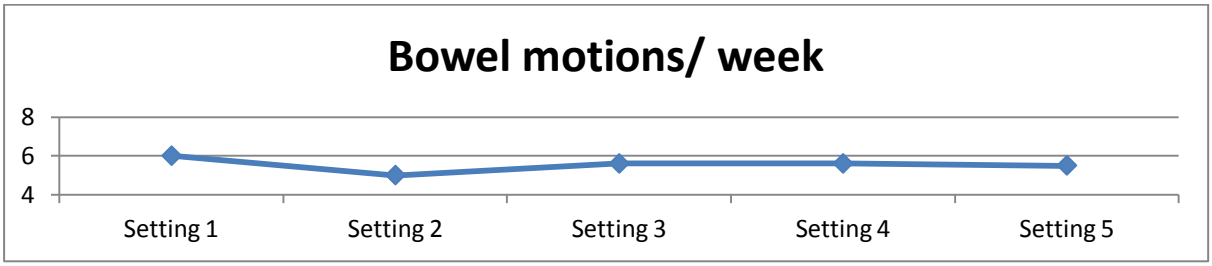
Table.3. Patient characteristics

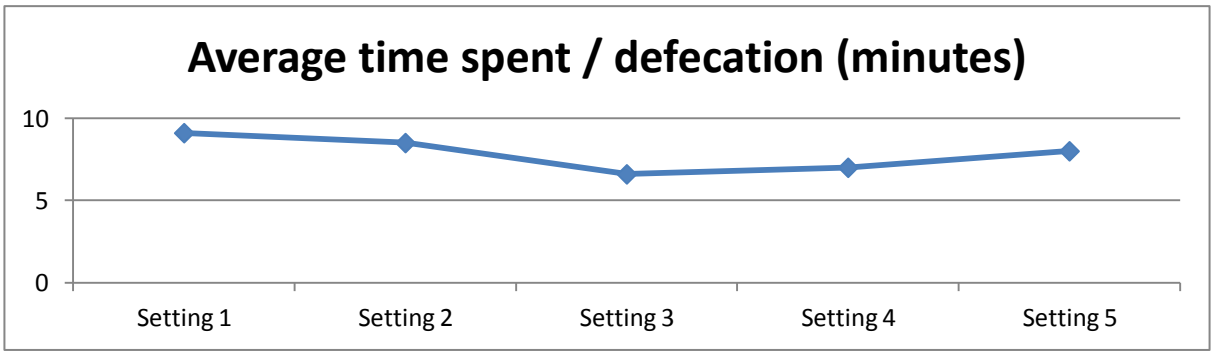
Patient	Age/ years	Duration of constipation/ years	Duration of SNS/ years	Defecating proctogram	Colonic transit time	Cleveland Clinic score before SNS	Percentage improvement in Cleveland Clinic score at baseline
1	64	40	7	Small rectocele	Delayed	24	50
2	31	10	6	Perineal descent	Delayed	16	44
3	32	16	8	Normal	Normal	15	27
4	69	20	4	Small rectocele	Delayed	17	0
5	37	30	3	Small rectocele	Delayed	24	4
6	21	16	1	Normal	Delayed	15	0
7	44	3	1	Normal	Delayed	14	0
8	44	20	5	Normal	Delayed	11	0
9	52	10	1	Normal	Delayed	14	14
10	43	11	6	Small rectocele	Delayed	24	46

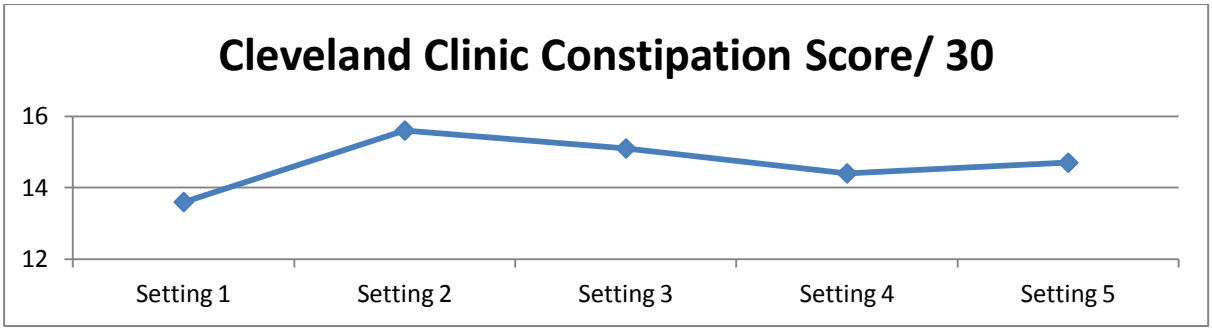
Figure 1. Mean outcome measures for each setting

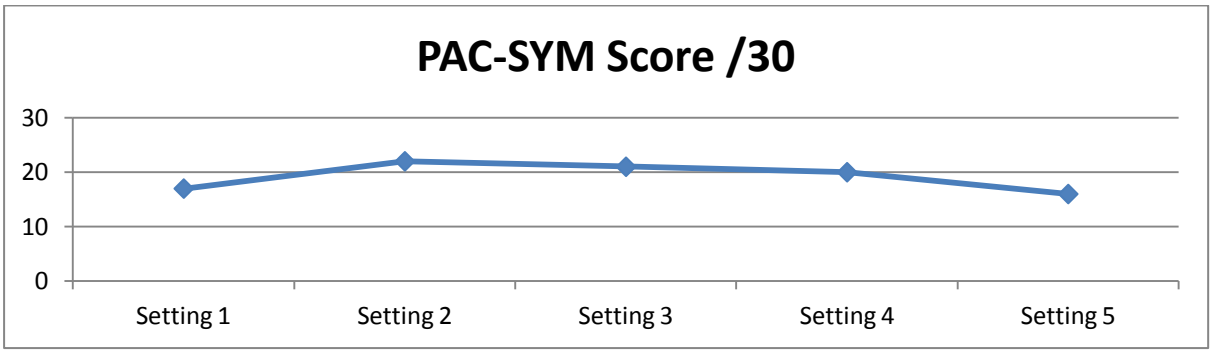









Cleveland Clinic Constipation Score/ 30
16
14
12
Setting 1
Setting 2
Setting 3
Setting 4
Setting 5


PAC-SYM Score /30
30
20
10
0
Setting 1
Setting 2
Setting 3
Setting 4
Setting 5

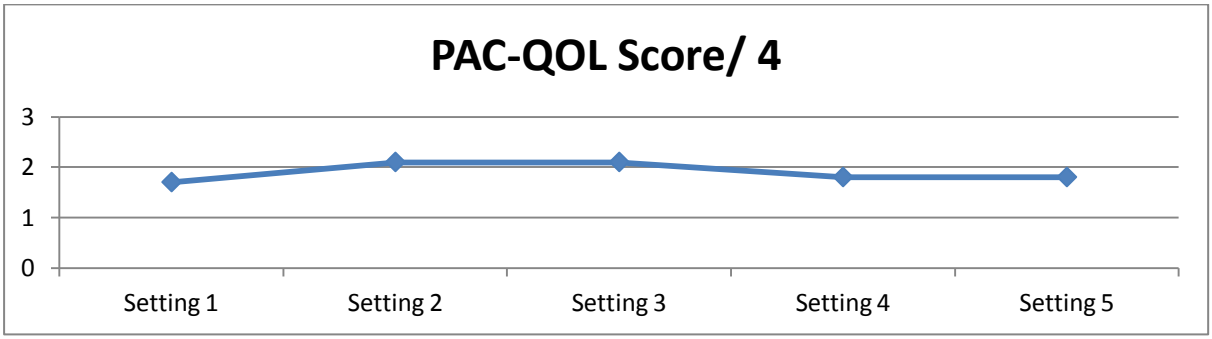

PAC-QOL Score/ 4
3
2
1
0
Setting 1
Setting 2
Setting 3
Setting 4
Setting 5

Table 4. Multi-level linear regression analysis

Outcome measure	Test group	Results*	Difference + (95% CI)	P value#
Mean BO/week	1	6.0 (3.7)	0	0.57
	2	5.0 (2.9)	-0.8 (-2.1, 0.5)	
	3	5.6 (3.1)	-0.7 (-2.0, 0.6)	
	4	5.6 (2.7)	-0.2 (-1.5, 1.0)	
	5	5.5 (3.2)	-0.9 (-2.2, 0.4)	
% of defecations associated with strain	1	41 (37)	0	0.96
	2	36 (39)	-1 (-14, 13)	
	3	38 (41)	4 (-9, 18)	
	4	41 (43)	0 (-13, 14)	
	5	37 (41)	0 (-13, 14)	
% of defecations associated with sensation of incomplete emptying	1	61 (29)	0	0.82
	2	60 (32)	-1 (-15, 13)	
	3	54 (36)	-3 (-18, 11)	
	4	54 (31)	-7 (-21, 7)	
	5	56 (27)	1 (-14, 15)	
Time spent per defecation/ minutes	1	9.1 (8.8)	0	**0.04**
	2	8.5 (6.8)	-0.8 (-2.6, 1.1)	
	3	6.6 (5.0)	-1.6 (-3.4, 0.3)	
	4	7.0 (4.8)	-2.5 (-4.2, -0.7)	
	5	8.0 (8.9)	-0.1 (-2.0, 1.7)	
Cleveland clinic score/ 30	1	13.6 (4.6)	0	0.11
	2	15.6 (4.1)	2.0 (0.2, 3.8)	
	3	15.1 (4.2)	2.1 (0.2, 3.9)	
	4	14.4 (3.7)	0.7 (-1.1, 2.5)	
	5	14.7 (5.7)	1.8 (-0.1, 3.7)	

PAC-SYM score/ 30	1	17 (9)	0	0.33
	2	22 (6)	6 (0, 12)	
	3	21 (6)	4 (-2, 10)	
	4	20 (11)	4 (-2, 10)	
	5	26 (9)	4 (-2, 9)	
PAC-QOL score/ 4	1	1.7 (1.0)	0	0.05
	2	2.1 (0.6)	0.4 (0.0, 0.9)	
	3	2.1 (0.7)	0.5 (0.1, 1.0)	
	4	1.8 (0.8)	0.1 (-0.3, 0.5)	
	5	1.8 (1.1)	0.1 (-0.3, 0.6)	
Overall Satisfaction/ 100	1	53 (35)	0	0.06
	2	38 (29)	-15 (-28, -1)	
	3	36 (28)	-20 (-34, -6)	
	4	42 (35)	-11 (-25, 2)	
	5	49 (36)	-8 (-22, 6)	

*Mean (standard deviation)

+Mean difference in outcome (after adjusting for treatment order) between each stimulation parameter and the first set of settings. Corresponding confidence intervals are given for each estimated difference.

P-value to indicate the significance of the overall difference in outcome between the five settings.

BO = bowels open. PAC-SYM = Patient assessment of constipation-symptoms

PAC-QOL = Patient assessment of constipation-quality of life

Table 5. Patient preferences

Test group	Number of patients and their preferred group (%)	p value
1	5 (56%)	0.08
2	2 (22%)	
3	0 (0%)	
4	1 (11%)	
5	1 (11%)	

Chapter 6

Transcutaneous stimulation over the sacrum for faecal incontinence

6. 1 A pilot study of transcutaneous stimulation over the sacrum for faecal incontinence

Introduction

Sacral nerve stimulation (SNS) appears to be effective in both short and longer term, but it is expensive. The equipment costs around £11500. Post operative infection has been reported in three to 10% [104, 105] of cases. There is also a risk of and loss of efficacy in up to 40% [106].

Transcutaneous electrical stimulation can be used as a cheap and safe treatment for faecal incontinence. Stimulation of the posterior tibial nerve (PTNS) [111] and dorsal clitoral nerve have previously been described [163]. When this study was designed, only one paper on transcutaneous stimulation over the sacrum (tSNS) for faecal incontinence had been reported [87] and a second was published in 2013 [88]. Both described a significant improvement in incontinence scores following unilateral stimulation over S3 for several hours a day. We hypothesised that a more intense treatment regimen might have a greater therapeutic effect. To achieve an increase in treatment intensity, the duration of stimulation was increased and applied to a larger area over the sacrum. The aim of this study was to evaluate further transcutaneous SNS (tSNS), using bilateral stimulation over the entire sacrum.

Method

Ethical approval was granted by the local ethics committee (NRES Committee London- Bentham, reference 12/LO/0011). Patients entered the study according to the inclusion and exclusion criteria shown in Table 1. Informed consent was obtained. They were recruited from the outpatient clinic at the authors' institution. Baseline assessment of the anorectum was made by anorectal physiology testing and endoanal ultrasonography. A two week bowel diary was kept, which recorded the frequency of episodes of faecal incontinence, frequency of defecation and deferral time to defecation. A visual analogue scale rated on the patient response to "*how happy are you with the way your bowels have been functioning*?" was recorded. The patient placed a mark on a visual analogue scale of 0 to 100 from with very unhappy (0) very happy (100). The Rockwood faecal incontinence quality of life score [54], the St Mark's faecal incontinence score [89] and the Short Form 36 quality of life, SF-36, score were also completed [164].

tSNS was applied using a NeuroTrac ™ Continence device (Verity Medical Ltd, UK) via four 100mm x 50mm electrode pads. The live pads were positioned next to each other over the sacrum. The earth

pads were placed lateral to these (Photograph 1). Continuous stimulation at a pulse width of 210μsecs and a frequency of 14 Hz was used. The amplitude was set at sub sensory level. Stimulation was given for 12 hours every day. All patients performed tSNS at home for four weeks. They were given written instructions on the use of the device and a photograph demonstrating the electrode pad and lead position. Markings were made over the sacrum, to indicate correct pad positioning. Each kept a two week bowel diary for weeks three and four. The remaining questionnaires were completed at the end of the four week treatment. After four weeks of tSNS the device was returned and the patients were followed by telephone consultation at monthly intervals. They were withdrawn the study when the frequency of incontinent episodes had returned to baseline level.

The primary outcome was the change in frequency of incontinent episodes per week. This was calculated as the mean frequency of incontinent episodes from the two week bowel diary used before treatment and at weeks three and four of treatment. Secondary outcome measures included the ability to defer defecation, frequency of defecation, changes in the St Mark's score and quality of life.

Statistical Analysis

This was a pilot study and a sample size calculation was not performed. Since the data were non-parametric, variance was expressed by the median and the interquartile range. The Wilcoxon Rank test was used for comparison of paired data. Statistical analysis was performed using SPSS computer software (IBM, version 20).

Results

Ten patients were recruited and all completed four weeks of treatment. Patient characteristics are summarised in Table 2. At the end of treatment, seven achieved a greater than 50% reduction in the frequency of incontinent episodes, and two of these two achieved complete continence. Of the three who failed to achieve a ≥50% reduction, two were male. There was a statistically significant improvement in the median (IQR) frequency of incontinent episodes per week from 9.5 (7.5) to 3 (7.38) ($p=0.028$), and in the frequency of defecations per week from 25.5 (19.5) to 14.5 (14.88) ($p=0.007$). There was a statistically significant improvement in the ability to defer defecation from 1 (1.25) to 4.5 (4.5) minutes ($p=0.017$). There were statistically significant improvements in the St Mark's score from 20/ 24 (5.25) to 14.5/24 (8) ($p=0.012$), and in the bowel habit satisfaction score, from 8.5 (20) to 45 (33) ($p=0.008$), see Table 3. There were no statistically significant changes seen in the quality of life measures, see Tables 4 and 5. Body mass index did not have a significant effect on change in frequency of incontinent episodes. After four weeks of treatment, symptoms returned to pre treatment levels at a median of 2 (4.5) weeks. No complications were reported, including no reports of skin irritation. No adverse device-related effects on daily activities were reported.

Discussion

These results suggest that tSNS may be an effective treatment for faecal incontinence in the short term. Seven out of the ten achieved a greater than 50% improvement in the frequency of incontinent episodes and two became completely continent. Statistically significant improvements were seen in the St Mark's incontinence score and in the frequency of incontinent episodes. The study has several limitations, however. The number of patients was small and the duration of treatment was short. There was no control group or direct comparison to another therapy.

This appears to be is the third study to report the outcome of tSNS for faecal incontinence. It is the first to report the use of bilateral stimulation over the entire sacrum. Chew and colleagues [87] reported the outcome of seventeen patients who underwent cutaneous stimulation over S3 for two hours a day for three months. Statistically significant improvements were seen in the mean faecal incontinence severity index from 40 to 28, in the frequency of incontinent episodes per week of 19.7 (16.2) to 12.1 (10.9) and in one domain of the Rockwood quality of life score. No assessment of change in urgency was made. The results from our study appear superior to those achieved by Chew and colleagues. This may be because a more intensive treatment regimen was used or because stimulation was applied to a larger area. In 2013 Leung and colleagues [88] reported the outcome of twenty women who had undergone tSNS over S3. They used a single small electrode pad, for up to eight hours a day. At a median follow up of 10 (5-12) months, the mean Cleveland clinic incontinence score had improved from 7.9 (4.2) to 4 (3.1) ($p<0.0001$) and the St Mark's incontinence score from 12.7 (5.7) to 5.8 (5.6) ($p<0.0001$). These results are encouraging and the St Mark's incontinence score, at latest follow up was considerably lower that obtained by our study. However, it should be noted that treatment was applied for a longer duration and the baseline St Mark's score was considerably lower.

The improvements in frequency of incontinent episodes, ability to defer defecation and in the St Mark's score compare favourably with SNS and percutaneous PTNS. There was no significant improvement in quality of life measures. This may be explained by the short assessment period. It may be that over a longer period, the quality of life measures will reflect the improvement seen in the bowel diary data and St Mark's scores.

As with other forms of neuromodulation the mechanism of action of tSNS is uncertain. This is considered in more detail in section 6.2. Patients were given clear instruction regarding electrode pad placement and markings were made over the sacrum to ensure this, but it is unlikely that the pads were positioned correctly every time. This may have affected the results adversely, but it may also imply that the pads do not need to be positioned precisely over the sacrum to produce a therapeutic effect.

tSNS is cheaper than SNS, and can be used easily at home. The stimulator costs around £60 and the reusable electrode pads cost £4, for four weeks of daily treatment. This is cheaper than percutaneous PTNS, for which the stimulator costs approximately £500 and 12 disposable electrodes cost around £200 are required. The device used in this study is, however, not suitable for long term use. The electrode leads were too long and became uncomfortable, and the stimulator needed to be reactivated every 90 minutes. A more suitable device is required for longer use. As with PTNS[165], some residual therapeutic effect is also seen and this may allow less intensive stimulation for longer term treatment.

Conclusions

At present the evidence for tSNS is limited and consists of three small series. Further work is needed to evaluate this treatment, using larger numbers of patients, examined over a longer period of time. The placebo effect should be considered to compare tSNS to a control group and to other treatments. tSNS may be an effective treatment for faecal incontinence. Further work is needed to confirm this.

6.2 Study to assess the effect of transcutaneous sacral nerve stimulation on external anal sphincter activity

Introduction

The mechanism of action of both tSNS and SNS is unknown, but stimulation of the third sacral nerve root will cause contraction of the external anal sphincter. This is seen during SNS lead placement, and is used to confirm correct lead position. It is unclear whether tSNS can cause EAS contraction. If it can, then one may hypothesise that tSNS has an effect on S3 and may share a similar mechanism of action with SNS. The aim of this study was to assess the activity of the external anal sphincter (EAS) during tSNS.

Method

Ethical approval was granted by the local ethics committee (NRES Committee London- Bentham, reference 12/LO/0011). Consecutive patients were recruited from the authors' institution according to the inclusion and exclusion criteria shown in Table 6. All were due to undergo SNS electrode insertion for faecal incontinence under general anaesthetic. The study was performed for each patient during this operation. The patient was positioned prone with the buttocks strapped apart. A 30 gauge 25 x 0.3mm electrode needle (Alpine Biomed, Denmark) was placed percutaneously into the external anal sphincter. A 10 x 25 mm earth plate was placed on the thigh. The electrode needle and ground pad were connected to an electromyography (EMG) machine (Dantec Keypoint 952, Dantec Dynamics UK). tSNS was applied using a NeuroTrac ™ Continence device (Verity Medical Ltd, UK) via four 90mm x 50mm electrode pads. The live pads were positioned next to each other over the sacrum and the earth pads placed laterally. Continuous stimulation over the sacrum was performed using a pulse width of 210μsecs, frequency of 14 Hz and amplitude of 60 mAmps. The movements of the buttocks and EAS were recorded and compound muscle action potentials (CMAPs) in the EAS were recorded. Following this, each patient underwent insertion of the SNS electrode.

Results

Five patients were recruited. Buttock contractions were seen in all during tSNS, but no visible EAS activity or CMAPs were observed. When the SNS electrode was inserted, however, EAS contractions were seen in all patients. There were no post-operative complications.

Discussion

Stimulation of the third sacral nerve root will cause EAS contraction and a sensory stimulus at the anus or perineum. The motor response is used to guide SNS lead placement when performed under general anaesthesia. The sensory response is used to guide device reprogramming during chronic stimulation and lead placement when performed under local anaesthesia. Fowler and colleagues [135]

investigated this motor response in nine females with bladder dysfunction. They found a latency of 98 (52-140) milliseconds between stimulation of S3 and sphincter CMAP. Previous work suggested that direct efferent stimulation of the sphincter should have a latency of between three to five milliseconds. The authors concluded that this delay meant that the sphincter contraction was a reflex-mediated action from activation of ascending afferent spinal pathways, and was not due to direct stimulation of efferent motor fibres. The pulse width and frequency used in this study were identical to the settings commonly used for SNS. The stimulation amplitude of 60mAmps was adequate to generate buttock contractions, and more than enough for a strong sensory response in the awake patient. tSNS failed to generate any EAS activity suggesting that it does not activate the afferent pathways necessary for the reflex mediated EAS contraction. It is unlikely, therefore, that tSNS has a significant effect on the sacral nerve roots. This is not unexpected when one considers the thickness of skin, fat and bone which lie between the electrode pad and the nerve roots. tSNS may therefore only produce stimulation of the cutaneous nerves. If so, stimulation of the sensory cortex would occur via ascending sensory pathways and this might explain its observed clinical effect. SNS has been shown to have a modulatory effect on cortical function [99, 100, 166] and this is postulated to be an important reason for its efficacy [90]. It may therefore be that tSNS and SNS produce a similar cortical effect, although it is not clear how this may influence incontinence. Various complementary therapies for bowel dysfunction utilise cutaneous stimulation. There are a small number published reports of acupuncture [129], reflexology [167] and massage [168] for bowel dysfunction. The application of electrical stimulation to another area of the body is addressed in section 6.3.

Conclusions

It is unlikely that tSNS affects the sacral nerve roots, and therefore it is unlikely to share all aspects of the mechanism of action of SNS.

6.3 Study to assess the effect of transcutaneous electrical stimulation of the anterior abdominal wall

Introduction

This study was limited by the absence of a control group. This meant that a placebo effect may have influenced the results. To address this issue, a second group of patients underwent transcutaneous stimulation to a different area of the body. The area chosen was the upper anterior abdominal wall. There were several reasons for this. This part of the body can be accessed with ease by the patient and is hidden by clothes. Electrical stimulation of the upper abdominal wall is not known to be a treatment for faecal incontinence. Importantly, patients may believe that stimulation over the abdomen may influence bowel dysfunction.

Method

Ethical approval was granted by an ethics committee (NRES Committee North West- Lancaster, reference 13/NW/0187). With the exception of electrode pad position, all aspects of the methodology were retained from study 6.1. The patients were instructed to place the active pads over the epigastric area and the ground pads were placed lateral to these.

.

Statistical analysis

This was a pilot study and a sample size calculation was not performed. Since the data were non-parametric, variance was expressed by the median and the interquartile range. The Wilcoxon Rank test was used for comparison of paired data. Statistical analysis was performed using SPSS computer software (IBM, version 20).

Results

Six patients were recruited, all were female. One patient withdrew from the study after one week due to a perceived lack of efficacy. This patient was withdrawn from further analysis. The characteristics of these patients are shown in table 7. There was no significant improvement in the frequency of incontinent episodes per week, frequency of defecations per week, the ability to defer defecation, the bowel satisfaction visual analogue scale or in the St Mark's incontinence score, see Table 8. There were no significant improvements in the quality of life measures (Tables 9 and 10). The study was stopped because of the poor response.

Discussion

Transcutaneous stimulation of the anterior abdominal wall does not improve faecal incontinence. There was no significant improvement in the symptoms of incontinence or in quality of life. This study was intended to act as a control for the study reported in section 6.1. The inclusion and

exclusion criteria are the same. The treatment regimen and data collection tools are also identical. The failure of abdominal stimulation may suggest that the effect of tSNS is not influenced significantly by a placebo effect. It is unclear why a therapeutic effect can be achieved by stimulating one area of the body and not another. Cortical stimulation is believed to be an important reason for the efficacy of SNS [90]. It may be that tSNS stimulates the necessary area of the sensory cortex, whereas abdominal wall stimulation does not.

This study is limited. It would have been preferable to use the same cohort of patients from study 6.1, but most had undergone SNS by the time this study was planned. The absence of blinding and the experience of a positive effect from stimulation over the sacrum would also have made their involvement difficult. The patients in this study were waiting for SNS. With high expectations of sacral stimulation, they may not have viewed abdominal stimulation in the same way. This may have adversely influenced the results. It would have been preferable to have used a double blind cross over study with a sham stimulator. This will be addressed in chapter 10.

Conclusion

Transcutaneous stimulation of the anterior abdominal wall is not effective for faecal incontinence. This study suggests that tSNS may be a genuinely effective treatment.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age over 18 years	Inability to use stimulation device
Faecal incontinence, defined as the involuntary loss of solid or liquid stool, two or more times per week.	Rectal prolapse
Intact external anal sphincter on endo anal ultrasound	Active inflammatory bowel disease
Previous conservative therapy, including biofeedback, without symptom resolution	Pregnancy
	Spinal injury/ neurological disorders
	Metal implant in lower back
	Previous neuromodulation
	Other implanted electrical device, such as cardiac pacemaker

Photograph 1.

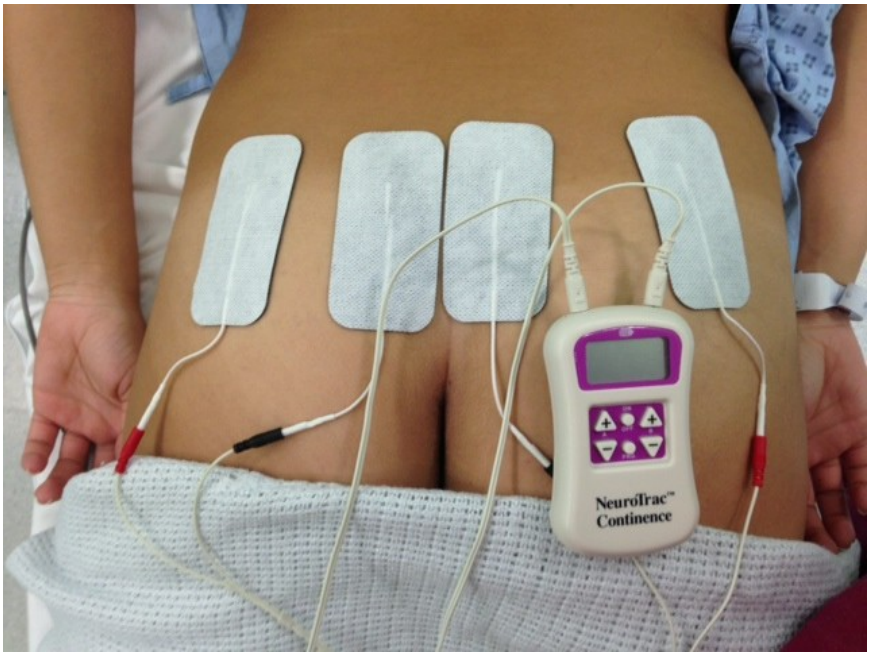


Table 2. Patient characteristics

Total number	10
Gender	8 female
Age	49 (8.25)* years
Type of incontinence	8 mixed, 2 urge
Duration of symptoms	5 (2.25)* years
BMI	29.5 (11.75)* kg/m2
No of vaginal deliveries	1.5 (2.75)*
Internal anal sphincter defect	3

Table 3. Bowel diary data, St Mark's score and visual analogue scale

	Baseline	**After treatment**	**p value**
Incontinent episodes/ week	9.5 (7.5)	3 (7.38)	**0.028**
Defecations/ week	25.5 (19.5)	14.5 (14.88)	**0.007**
Ability to defer defecation/ minutes	1 (1.25)	4.5 (4.5)	**0.017**
St Mark's score/ 24	20 (5.25)	14.5 (8)	**0.012**
Visual analogue scale/100	8.5 (20)	45 (33)	**0.008**

Table 4. Rockwood FI quality of life scores

Domain	**Baseline**	**After treatment**	**p value**
Lifestyle	2 (0.52)	2.2 (1.15)	0.62
Coping	1.35 (0.5)	2.0 (1.10)	0.06
Depression	2.2 (1.32)	2.7 (1.15)	0.93
Embarrassment	1.7 (0.62)	2.3 (1.7)	0.08

Table 5. SF-36 quality of life scores

Domain	Baseline	After treatment	p value
Physical functioning	32 (22.05)	29.9 (22)	0.89
Role physical	42.1 (28.2)	35 (28.2)	0.29
Bodily pain	37.5 (22.95)	33.6 (17.8)	0.92
General health	34.5 (19.7)	35.9 (20.4)	0.62
Vitality	44.3 (9.45)	46.7 (16.55)	0.62
Social functioning	35.4 (16.3)	30.0 (19.5)	0.68
Role emotional	34.3 (31.6)	55.3 (31.6)	0.14
Mental health	36.8 (15.9)	41.4 (18.2)	0.40
Physical cumulative	29.6 (28.45)	32.7 (21.9)	0.21
Mental cumulative	40.3 (19.25)	43.1 (24.0)	0.77

Table 6. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age over 18 years	Inability to use stimulation device
Faecal incontinence, defined as the involuntary loss of solid or liquid stool, two or more times per week.	Rectal prolapse
Intact external anal sphincter on endo anal ultrasound	Active inflammatory bowel disease
Previous conservative therapy, including biofeedback, without symptom resolution	Pregnancy
	Spinal injury/ neurological disorders
	Metal implant in lower back
	Previous neuromodulation
	Other implanted electrical device, such as cardiac pacemaker

Table 7. Patient characteristics

Total number	5
Gender	female
Age	64 (24.5)*
Type of incontinence	3 mixed, 1urge, 1 passive
Duration of symptoms	7 (7.5)*
BMI	25 (12)*
No of vaginal deliveries	2 (0.5)*
Internal anal sphincter defect	2

Table 8. Bowel diary data, St Mark's score and visual analogue scale

	Baseline	After treatment	p value
Incontinent episodes/ week	4.9 (2.75)	2 (12.3)	0.50
Defecations/ week	13.5 (14.35)	12 (7)	0.89
Ability to defer defecation/ minutes	7 (10.5)	5 (10.5)	0.85
St Mark's score/ 24	0 (20.0)	20 (50)	0.19
Visual analogue scale/100	19 (1)	18 (7)	0.49

Table 9. Rockwood FI quality of life scores

Domain	Baseline	After treatment	p value
Lifestyle	2.5 (1.45)	2.7 (1.35)	1.0
Coping	1.8 (0.9)	2.0 (1.3)	0.85
Depression	2.3 (1.0)	2.4 (0.4)	0.71
Embarrassment	1.3 (0.65)	1.7 (0.65)	0.10

Table 10. SF-36 quality of life scores

Domain	Baseline	After treatment	p value
Physical functioning	46.7 (15.6)	50.9 (16.7)	0.66
Role physical	49.2 (24.7)	56.2 (28.2)	1.00
Bodily pain	51.6 (19.7)	37.5 (27.2)	0.29
General health	50.6 (15.7)	50.9 (22.3)	1.00
Vitality	42.0 (17.8)	42.0 (21.4)	0.79
Social functioning	46.3 (18.9)	57.1 (23.1)	0.26
Role emotional	34.3 (26.3)	55.3 (31.6)	1.00
Mental health	45.9 (14.8)	50.4 (9.25)	0.14
Physical cumulative	53.4 (51.9)	46.0 (23.1)	0.23
Mental cumulative	44.0 (23.1)	47.1 (16.4)	0.50

*Data expressed as median (interquartile range).

Chapter 7

Pudendal nerve stimulation for faecal incontinence

Introduction

When sacral nerve stimulation (SNS) for faecal incontinence (FI) [45] is evaluated on an intention to treat basis, around 60% of patients will experience a greater than 50% reduction of incontinent episodes, and 30% will become fully continent. Approximately one third of patients will not improve with chronic stimulation. In these further treatment is difficult and many will progress to a defunctioning colostomy.

SNS is believed to work partly by the activation of ascending afferent sensory fibres in the sacral nerve roots [135]. Stimulation is believed to modulate local reflex pathways at the spinal cord level, which are integral to colonic, rectal and pelvic floor function [90]. Central effects on the sensory cortex and cerebral evoked potentials have also been described [98, 99]. One limitation of sacral nerve stimulation is that usually only one nerve root is stimulated. The sensory outflow from the pelvic floor, distal bowel and anal sphincter is predominantly found in the second and third sacral nerve roots and in some patients may be asymmetric or at a single level [130, 136]. SNS is most frequently performed at the third root (S3) since direct stimulation of S2 can lead to adverse effects such as pain in the buttock, leg or foot. Absence of sensory outflow at the S3 level may explain why SNS fails to benefit some patients. The pudendal nerve is derived from three sacral nerve roots, S2-S4. In theory, greater afferent stimulation may be achieved by stimulation of this nerve than by stimulation of a single sacral nerve root. In some patients this might result in an improved therapeutic effect. In addition, as the pudendal nerve is an isolated structure at the level of the ischial spine there is less risk of unwanted stimulation of adjacent nerve roots.

At present, only two case reports have reported the use of pudendal nerve stimulation (PNS) for non-neurogenic FI [140, 141]. One paper has described its effect in 13 patients with bowel dysfunction secondary to complete cauda equina syndrome [169]. PNS has been used in a small number of patients

with urinary voiding dysfunction and interstitial cystitis, including those who have failed to benefit from SNS [137, 138]. Two cross-over studies have suggested that SNS is superior to PNS for the treatment of bladder dysfunction [142, 170]. The aim of this pilot study was to assess the efficacy of PNS for FI for patients who have failed to respond to SNS.

Method

Ethical approval was for the study was granted by the local ethics committee (NRES Committee London-Harrow, reference number 05/Q0405/112). All patients provided full written consent prior to study entry. Patients who had previously failed to benefit from temporary or chronic sacral nerve stimulation were identified from a departmental database. They were recruited according to the inclusion and exclusion criteria shown in Table 1. Failure to improve from SNS was defined as less than 50% improvement in symptoms compared to baseline. Prior to PNS, patients were instructed to keep a baseline bowel habit diary that assessed frequency of defaecation, number of incontinent episodes and ability to defer defaecation. The St. Mark's incontinence Score [89], Rockwood faecal incontinence quality of life (FIQL) Score [171] and Short Form 36 (SF-36) Quality of Life Score [164] were also measured. Anorectal physiology testing was performed. Anal manometry was performed using an eight channel water-perfused catheter (Medical Measurement Systems, New Hampshire, USA). Anal and mid rectal electrical sensitivities were tested using a Gaeltec EMG-2 catheter (Medical Measurement Systems, New Hampshire, USA). Rectal sensitivity to distension was tested using a polyisoprene inflatable balloon (Stericom Ltd, Chesham, UK) inflated with air from a 50 ml syringe.

Surgical technique

PNS was delivered using a Medtronic model 3093 lead (Medtronic Inc, Minnesota, USA) inserted under general anaesthesia. This was performed using a technique reported by George and colleagues in 2011 [139].

The same surgeon (CJV) was the primary surgeon for all lead placements. The patient was placed in the prone position and the buttocks were strapped apart. A mark was made on the buttocks at the intersection of a horizontal line from the greater trochanter of the femur and a vertical line from the

ischial tuberosity of the pelvis. A hollow SNS foramen needle was inserted at this point. This was connected to an external stimulation device (Interstim test stimulator 3692, Medtronic Inc, Minnesota, USA). A digit was placed into the anus. The foramen needle was advanced to the ischial spine. Anal sphincter contraction was felt when the pudendal nerve was stimulated by the needle. A guide wire was inserted down the needle and the needle removed. The skin at the point of puncture was opened a little by a number 11 scalpel, and an introducer sheath (Interstim Model 3550-18) passed over the guide wire. This was advanced until sphincter contraction was felt again. The electrode lead was placed down the introducer (Interstim model 3093). Its positioning on the nerve was confirmed by sphincter contraction and by an anterior-posterior view plain radiograph of the pelvis. The lead was placed on the side which produced the strongest anal motor response. In patients who had an SNS device already *in situ*, the lead was removed and the PNS lead after insertion was connected directly to the implantable pulse generator (IPG). In those with no previous implanted SNS, the PNS lead was connected to an external stimulator (Interstim test stimulator 3692) inserted into the subcutaneous tissues of the buttock.

Peripheral nerve evaluation (PNE)

Test stimulation was performed at a subsensory level for a three week period. During this period, patients kept a further bowel habit diary that recorded the response of the therapy on their symptoms. If the fall of the frequency of incontinent episodes with stimulation was less than 50%, the patient was withdrawn from the study and the lead was removed under general anaesthetic. If the reduction in the frequency of incontinent episodes was more than 50%, the patient underwent continuous chronic stimulation. In patients whose PNE was satisfactory, the 3093 lead was connected under general anaesthetic to a pulse generator (IPG), model 3023 or model 3058 (Medtronic Inc, Minnesota, USA) implanted in the ipsilateral buttock. .

Stimulation was set to the parameters commonly used for sacral nerve stimulation, including a pulse width of 210μsec and pulse frequency of 14Hz. Electrode configuration was altered so that the sensory stimulus was felt in the perianal area. After initial programming, the amplitude was set at a

sub-sensory level. Follow-up was performed at one, three and six months and then annually. At each follow-up the bowel habit diary, St Mark's continence score, quality of life assessment and anorectal physiology studies were repeated. A study flow diagram is shown in Figure 1.

Statistical analysis

Since this was a pilot study to assess the possible benefits of a new treatment, a power calculation was not performed. The data were continuous and distributed in a non-parametric fashion. Variance was expressed as median with interquartile range (IQR). Data were compared using the Wilcoxon signed rank test. The defecatory deferral times in minutes were expressed as categorical data and analyzed using the Chi-squared test. Statistical analysis was performed using SPSS computer software (IBM, version 20).

Results

Ten patients who had failed to respond to SNS were recruited. Their characteristics and response to test PNS are shown in Table 2. Five achieved a greater than 50% reduction of incontinent episodes and proceeded to chronic stimulation. One patient (Patient 4) withdrew from the study at six months owing to mental health problems. Her data were included in the analysis up to this point. Four patients remained in the study. The median duration of follow up was 24 (6-36) months. No complications were reported. The bowel diary results and St Mark's scores for all ten patients are shown in Table 3.

Of those who had had a good response to test stimulation, a significant improvement was seen in the frequency of incontinent episodes from a median (IQR) of 5 (18.25) per week at baseline to 2.5 (3) per week at latest follow-up ($p=0.043$). No patient achieved complete continence. There was no significant change in the median (IQR) frequency of defecation per day (1 (0.75) to 1.7 (1), $p= 0.11$) or in the ability to defer defecation ($p= 0.89$). There was a significant improvement in the St. Mark's incontinence score from a median (IQR) of 19 (6.0) at baseline to 16 (4.5) at latest follow-up ($p=0.042$). Three of the four patients remaining in the study had maintained a greater than 50% reduction of incontinent episodes at the latest median follow up 24 (6-36) months. The results for

these five patients are summarised in Table 4. There was no significant change in the Rockwood Faecal Incontinence Quality of Life Score or in the SF-36 Quality of Life Score (Tables 5 and 6). Anorectal physiology testing showed significant reductions in median (IQR) rectal sensation to distension at urge (90 (102.5) to 50 (65)) [p=0.043] and maximal volumes (140 (102.5) to 80 (92.5)) [p=0.042]. Anal manometry showed no significant changes, see tables 7 and 8.

Discussion

Of the ten patients selected for PNS after a failed SNS, five fulfilled the PNE criteria for chronic stimulation. All five seemed to respond to the treatment initially, but only three maintained a reduction in the frequency of incontinent episodes by more than 50% at a median follow up of 24 (3-36) months. There was no improvement in the ability to defer defecation or in general and disease-specific quality of life measurements. Only a third had showed improvement in their pre-PNS symptoms at the latest follow up, suggesting that PNS does not benefit all patients who do not respond to SNS. There was no significant improvement in the quality of life. No patient was made completely continent. These results are disappointing.

Significant reductions in urgency and maximal rectal volumes were observed. However, it is unclear why this should have occurred. Given the improvement in incontinence, one might have expected to see an increase rather than a decrease in rectal volume, but the results may have been due to small sample size. No significant changes were observed in anal sphincter pressure recorded by manometry. It is unlikely that PNS has a direct motor effect upon the sphincter complex. This would be consistent with the lack of effect of SNS on sphincter motor function. This study only included patients with an intact external anal sphincter. It is known that SNS is effective in the presence of a sphincter defect [105] and further studies on PNS are required to evaluate whether it is effective in such patients.

The efficacy of SNS can be improved by alteration of the stimulation parameters [102]. The use of sub-sensory stimulation and the stimulation parameters used in this study were the same as those used for

SNS. However, given the differences between the pudendal nerve and the third sacral nerve root, they may not be suitable and alternative settings may yield a better outcome from chronic stimulation.

There is a paucity of information on the outcome of PNS for FI. The report by Matzel and colleagues [140] described the use of a Bion microstimulator (Advanced Bionics Corporation, CA, USA) to stimulate the pudendal nerve in a patient with bowel and bladder dysfunction following an extensive pelvic fracture. Bock and colleagues [141] reported the successful use of the Interstim device (Medtronic Inc, Minnesota, USA) for PNS for two patients who had failed to improve with SNS. George and colleagues suggested that PNS may be effective for bowel dysfunction in cauda equina syndrome [169].

Only a third of patients who had failed to improve with SNS experienced any improvement with PNS. PNS is unlikely to benefit those who have failed SNS. This suggests that failure to respond to one form of neuromodulation may predict failure to respond to any form, although this would be in contrast to the findings of Hotouras et al who reported a good response to SNS in 14 out of 20 patients who had failed to improve respond to posterior tibial nerve stimulation (PTNS) [172] and by the results obtained by Peters and colleagues who reported a favourable outcome from PNS in 41 of 44 patients with bladder dysfunction who had failed to improve with SNS [138].

PNS lead is more difficult than SNS lead insertion. Patients without an indwelling SNS device had to undergo two operations three weeks apart, including insertion of the PNS lead and connection to an IPG or removal in the event of no response to PNE. Both procedures were performed under general anaesthetic, with the patient in the prone position, but in future it should be possible to insert the permanent implant under local anaesthetic. PNS has particular appeal for those who already have an implantable pulse generator in place, since only one operation, insertion of the PNS lead, is required.

The study is limited in being small, underpowered and uncontrolled, but it is not certain whether larger numbers would have altered its conclusion. The patients had all failed SNS and although it is

possible that the results would have been different if neuromodulation-naïve subjects had been chosen. It is unclear how effective PNS is in these patients. More work is needed to investigate the effect of PNS and to compare it directly with other treatments such as SNS.

Conclusion

PNS was ineffective in most patients who had failed to respond to SNS.

Table 1- Inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
Age 18-75 years	Complete spinal cord injury
Signed informed consent	Congenital anorectal malformations
Faecal incontinence, two or more episodes per week	Previous rectal surgery within last 12 months, or 24 months for cancer
Failed previous SNS (temporary or chronic SNS)	History of Inflammatory bowel disease
Intact external anal sphincter	Chronic diarrhoea
Failed medical therapy	Stoma
Failed behavioural therapy	Active perianal sepsis
	Concurrent neurological disease
	Concurrent haematological disease
	Pregnancy

Figure 1. Study Flow Chart

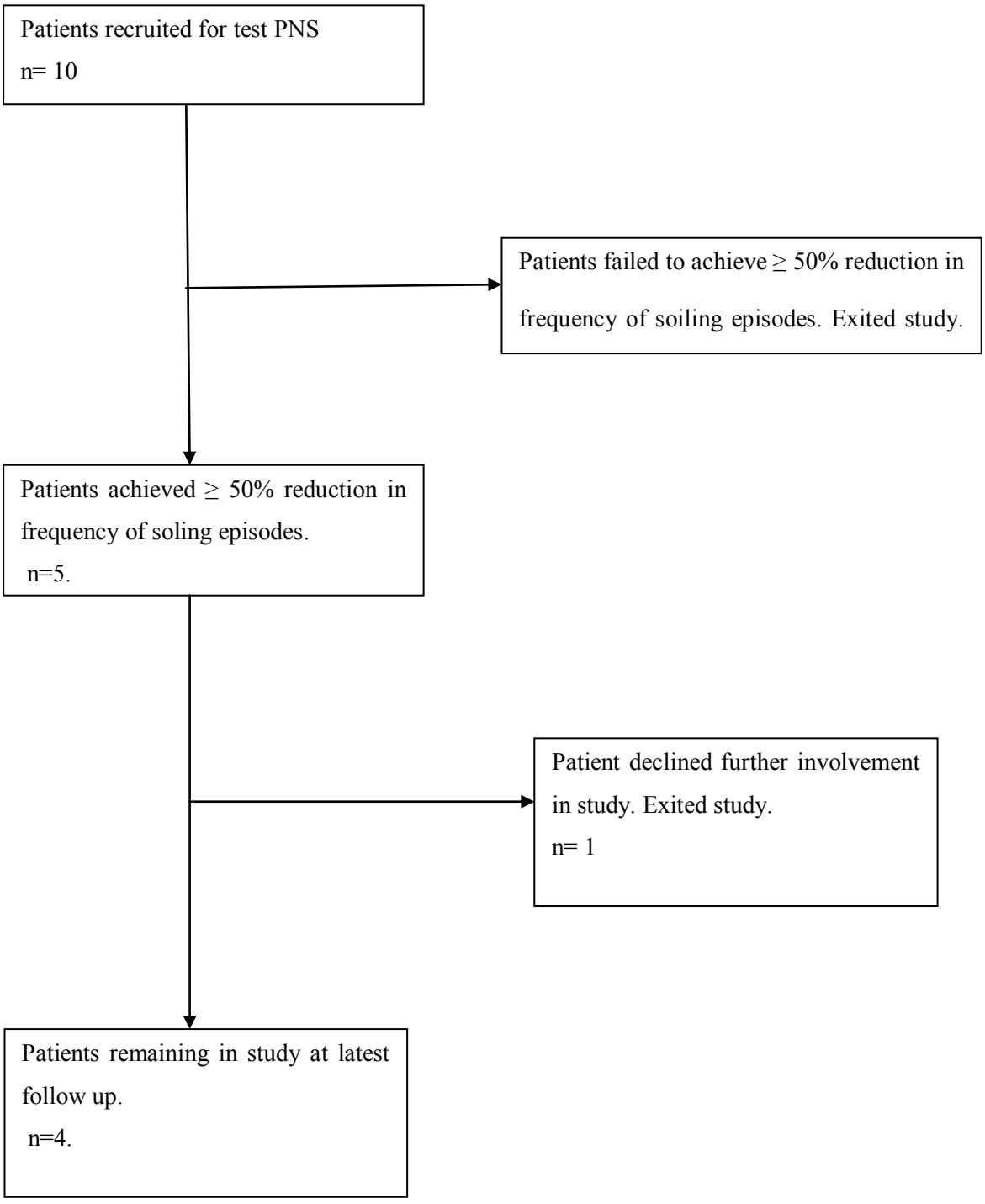


Table 2. Patient characteristics and response to test PNS

Patient	Age/ years	Duration of symptoms/ years	Type of FI	Previous anal surgery	Obstetric history			Type of neuromodulation used previously	Successful response to PNS
					Number of vaginal deliveries	Number of obstetric tears	Deliveries using instrumentation		
1	46	13	Mixed	Sphincteroplasty	2	2	0	PNE*	Yes
2	69	15	Mixed	Sphincteroplasty	3	0	0	PNE*	Yes
3	43	16	Mixed	No	2	1	0	SNS#	Yes
4	63	11	Mixed	No	4	0	1	SNS#	Yes
5	73	4	Mixed	No	4	1	0	PNE*	No
6	68	15	Mixed	No	2	0	1	PNE*	No
7	58	7	Mixed	Sphincteroplasty	4	0	0	PNE*	No
8	63	10	Mixed	No	2	0	0	SNS#	Yes
9	74	12	Mixed	No	2	1	0	SNS#	No
10	61	15	Passive	No	2	1	0	SNS#	No

SNS= chronic sacral nerve stimulation

*PNS= peripheral nerve evaluation

FI= faecal incontinence

Table 3. Bowel diary and St Mark's score results

Patient	Baseline			Test PNS			Chronic PNS			
	FI /week	Deferral time/ minutes	St Mark's score /24	FI/week	Deferral time/ minutes	St Mark's score /24	Latest follow up/ months	FI/week	Deferral time/ minutes	St Mark's score /24
1	2	<1	17	0.3	1-5	15	24	0.5	1-5	15
2	35	1-5	24	1	>15	6	36	2.5	5-15	16
3	5	<1	19	1.5	1-5	18	24	1.5	1-5	16
4*	7	<1	20	1	>15	0	6	5	1	19
5#	7	1-5	18	5	1-5	15				
6#	20	<1	22	20	<1	17				
7#	18	1-5	18	14	1-5	17				
8	3.5	1-5	15	1	<1	13	6	3	>15	13
9#	11	1-5	16	19.5	1-5	17				
10#	9.5	15	13	16	10	17				

Blacked out areas indicate that the patient did not undergo chronic stimulation

* Patient 4 withdrew from study after six months follow up

Patients 5, 6, 7, 9 and 10 all failed to achieve a >50% improvement in symptoms and left study

St Mark's score, 0 = perfect continence, 24 = severe incontinence

FI= faecal incontinence

PNS= peripheral nerve stimulation

Table 4- Bowel diary and St Mark's score for those having chronic PNS

Outcome measure	Baseline	Most recent follow-up (Median 24 months)	p-value
FI/ week	5 (18.25)	2.5 (3)	**0.043**
Defecations/day	1 (0.75)	1.7 (1)	0.109
Deferral time (n)	<1 minute- 3 1-5 minutes- 2 5-15 minutes- 0 >15 minutes- 0	<1 minute- 1 1-5 minutes- 2 5-15 minutes- 1 >15 minutes- 1	0.89
St Mark's score*	19 (6)	16 (4.5)	**0.042**

* = St Mark's continence score (maximum 24 [severe incontinence], 0, perfect continence)

Variance expressed as median (interquartile range)

FI= faecal incontinence

Table 5 Median (IQR) Rockwood FI QOL scores for patients having chronic PNS

Domain	Baseline	Latest follow up	p value
Lifestyle	1.9 (1.4)	2.2 (1.95)	0.42
Coping/ Behaviour	1.4 (0.65)	1.4 (0.55)	1.0
Depression/ Self perception	2.3 (1.3)	2.1 (0.6)	0.28
Embarrassment	1.7 (0.7)	1.3 (1.0)	0.29

FIQOL= faecal incontinence quality of life

Table 6- Median (IQR) SF-36 QOL score changes for patients having chronic PNS

Domain	Baseline	Latest follow up	p value
Physical functioning	50.9 (57.15)	55 (37.3)	0.47
Role physical	56.2 (51.6)	50 (42.2)	0.79
Bodily pain	55.9 (43.0)	51.6 (27.9)	0.27
General Health	57 (33.5)	50.9 (35.7)	0.5
Vitality	60.9 (31.6)	44.3 (34.2)	0.29
Social functioning	57.1 (32.3)	37 (48.6)	0.85
Role emotional	55.3 (60.5)	34.3 (60.5)	0.29
Mental health	57.3 (39.5)	48.2 (26.2)	0.08

Table 7. Anorectal physiology

Patient	Baseline								Latest follow up						
	RP	PS	ES	IS	RT	RU	RM	IAS defect on endoanal ultrasonography	RP	PS	ES	IS	RT	RU	RM
1	33	29	12	58	25	40	65	Yes	36	18	19	14	25	35	50
2	9	43	11	44	20	90	140	Yes	12	54	21	26	25	50	125
3	84	48	61	17	100	130	150	No	72	69	9	28	50	65	80
4	46	70	0	45	80	180	200	No	50	39	11	57	95	150	180
5*	24	97	20	138	30	40	70	No							
6*	12	11	0	9	30	40	50	Yes							
7*	70	30	9	40	100	150	200	No							
8	41	22	10	35	35	65	80	No	42	20	19	30	20	50	70
9*	56	22	0	43	25	70	95	Yes							
10*	9	20	19	77	30	50	75	No							

Blacked out sections indicate that these patients did not undergo chronic stimulation

* failed to achieve >50% improvement in symptoms from test PNS

Key to abbreviations (normal range in brackets)

RP= resting pressure cmH2O (60-160)

PS= peak squeeze cmH2O (50-180)

ES= 5 second endurance squeeze cmH2O (40-160)

IS= involuntary squeeze cmH2O (50-100)

RT= rectal threshold volume to distension ml air (20-70)

RU= rectal urge volume to distension ml air (35-120)

RM= rectal maximal volume to distension ml air (100-260)

IAS= internal anal sphincter

Table 8- Table to show anorectal physiological parameters for patients having chronic PNS

Parameter	Baseline	Latest follow up	p value
Resting pressure cmH_2O	41 (44)	42 (37)	0.49
Peak squeeze increment cmH_2O	43 (33.5)	39 (42.5)	0.79
Five second squeeze increment cmH_2O	11 (31.5)	19 (10)	0.5
Involuntary squeeze increment cmH_2O	44 (25.5)	28 (23.5)	0.5
Rectal threshold volume (air) mls	35 (67.5)	25 (50)	0.58
Rectal urge volume (air) mls	90 (102.5)	50 (65)	**0.043**
Rectal maximal volume (air) mls	140 (102.5)	80 (92.5)	**0.042**
Anal electrical sensitivity mAmps	11.8 (6.35)	9.5 (2.75)	1.0
Rectal electrical sensitivity mAmps	19.4 (7.3)	23 (20.5)	0.228

Data expressed as median (interquartile range)

Chapter 8

Transcutaneous posterior tibial nerve stimulation for faecal incontinence

8.1 A randomised blinded study comparing daily with twice weekly transcutaneous posterior tibial nerve stimulation for faecal incontinence

8.1 Introduction

Many different regimes of posterior tibial nerve stimulation (PTNS) have been reported. These range from once daily to once weekly treatments given over four to 12 weeks. It is unclear what the optimum treatment regimen should be. No published studies have attempted to determine this. The aim of this study was to compare the outcome of daily transcutaneous PTNS with twice weekly PTNS.

8.1 Method

Ethical approval was granted by the local ethics committee (NRES Committee London- Queen Square, reference 11/LO/1702). Patients fulfilled the inclusion and exclusion criteria shown in Table 1. They were recruited from the outpatient clinic at the authors' institution. Once informed consent had been obtained, patients were randomised to receive once daily or twice weekly unilateral transcutaneous PTNS. Randomisation was performed by a third party, who had no part in the analysis of the results by random selection of a sealed opaque envelope which contained the group allocation. The primary investigator was blind to the group allocation during the study.

A two-week continence diary was kept which recorded baseline symptoms prior to therapy, including the frequency of episodes of faecal incontinence, frequency of defaecation, deferral time to defaecation in minutes [urgency], the number of episodes of soiling and pad usage. Assessment was also obtained by a visual analogue scale (0 'very unhappy'; 100 'very happy') based on the patient response to "*how happy are you with the way your bowels have been functioning*?" The Rockwood Faecal Incontinence Quality of Life score [54], the St Mark's Faecal continence Score [89] and a short form 36 (SF-36) survey were also measured [164]. Changes in anorectal physiology were not measured.

All patients carried out the treatment at home for six weeks. They were given one to one instruction on PTNS, written instructions and a photograph demonstrating the position of the electrode pad and lead. They were also asked to use the same leg. Each patient completed a further two week continence diary during weeks 5 and 6. Questionnaires were completed at the end of the six week treatment. The PTNS device was then returned to the hospital. All patients were interviewed by telephone at one

month after treatment. They were withdrawn from the study when the frequency of incontinent episodes had returned to the baseline level. A CONSORT study flow diagram [173] is shown in Figure 1.

PTNS was given using a NeuroTrac ™ TENS transcutaneous electrical nerve stimulator (Verity Medical Ltd, UK) via two 50mm x 50mm electrode pads. The live pad was placed posterior and superior to the medial malleolus and the ground pad was placed approximately 10cm cephalad to this, see photograph one. Continuous stimulation at a pulse width of 200 μsec and a frequency of 10 Hz was used. The amplitude was set to produce a sensory stimulus in the ipsilateral foot at an intensity tolerable to the patient. Stimulation was given for 30 minutes.

The primary outcome measure was the frequency of faecal incontinence episodes per week. Secondary outcome measures included the ability to defer defecation in minutes, frequency of defaecation, changes in the St Mark's score and quality of life assessment. Patients were advised to stop any antidiarrhoeal agents, or only to use them if necessary.

8.1 Statistical Analysis

Since there were few previous studies on PTNS, it was not possible to perform a power calculation based on available information. The data were non-parametric and variance was therefore expressed by the median and inter-quartile range. The Wilcoxon Rank test was used for comparisons between the groups. Deferral times were analysed as categorical variables using the Sign test. Analysis was performed using the SPSS computer software (IBM, version 20).

8.1 Results

Thirty patients were randomised to 15 in each group. One patient failed to attend the six week follow-up appointment and was therefore excluded from the analysis. Baseline data are shown in Table 2. No adverse events were reported. At six weeks three patients in the daily PTNS group had achieved complete continence (Table 3), while none in the twice weekly PTNS group had done so. In the daily group there was a significant reduction in incontinent episodes from a median of 5 (11) to 3.5 (4.3) episodes per week (p=0.025). In the twice weekly group there was a non-statistically significant (p= 0.31) reduction in the number of incontinent episodes from 6.5 (5) to 3 (6.5) episodes per week. The percentage reduction in the frequency of incontinent episodes was a median of 60 (87) % in the daily group and 50 (60) % in the twice weekly group. There were no significant changes in either group in the weekly frequency of defecation or the ability to defer defaecation. The twice weekly group patients showed a significant improvement in the St Mark's score (21 (4) to 17 (7), p = 0.012), not seen in the daily group. The bowel satisfaction score improved significantly in each group (Table 3). There was improvement in the daily group but not in the twice weekly group in the domains of

lifestyle and embarrassment in the Rockwood FI-QOL score. (Table 4). In the SF-36 QOL assessment the physical domain fell in the daily group (Table 5). Body mass index and ankle circumference had no statistically significant effect upon the change in incontinent episodes. The patients who experienced improvement in the number of incontinent episodes per week returned to the baseline value at a median of 4 (2.75) weeks. Those in the twice weekly group who had an improvement returned to baseline at a median of 4 (3.5) weeks.

8.1 Discussion

To the best of our knowledge, this is the first study which has attempted to compare different stimulation regimens of PTNS. When paired data were compared in each group daily transcutaneous PTNS achieved a statistically significant reduction in episodes of faecal incontinence, whereas twice-weekly treatment failed to do so. In the daily treatment group, improvement in continence correlated to a significant improvement in two domains of the Rockwood FI-QOL score and adequate patient satisfaction. This may suggest that daily stimulation is more effective than twice weekly. However, this conclusion cannot be supported by comparison of the two groups, because the study was insufficiently powered, although it gives useful information for the planning of a larger randomised trial to investigate further the optimum regimen of PTNS.

The 50% reduction in incontinent episodes in about half the patients in each group was similar to that reported by Govaert and colleagues [114], in which 59% achieved this outcome with percutaneous PTNS. When sacral nerve stimulation (SNS) is assessed on an intention to treat basis, about 60% of patients would be expected to experience a 50% or more reduction in incontinent episodes [107]. SNS and percutaneous PTNS have both been shown to improve urgency, but disappointingly this was not seen in either group in the present study.

The improvement following transcutaneous PTNS in the study was less than that obtained for percutaneous stimulation in a larger study [165], here a reduction in the frequency of incontinent episodes of 4 (0-30) to 0 (0-10) and 5 (0-35) to 1 (0-27) was found for patients with urge and mixed incontinence. Leroi and colleagues [123] randomised 144 patients to receive unilateral transcutaneous PTNS or sham stimulation in a double blinded controlled trial. They found no significant difference between the two treatment arms. Although our study cannot allow a direct comparison to be made between transcutaneous and percutaneous PTNS, one may hypothesise that unilateral transcutaneous PTNS, irrespective of the treatment regimen, is not as effective as percutaneous PTNS. This finding was supported by a recent randomised controlled study by George and colleagues [122].

It is unclear why there was a statistically significant improvement of the St Mark's score in the twice weekly group and not in the daily group. Perhaps this was due to the inclusion in the St Mark's score

of factors resulting from learned behaviour such as pad and anti-diarrhoeal usage. Self-assessment of urgency is included and the patient may not readily appreciate a change in this, if they have had severe urgency for a long time. Thus the St Mark's score and other FI severity scoring systems may not be able to discern short term changes in severity. The twice weekly group were exposed to a total of 12 sessions of PTNS, whereas the daily group had 42. This difference may go some way to explain the difference in outcome observed at six weeks.

Once treatment had finished the therapeutic effect lasted for about four weeks in both groups. It is difficult to assess this accurately since information was obtained by telephone and the patient's subjective recollection. Objective assessment using continence diaries would only be able to give this information if maintained continuously, which would not be practical. Four weeks is similar to the duration of efficacy reported by others. It might be possible then to adopt a less intensive treatment, so called 'top up' treatment as described by Govaert [114] and Hotouras [165] .

PTNS is cheaper than SNS and transcutaneous PTNS is cheaper than percutaneous. The stimulator costs approximately £50 and four reusable electrode pads £3. These would suffice for at least six weeks of daily treatment. The percutaneous PTNS stimulator costs £500 and the disposable electrodes cost £200 for 12 sessions. Percutaneous PTNS also requires the patient to attend the hospital for the treatment to be delivered by a trained professional. In contrast, transcutaneous PTNS can be performed safely by the patient at home. This may be a more suitable for those who are unable to attend hospital on a regular basis.

8.1 Conclusion

Transcutaneous PTNS is safe and moderately effective in FI. It can be used from home. Daily stimulation achieved a significant improvement in the frequency of incontinent episodes, but twice weekly stimulation did not. This may mean that daily stimulation is a more effective treatment regimen. However, a larger study is needed to determine this question.

8.2 Bilateral transcutaneous posterior tibial nerve stimulation for faecal incontinence

8.2 Introduction

Neuromodulation is believed to work via stimulation of multiple afferent sensory pathways in the spinal cord. This has an effect on the pelvic viscera, lower gut and the sensory cortex.[90] Bilateral neuromodulation may activate a greater number of afferent sensory pathways, which could lead to an improved therapeutic effect. In a proportion of patients the pelvis is innervated asymmetrically [130] and unilateral stimulation may therefore not achieve optimal treatment outcome depending on the site used for stimulation. Bilateral SNS has been described for faecal incontinence [71] and bladder dysfunction.[174] There are no reports of bilateral PTNS in the published literature. We therefore aimed to assess the effect of daily bilateral transcutaneous PTNS in a prospective pilot study. A daily treatment regimen was used since the previous study had suggested that this may be more effective than twice weekly treatment.

8.2 Method

Ethical approval was granted by the local ethics committee (NRES Committee London- Dulwich, reference 12/LO/0589). Patients fulfilled the inclusion and exclusion criteria shown in Table 1. Informed consent was obtained. A two week faecal incontinence bowel diary was kept, which recorded the frequency of episodes of FI, frequency of defecation and deferral time to defecation. A visual analogue scale rated on the patient response to "*how happy are you with the way your bowels have been functioning*" was recorded. The patient placed a mark on a visual analogue scale of 0 to 100; zero indicated that they were very unhappy and 100 indicated that they were very happy. The Rockwood Faecal Incontinence Quality of Life score,[54] the St Mark's continence Score [89] and the SF-36 score were also recorded.[164] The body mass index was calculated. The ankle circumference was also estimated, this was measured immediately above the malleoli.

After receiving initial in-hospital teaching, all patients were taught to administer PTNS at home. Written instructions on the use of PTNS and a photograph demonstrating the electrode pad and lead position were also given. PTNS was performed on both ankles simultaneously for 30 minutes daily, for a six week period. PTNS was given using a NeuroTrac ™ Continence device (Verity Medical Ltd, UK) via two 50mm x 50mm electrode pads. The live pad was placed posteriorly and superiorly to the medial malleolus and the ground pad was placed approximately 10cm cephalad to this. Continuous stimulation at a pulse width of 200μsecs and a frequency of 10 Hz was used. The amplitude was set to produce a sensory stimulus in the ipsilateral foot at an intensity tolerable to the patient.

Each patient kept a two-week bowel habit diary during the fifth and sixth week of therapy. The remaining questionnaires were completed at the end of the six week treatment. The PTNS devices

were then returned and patients were followed up by telephone consultation at one month after treatment had ceased. They were withdrawn from the study when the frequency of incontinent episodes had returned to baseline. A study flow diagram is shown in figure 2.

The primary outcome measure was the change in frequency of FI episodes per week. Secondary outcome measures were included the ability to defer defecation measured in minutes, frequency of defecation, change in the St Mark's continence score and quality of life. Patients were advised to abstain from anti-diarrhoeal agent use during this study. All medication use was recorded.

8.2 Statistical Analysis

This was a non-randomized pilot study. There were insufficient data to perform a sample size calculation. Since the data were non-parametric, variance was expressed by the median and the interquartile range. The Wilcoxon Rank test was used for comparison of paired data. Statistical analysis was performed using SPSS computer software (IBM, version 20).

8.2 Results

Twenty patients were recruited into the study. Three patients were excluded from the analysis. Two did not complete six weeks of treatment and failed to return at six weeks. It was not clear why this occurred. One patient unwittingly entered the study in early pregnancy. She suffered a spontaneous miscarriage during PTNS therapy. The ethics committee and study's sponsors were notified of this adverse event.

Seventeen patients were included in the analysis. Baseline data are shown in Table 2. There was a significant reduction in the frequency of FI episodes from a median (IQR) of 6 (8.25) per week at baseline to 2 (7.25) per week at six-weeks (p= 0.03). At six weeks, only two patients had achieved complete continence. Ten (59%) patients achieved a reduction of incontinent episodes per week of 50% or more. The remaining five (29%) had less than 50% reduction of incontinent episodes. The median percentage reduction in frequency of incontinent episodes was 66% for the whole group.

The ability to defer defecation was significantly improved from a median (IQR) of 3 (4) minutes to 5 (8) minutes (p= 0.03). The bowel satisfaction score improved significantly from a median of 10 (25) to 20 (52.5) (maximum score 100; p= 0.02). There was no significant change in the St Mark's continence score (Table 3*)*. Those patients who had experienced a reduction in frequency of incontinent episodes returned to the baseline value at a median of 3 (1) weeks. Body mass index and ankle circumference had no significantly significant effect upon the change in incontinent episodes.

A significant improvement was seen in the lifestyle domain of the Rockwood FI-QOL Score. There was also a significant improvement in the general health domain of the SF-36 QOL assessment (tables four and five).

8.2 Discussion

The treatment of faecal incontinence in patients who have failed conservative therapy is difficult. Surgical treatments are invasive, expensive and often give uncertain results. Transcutaneous PTNS has the advantage that it can be performed at home by the patient after simple training. The therapy does not require expensive or invasive equipment. The time required to perform the treatment may be inconvenient, but the direct and indirect costs are likely to be considerably lower than treatments that require surgery or numerous visits to and from a hospital.

To the best of our knowledge this is the first study that has reported the outcome of bilateral transcutaneous PTNS for faecal incontinence. This treatment achieved a significant short-term improvement in the frequency of incontinent episodes and in the ability to defer defecation. This study was, however, limited by small numbers and the lack of a control group.

In the largest published series to date, Hotouras and colleagues [165] reported the outcome of 60 patients with mixed FI who had undergone unilateral percutaneous PTNS. They found a statistically significant improvement in the median (range) frequency of incontinent episodes per week from 5 (0-35) to 1 (0-27) and in the ability to defer defecation from 1 (0-15) to 5 (0-25) minutes. When the outcome of SNS is assessed on an intention to treat basis, around 70% can be expected to experience a 50% or greater reduction in the frequency of incontinent episodes.[107] Using an arbitrary 50% percentage reduction in symptoms as an end-point, the results achieved by bilateral transcutaneous PTNS in this study are therefore comparable to those achieved by both percutaneous PTNS and by SNS. However it must be appreciated that in this study and in those previously published on percutaneous PTNS, fewer patients appear to gain full continence with PTNS compared with sacral nerve stimulation and in many a 50% reduction in symptoms may not be sufficient to improve quality of life. The reduction of incontinent episodes with SNS appears to be more pronounced than PTNS in those who respond to treatment by demonstrating a positive PNS leading to permanent implantation[56, 57].

George [122] and Leroi [123] have cast doubt on the effectiveness of unilateral transcutaneous PTNS. It is possible that transcutaneous PTNS can only be effective when used in a bilateral fashion although a significant placebo response may exist.

Disappointingly, there was no significant improvement in the St Mark's continence score and patient satisfaction scores remained low despite a reduction in the number of incontinent episodes. As only two patients achieved full continence this finding may reflect dissatisfaction with any level of incontinence even if the frequency of episodes has been reduced. In addition, learned behaviour such as pad use, lifestyle changes and use of anti-diarrhoeal agents may continue. Such behavioural factors may take a long time to change once they have become established. Thus the St Mark's continence score and other measures of incontinence may be unsuitable to detect short term changes in severity.

Once treatment had finished the therapeutic effect lasted for a median of three weeks. It is difficult to measure this accurately. Assessment was performed by telephone consultation and relied upon the patient's recollection of their recent symptoms. Objective assessment using bowel diaries would only work if performed continuously, this would not be practical. Three weeks is similar to the duration of efficacy reported by others. Govaert [114] and Hotouras [165] described a less intensive treatment regimen, so called "top-up" treatment. Consideration needs to be given to how such a regimen could be applied to bilateral transcutaneous PTNS.

One patient suffered a miscarriage during PTNS. There are no reports of the use of PTNS during pregnancy in the published literature. A few case reports have described SNS during pregnancy.[175-178] All pregnancies were uneventful, except for one which resulted in an infant with a chronic motor tic syndrome and a pilonidal sinus and another which resulted in premature delivery. Although it is unlikely that PTNS was responsible for the miscarriage, the authors suggest that PTNS should not be used by those who are pregnant. It may be advisable that all females of child-bearing age should undergo a pregnancy test before PTNS.

8.2 Conclusion

Bilateral transcutaneous PTNS appears to be effective for some patients with urge and/or passive faecal incontinence. Further studies are required to compare the clinical outcome and cost effectiveness of bilateral transcutaneous PTNS with existing, more invasive treatments.

8.3 Predictive factors for success of transcutaneous posterior tibial nerve stimulation for faecal incontinence

8.3 Introduction

The studies in sections 8.1 and 8.2 suggest that transcutaneous PTNS may be effective for faecal incontinence. It is, however, uncertain which patients are likely to benefit the most from PTNS.

The aim of this study was to analyse the previous two studies to see which patient or pre-treatment, factor had a significant effect upon the outcome.

8.3 Method

The prospectively collected data from studies 8.1 and 8.2 were analysed. The two outcome measures of interest included the percentage reduction in the number of incontinent episodes per week and the change in urgency in minutes.

8.3 Statistical Analysis

Linear regression analysis was used for both outcomes of interest. The analysis was performed in two stages. First the separate association between each factor and the outcome was assessed using univariate analysis. Any association between any variable and the outcome was then assessed by multivariate analysis. Due to the small sample size, only variables showing some association with the outcome in the univariate analysis (p value of <0.2) were included in the multivariate analysis. A backwards selection procedure was used to retain only the statistically significant variables.

The percentage reduction in incontinent episodes per week was measured as a continuous scale. The ability to defer defecation in minutes was measured in some cases using a continuous scale and for others as an interval. For these patients, the midpoint of the interval was used as the deferral time.

Patient or pre treatment factors chosen for analysis were age, gender, duration of symptoms, type of faecal incontinence, body mass index, ankle circumference, external and internal sphincter defect, PTNS regimen and pre treatment anal manometry measurements.

8.3 Results

Reduction in the number of incontinent episodes per week.

The results of the univariate analysis into the reduction of frequency of incontinent episodes per week are shown in table 11. No patient factor was significantly associated with the percentage reduction in incontinent episodes per week. The presence of a sphincter defect came close to achieving statistical significance ($p=0.07$). The presence of either an external or internal sphincter defect was associated with a 68% percentage reduction in the improvement of incontinent episodes compared to patients without a sphincter defect. Multivariate analysis showed that a sphincter defect was not significantly

related to the percentage reduction of frequency of incontinent episodes when adjusted for other factors.

Change in the ability to defer defecation (urgency).
Univariate analysis suggested that the peak increment voluntary squeeze pressure and peak involuntary increment squeeze pressure were significantly associated with the ability to defer defecation associated with the outcome ($p = 0.05$ and 0.04; Table 12). Higher values of both variables were associated with higher deferral times. An increase in peak increment involuntary squeeze pressure by 10 mm Hg was associated with an increase in deferral time of 0.3 minutes, whilst an increase in peak increment voluntary squeeze pressure of 10 mm Hg was associated with an increase of 0.2 minutes in deferral time. Multivariate analysis showed that peak increment involuntary squeeze pressure had a significant effect on urgency ($p=0.04$). The effect of peak increment voluntary squeeze pressure was not significant once it had been adjusted for the other variables.

8.3 Discussion

The study suggests that patients with higher pre treatment voluntary and involuntary peak increment squeeze pressures may experience a greater improvement in urgency following transcutaneous PTNS. Although statistically significant, it is uncertain how clinically significant this relationship is. No other patient factor had a statistically significant influence on the frequency of incontinent episodes. This is consistent with the findings of Hotouras and colleagues [179], who reported the outcome among 88 patients who had undergone percutaneous PTNS for FI. These authors attempted to see whether a sphincter defect and abnormal rectal sensitivity affected the outcome, assessed by the Cleveland Clinic incontinence score [54], the ability to defer defecation and the frequency of FI episodes per week. No statistically significant association between these factors and outcome was observed. No other published report has attempted to relate patient factors with outcome after PTNS for FI.

Sacral nerve stimulation (SNS) has been reported more extensively. Maeda and colleagues [180] described 244 patients who had undergone peripheral nerve evaluation (PNE) to determine whether permanent SNS should be carried out. They were unable find a pre-procedure factor that could predict the outcome of the PNE. In contrast, Dudding [181] and Govaert [182] suggested that an external anal sphincter defect may adversely influence the outcome of SNS in 81 and 245 patients who had undergone PNE. This conclusion is supported by a meta-analysis of all reports of SNS for faecal incontinence between 1995 to 2008 [105].

The present study was limited in several ways. First patient numbers were small, secondly there was considerable variation in the regimen of PTNS and thirdly the follow up was short. Sphincter defects should be classified more precisely with regard their size and function should be reported as

accurately as possible. The anal manometry data are susceptible to inter-observer variability. The improvement in deferral time seen with higher anal sphincter pressures is small and although statistically significant, the clinical significance of this finding is questionable.

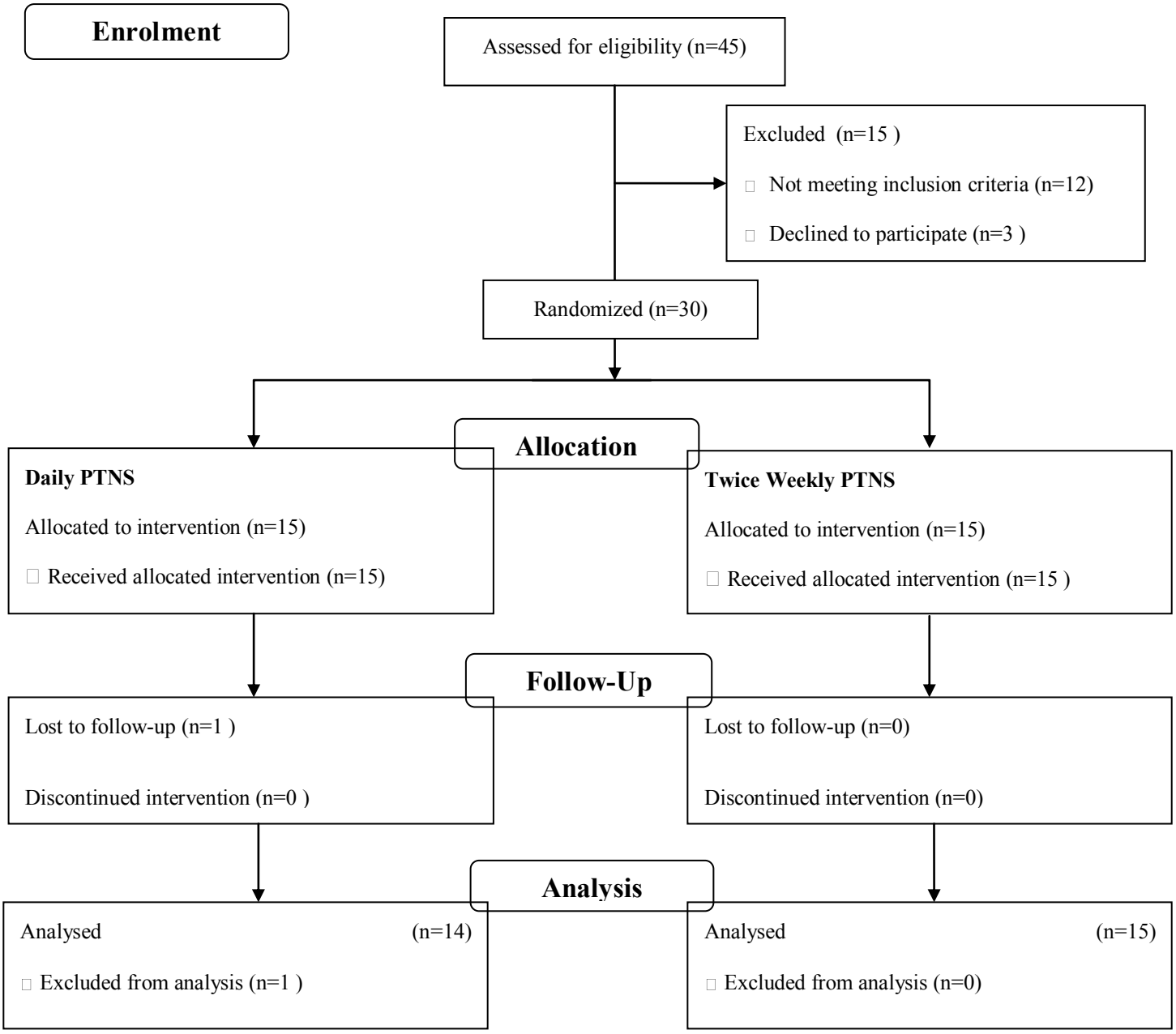
8.3 Conclusion

This study suggests that patients with a higher peak involuntary squeeze pressure may have a greater improvement in urgency from transcutaneous PTNS, but more work is needed to be sure on this point.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Signed consent form	Previous congenital or acquired spinal injury, tumour or surgery
18-80 years of age	Peripheral vascular disease
Faecal incontinence defined as at least two episodes per week of involuntary loss of either liquid or solid stool, as demonstrated by a baseline bowel diary	Peripheral neuropathy or neurological disorder
Previous unsuccessful biofeedback	Ano-rectal surgery within the last year
Willing and able to travel up to the investigational centre for the duration of the study.	Full thickness rectal prolapse
Willing and able to complete the necessary questionnaires and bowel diaries.	Active inflammatory bowel disease
No previous neuromodulation	Psychological or physical inability to deal with the study protocol
	Pregnancy or attempting to become pregnant

Figure 1. CONSORT Study Flow Diagram



Phtograph 1.



Table 2. Baseline characteristics of the patients

	Daily PTNS	**Twice weekly PTNS**
Total	14	15
Gender	F=14	F=12
Median age	54.5 (8.5)	51 (29)
Type of FI	Urge- 5 Passive- 4 Mixed- 5	Urge- 4 Passive- 2 Mixed- 9
Median duration of symptoms/ years	6 (4.13)	5 (9)
Median BMI (kg/m^2)	25.5 (7.4)	25 (4)
Median ankle circumference/ cm	20.7 (3.63)	20.5 (1)
Anal sphincter defect	n=7	n=6

Table 3. Bowel diary data, St Mark's FI score and visual analogue score results

	Daily PTNS			Twice weekly PTNS		
	Baseline	**Six weeks**	**p value**	**Baseline**	**Six weeks**	**p value**
FI episodes / week	5 (11.13)	3.5 (4.31)	**0.025**	6.5 (5)	3 (6.5)	0.31
Defecations/ week	10.3 (16)	13 (11.35)	0.43	13 (14)	12.5 (15)	0.125
Deferral time/ minutes* (n)	<1 min (5) 1-5 mins (7) 5-15 mins(1) >15 mins (1)	<1min (4) 1-5mins (6) 5-15mins(3) >15mins (1)	0.25	<1 min (7) 1-5 mins (6) 5-15 mins(2) >15 mins (0)	<1min (3) 1-5mins (9) 5-15mins(3) >15mins (0)	0.125
St Mark's FI Score	18 (5.25)	18 (4.50)	0.07	21 (4)	17 (7)	**0.012**
Visual analogue bowel satisfaction score	10 (21)	30 (23.25)	**0.01**	10 (39)	30 (40)	**0.004**

	Daily PTNS	**Twice weekly PTNS**
% achieved complete continence	21 (n=3)	0
% achieved a greater or equal to 50% reduction in symptoms	57 (n=8)	53 (n=8)

Table 4. Rockwood faecal incontinence quality of life score

FI-QOL Domains	**Daily PTNS**			**Twice weekly PTNS**		
	Baseline	**Six weeks**	**p value**	**Baseline**	**Six weeks**	**p value**
Lifestyle	2.2 (1.7)	2.6 (1.65)	**0.04**	2.7 (1.15)	2.75 (1.35)	0.79
Coping	1.8 (0.95)	1.75 (1.35)	0.54	1.7 (1.02)	1.75 (0.78)	0.76
Depression	2.4 (1.15)	2.4 (1.10)	0.61	2.6 (1.33)	2.9 (0.92)	0.48
Embarrassment	1.7 (0.85)	2.15 (0.4)	**0.04**	1.85 (1.10)	1.85 (0.7)	0.60

Table 5. SF-36 quality of life score

SF-36 Domains	Daily PTNS			Twice weekly PTNS		
	Baseline	**Six weeks**	**p value**	**Baseline**	**Six weeks**	**p value**
Physical Functioning PF	47.75 (20.48)	44.6 (19.95)	0.15	47.75 (15.13)	50.90 (6.20)	0.24
Role Physical RP	42.1 (21.20)	28.00 (14.10)	**0.04**	52.70 (15.88)	56.20 (21.20)	0.55
Bodily Pain BP	37.50 (24.35)	33.20 (23.82)	0.21	52.90 (13.10)	54.20 (16.20)	0.92
General Health GH	45.05 (15.90)	40.35 (24.35)	0.95	45.05 (12.33)	43.90 (14.00)	0.21
Physical Health total PCS	40.40 (20.25)	35.60 (25.72	0.29	47.75 (9.38)	48.30 (15.20)	0.75
Vitality VT	43.15 (28.43)	46.70 (22.48)	0.075	46.7 (14.80)	46.70 (14.20)	0.22
Social Functioning SF	40.85 (27.10)	32.70 (19.00)	0.089	46.30 (29.83)	46.30 (16.30)	0.72
Role emotional RE	50.05 (31.60)	39.55 (31.60)	0.68	55.30 (31.60)	55.30 (10.50)	0.29
Mental Health MH	42.50 (16.48)	42.50 (17.03)	0.57	47.05 (17.13)	45.90 (15.90)	0.62
Mental health total MCS	44.10 (27.08)	40.55 (23.42)	0.96	48.40 (24.00)	46.70 (18.70)	0.70

Table 6. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Aged 18-80 years	Spinal pathology, recent surgery
Faecal incontinence defined as at least two episodes per week of involuntary loss of either liquid or solid stool as defined by a baseline bowel diary	Peripheral vascular disease
Completed biofeedback and conservative therapy	Peripheral neuropathy
No previous neuromodulation	Previous anorectal surgery within the last year
	External rectal prolapse
	Active inflammatory bowel disease
	Pregnancy
	Inability to apply the device independently

Figure 2.

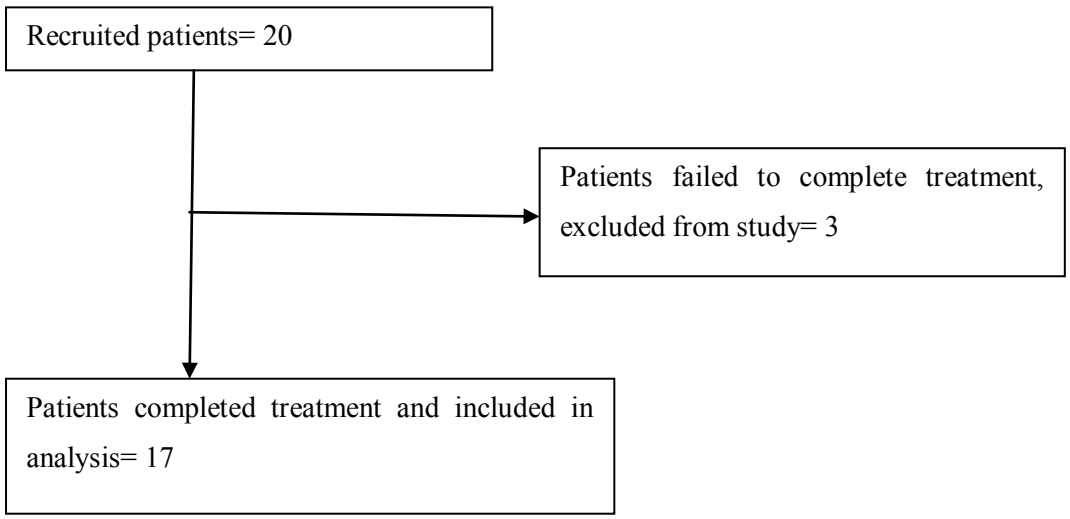


Table 7. Baseline characteristics of the patients

Total number of patients	17
Age/ years	61 (24.5)*
Gender	15 female
Duration of symptoms/ years	7 (6)*
Type of FI	Mixed 9 Urge 2 Passive 4
Vaginal deliveries	2 (1)*
Ankle circumference/ cm	23 (2.5)*
Body mass index/ kg/m^2	27 (5)*
Anal sphincter defect	5 *(External anal sphincter defect 2)* *(Internal anal sphincter defect 2)* *(Combined sphincter defect 1)*
Previous anorectal surgery	3 anterior sphincteroplasties 1 Delorme's procedure

Table 8. Bowel diary data, St Mark's FI score and visual analogue score results

	Baseline	Six weeks	p value
FI episodes / week	6 (8.25)	2 (7.25)	**0.029**
Defecations/ week	12 (7.75)	14 (8.25)	0.30
Deferral time/ minutes	3 (4)	5 (8)	**0.027**
St Mark's Score	20 (5)	19 (4.5)	0.23
Visual analogue bowel satisfaction scale	10 (25	20 (52.5)	**0.018**

Table 9. Rockwood Faecal Incontinence Quality of Life Score

Domain	Baseline	End of treatment	p-value
Lifestyle	2.1 (0.6)	2.5 (1.6)	**0.01**
Coping/ Behaviour	1.3 (0.55)	1.5 (0.55)	0.07
Depression/ Self-perception	21. (1.25)	2.4 (0.8)	0.47
Embarrassment	1.3 (1)	1.7 (0.7)	0.19

Table 10. SF-36 Quality of Life Scores

Domain	Baseline	End of treatment	p-value
Physical functioning	46.7 (18.8)	46.7 (12.5)	0.59
Role physical	35 (28.2)	35 (28.2)	0.76
Bodily pain	41.8 (22.5)	51.6 (25.2)	0.17
General health	41.5 (15.7)	46.2 (14.9)	**0.04**
Vitality	44.3 (17.8)	44.3 (14.2)	0.52
Social functioning	40.9 (32.5)	51.7 (27.1)	0.78
Role emotional	23.7 (31.6)	44.8 (31.36)	0.44
Mental health	43.6 (23.9)	45.9 (20.5)	0.61
Total physical score	0 (.7 (16.3)	47.6 (13.3)	0.15
Total mental score	43.2 (30.4)	44.9 (21.3)	0.88

Data expressed as median (interquartile range)

Table 11. Univariate analysis for percentage reduction in incontinent episodes per week

Variable	Category	Coefficient (95% CI) •	P-value
PTNS regimen	Unilateral	0	0.40
	Bilateral	14 (-19, 48)	
Gender	Female	0	0.81
	Male	6 (-46, 59)	
Type of faecal incontinence	Urge	0	0.69
	Passive	-6 (-53, 41)	
	Mixed	11 (-28, 49)	
Duration of symptoms	≤ 4 years	0	0.42
	4.1 - 8 years	25 (-15, 65)	
	> 8 years	8 (-33, 50)	
Body mass index kg/m^2 *	-	1 (-19, 21)	0.93
Ankle circumference cm	-	4 (-2, 11)	0.20
External anal sphincter defect	No	0	0.07
	Yes	-32 (-67, 3)	
Internal anal sphincter defect	No	0	0.07
	Yes	-32 (-67, 3)	
Age/ years **	-	5 (-7, 16)	0.42
Anal resting pressure cmH_2O **	-	-3 (-10, 5)	0.44
Peak voluntary squeeze pressure increment cmH_2O **	-	2 (-3, 6)	0.45
Five second squeeze increment cmH_2O **	-	2 (-5, 9)	0.54
Peak involuntary squeeze pressure increment cmH_2O **	-	0 (-5, 5)	0.97

* Regression coefficients given for a 5-unit increase in explanatory variable

** Regression coefficients given for a 10-unit increase in explanatory variable

• The figures reported are the regression coefficients, along with corresponding confidence intervals. For the variables measured on a categorical scale these represent the change in percentage reduction between each category and a baseline category. For variables measured on a continuous scale, these represent the change in percentage reduction for a one-unit increase in each variable (changes are reported for different unit increases where one-unit is a small amount).

Table 12. Univariate analysis of the ability to defer defecation

Variable	Category	Coefficient (95% CI)	P-value
PTNS type	Unilateral	0	0.33
	Bilateral	1.0 (-1.0, 2.9)	
Gender	Female	0	0.43
	Male	1.2 (-1.9, 4.3)	
Type of FI	Urge	0	0.81
	Passive	0.5 (-2.7, 3.6)	
	Mixed	-0.4 (-2.7, 2.0)	
Duration of symptoms	≤ 4 years	0	0.60
	4.1 - 8 years	0.9 (-2.5, 2.3)	
	> 8 years	-0.1 (-1.6, 3.6)	
Body mass index kg/m^2 (*)	-	0.0 (-1.1, 1.2)	0.94
Ankle circumference cm	-	0.3 (-0.2, 0.7)	0.21
External anal sphincter defect	No	0	0.74
	Yes	-0.4 (-2.6, 1.9)	
Internal anal sphincter defect	No	0	0.35
	Yes	-1.0 (-3.3, 1.2)	
Age/ years (**)	-	0.1 (-0.6, 0.8)	0.79
Resting pressure cmH_2O(**)	-	0.0 (-0.4, 0.5)	0.93
Voluntary squeeze pressure increment cmH_2O(**)	-	0.2 (-0.1, 0.5)	0.05
Endurance squeeze increment cmH_2O(**)	-	-0.1 (-0.5, 0.3)	0.72
Involuntary squeeze increment cmH_2O (**)	-	0.3 (0.0, 0.6)	0.04

(*) Regression coefficients given for a 5-unit increase in explanatory variable

(**) Regression coefficients given for a 10-unit increase in explanatory variable

The figures reported are the regression coefficients, along with corresponding confidence intervals. For the variables measured on a categorical scale these represent the change in deferral time between each category and a baseline category. For variables measured on a continuous scale, these represent the change in deferral time for a one-unit increase in each variable (changes are reported for different unit increases where one-unit is a small amount).

Chapter 9

Conclusions

The published evidence in support neuromodulation for faecal incontinence and constipation is generally poor. Few studies have attempted to control for placebo or compare sacral nerve stimulation (SNS) directly to another treatment. Most are single group series, often retrospective. Many have taken a greater than 50% improvement in symptoms to indicate a clinically successful outcome. This is too simplistic. It does not account for the wide variance seen often for each symptom. Nor does it reflect the impact on quality of life, which will vary from patient to patient. When analysed on an intention to treat basis, around 50% may achieve a significant improvement in symptoms. This means that a significant proportion of patients will not benefit.

The mechanism of action of these treatments is uncertain. There is no evidence to support efferent motor stimulation. It is likely that modulation of afferent sensory pathways and the subsequent effect on gut motility and the sensory cortex are responsible. The mechanism of action needs to be determined before any significant improvement in efficacy may be achieved. Such improvements may concentrate on improved patient selection, site of peripheral stimulation and stimulation technique.

Adjustment of the pulse width and frequency appeared to have no real effect on the efficacy of SNS for constipation. This may reflect the limited improvement achieved by SNS, and complexity of symptoms which are usually seen.

Transcutaneous stimulation of the sacrum (tSNS) appears to be effective in the short term. It is cheaper and less invasive than SNS. It does not appear to have precisely the same mechanism of action as SNS. Although promising, the technique must be investigated further. The effect of placebo should be addressed. The outcome of tSNS over the longer term should be measured in a larger cohort of patients. tSNS should be compared to alternative forms of neuromodulation, such as SNS or PTNS.

Transcutaneous posterior tibial nerve stimulation (PTNS) is also a promising treatment. Like tSNS, it is cheap and non-invasive. It can also be self administered at home. It is likely that its optimal form of administration is as bilateral stimulation during an intensive initial treatment regimen. It is unclear if it is effective in the longer term, or how it compares with other treatments. It may find a role in patients who are unwilling or too unfit for SNS.

Pudendal nerve stimulation (PNS) is likely to be ineffective for patients who have failed SNS, but a larger study may be needed to confirm this. Given the technical difficulties associated with placement

of the electrode and its relative poor efficacy, PNS is unlikely to replace SNS. Its only possible role would be as a second line treatment for those who have an SNS battery *in situ*. Its failure to work also raises questions about whether patients who have failed to respond to one form of neuromodulation may benefit from another.

Future research

A review of the literature in support of neuromodulation for faecal incontinence and constipation suggests that future research should follow certain broad approaches. These include the comparison with other treatments, the optimisation of treatment regimens, optimisation of different stimulation techniques and determination of the mechanism of action.

It is unclear whether the alteration of stimulation parameters such as pulse width and frequency will have any significant effect on the outcome of sacral nerve stimulation for constipation, but given the mixed results which are often seen, it possible that a different conclusion might be reached with more patients. It would be interesting to assess the response of patients who have experienced each different setting. A difference between baseline and follow up despite using the same stimulation parameters may suggest a strong placebo effect.

Unilateral posterior tibial nerve stimulation appears to have only limited clinical effect, as reported in this thesis. Leroi and colleagues [123] have suggested that it is little better than placebo. Despite this, transcutaneous stimulation of the tibial nerve is still an attractive prospect. It is cheap and non-invasive and can be used by the patient at home. It may be that bilateral is more effective than unilateral stimulation, but this is unproven and requires further investigation. A large randomised study to compare these two techniques is needed. Its effect in the longer term should also be investigated. Thought should be given to the study of tibial nerve stimulation carried out at a more proximal level. The nerve would be of a greater diameter due to the larger number of sensory and motor fibres. Stimulation at this point might be more effective, assuming that neuromodulation works through ascending sensory nerve fibres. The tibial nerve is positioned superficially in the popliteal fossa and this might be a suitable place for applying stimulation using pad electrodes.

Transcutaneous stimulation of the sacrum (tSNS) has shown some promise. Like transcutaneous tibial stimulation, it offers a cheap, non-invasive treatment which may be self-administered. It needs, however, to be evaluated in a larger group of patients over a longer period of time since at the moment it is unclear how it compares to placebo.

The devices used in this thesis are clearly unsuitable for long term application. The technical development of smaller, less intrusive, devices is needed for delivering chronic stimulation. The mechanism of action of tSNS is uncertain. It is likely to affect sensory pathways, perhaps in a way similar to sacral nerve stimulation. It may therefore be of interest to assess the effect of tSNS on the sensory cortex of the brain.

Pudendal nerve stimulation is ineffective for patients who have failed to respond to sacral nerve stimulation. Its efficacy is uncertain in patients who are neuromodulation naïve. This may merit further investigation. Unless significant superiority is shown, the technical difficulty associated with performing pudendal nerve stimulation will mean that it is unlikely to compete with sacral nerve stimulation,

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