Title Page

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Internal Anal Sphincter: clinical perspective

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Structured Abstract

Objective: To summarise current knowledge of Internal anal sphincter. Background: The internal anal sphincter (IAS) is the involuntary ring of smooth muscle in the anal canal and is the major contributor to the resting pressure in the anus. Structural injury or functional weakness of the muscle results in passive incontinence of faeces and flatus. With advent of new assessment and treatment modalities IAS has become an important topic for surgeons. This review was undertaken to summarise our current knowledge of internal anal sphincter and highlight the areas that need further development. Method: The PubMed database was used to identify relevant studies relating to internal anal sphincter. Results: The available evidence has been summarized and advantages and limitations highlighted for the different diagnostic and therapeutic techniques. Conclusion: Our understanding of the physiology and pharmacology of IAS has increased greatly in the last three decades. Additionally, there has been a rise in diagnostic and therapeutic techniques specifically targeting the IAS. Although these are promising, future research is required before these can be incorporated into the management algorithm.

Keywords

Internal anal sphincter, Anal sphincter, Internal sphincter, IAS
**Introduction**

Faecal incontinence is a debilitating condition which is often under-reported. Although it is difficult to accurately determine the incidence of faecal incontinence due to underreporting, a range of 2-24%, depending on the population studied, has been reported \(^1\). Despite a disagreement about prevalence rates of FI, there is a widespread acceptance of its increased prevalence in the older population \(^1\).

Maintenance of continence is a complex process requiring interplay between colon, rectum, the internal and external anal sphincter complex, pelvic floor and inter-related motor and sensory neural pathways, all governed by higher centres. Out of many factors controlling the continence, the anal canal, being the final determining step, with its sphincter complex is undoubtedly critical.

The anal canal is composed of two adjacent muscles – external and internal anal sphincter. This review will focus on the characteristics, pathology and therapeutic potential of the smooth muscle internal anal sphincter (IAS).

**Anatomy**

The internal anal sphincter is a ring of smooth muscle formed by the continuation of the involuntary circular muscle of rectum into the distal anal canal (Fig. 1). As such it is not under voluntary control. Caudally the IAS extends just proximal to the lowest part of the external anal sphincter (EAS) \(^2\). It is about 2.5 cm long and 2-5 mm thick in size. It increases in thickness with advancing age, a phenomenon more pronounced in females after the age
of forty to fifty \textsuperscript{3}. Histological studies have shown this rise in bulk to be due to an increase in the amount of connective tissue \textsuperscript{4}, a finding which correlates well with the manometry findings of decreased resting pressure with ageing.

Another factor that affects IAS thickness is female sex in whom the IAS has been found to be thicker in comparison to males \textsuperscript{3}. No correlation has been found between IAS size and body weight or parity \textsuperscript{5}.

[Insert Figure 1]

**Physiology**

**a. Innervation of IAS**

The IAS is dually innervated by the autonomic and the enteric nervous system. The parasympathetic and sympathetic nervous systems are responsible for exerting both excitatory and inhibitory influences on the smooth muscle whereas the enteric system influences the tone \textsuperscript{6}. Despite all these

In general, IAS is believed to be parasympathetically innervated by the first, second and third sacral nerves via pelvic plexus and sympathetically from both the thoracolumbar outflow and the hypogastric nerves \textsuperscript{7}.

The enteric nervous system is organised into an interconnected network of neurons and glial cells that are grouped into ganglia located in two major plexuses: the myenteric (Auerbach's) plexus and the submucosal (Meissner's) plexus. Its components form entire reflex pathways that control peristaltic contractions independent of extrinsic innervation from the autonomic nervous system.
b. Effects of parasympathetic innervation on IAS

The parasympathetic fibres have been shown to have an inhibitory effect on the tone of IAS thereby causing its relaxation. *In vitro* studies such as those by Burleigh *et al.* and O’Kelly *et al.* helped explain the effects of muscarinic receptors stimulation. The former study revealed that stimulation of muscarinic receptor by acetylcholine leads to relaxation of IAS\(^8\) and the latter demonstrated that muscarinic receptor stimulation is mediated indirectly via nitric oxide (NO) release\(^9\). The property of IAS relaxation, on stimulation of muscarinic receptors via acetylcholine, led to a trial of botulinum toxin, which acts on cholinergic neurones, for treating anal fissures.

c. Effects of sympathetic innervation on IAS

The effects of sympathetic system are known to be mediated via the alpha and beta adrenoceptors, both of which are present on the IAS. Depending upon which adrenoceptor subtype is stimulated, the sympathetic innervation exerts excitatory or inhibitory influence on the IAS.

Stimulation of alpha-adrenoceptors is known to have an excitatory effect on the smooth muscles of IAS\(^10\). Of the two known subtypes, \(\alpha_1\) and \(\alpha_2\), the former has been shown to cause IAS contraction without affecting the rectoanal inhibitory reflex (RAIR) induced IAS relaxation whereas the latter inhibits RAIR-induced IAS relaxation but does not increase the IAS contractility\(^11\). This IAS contraction inducing property of \(\alpha_1\) adrenoceptors has been clinically used in the form of phenylephrine and methoxamine,
both being potent α1 adrenoceptor agonist, to treat FI. However, trials for both the drugs failed to demonstrate any significant clinical improvement in patients with FI.

Beta-adrenoceptors, have been shown to mediate the inhibitory effects of sympathetic nerve stimulation in the IAS and other parts of the GI tract. In IAS, presence of all the three subtypes of β adrenoceptors (β1, β2 and β3) was established by a recent study, which found varying level of inhibitory effect was exerted on the IAS by each of the three receptor subtypes. β1-agonists were found to be the most superior inhibitors of IAS as compared to β2 or β3- agonists, producing about 70% IAS relaxation vs 40% and 30% by β2 and β3-agonists respectively. However, achieving selective gastrointestinal β1 or β2 adrenoceptor modulation alone without the associated cardiovascular effects is not possible thereby limiting the role of these pharmacological agents in gastrointestinal disorders. β3 adrenoceptor subtype, which received recognition only in the last two decades has led to a new interest in studying its use as potential adrenergic modulation site that can be used in the gastrointestinal motility disorders. Although it showed promising results in animal studies, producing up to 90% relaxation in rat IAS, it has been found to have only a limited capacity to relax human IAS (30%)\(^{12}\). Further studies are warranted before any conclusions can be made on the use of β3 adrenoceptor in GI disorders.

d. Effects of enteric innervation on IAS

The enteric nervous system (ENS) exerts its influence upon the IAS through the interplay of several neurotransmitters. These neurotransmitters cause relaxation of the IAS during defecation. Relaxation of IAS has been shown to occur in response to rectal distension (RAIR) and to electrical field stimulation in organ bath studies. Studies confirmed that the
relaxation response remained unaffected by muscarinic receptor and β-adrenoceptor antagonists but was blocked by tetrodotoxin, thereby confirming its non-adrenergic and non-cholinergic (NANC) origin.

A number of neurotransmitters have been identified over the years exerting an inhibitory (Nitrous Oxide (NO), Adenosine triphosphate (ATP), Vasoactive Intestinal Peptide (VIP), Carbon Monoxide (CO), ANF and Calcitonin gene-related peptide (CGRP)) and excitatory (Dopamine, Angiotensin II, Substance P, bombesin and Neuropeptide Y (NPY)) influence on the IAS. Of these NO appears to be the principal neurotransmitter mediating relaxation in the IAS. This generated an interest in researching exogenous sources of nitrates which when degraded by cellular mechanism release nitric oxide. One such Nitric oxide donor is nitro-glycerin ointment which has become a popular first choice in managing anal fissures.

e. Inherent myogenic tone

The majority of basal tone in the IAS is myogenic in nature owing to the specialized properties of the smooth muscle cells in the IAS. This myogenic nature of IAS was first reported by an in vivo study done by Frenckner et al. in 1976. They found that anal canal had a residual pressure despite maximal relaxation of IAS induced by rectal distension in patients who underwent either bilateral pudendal nerve block (thereby paralysing the striated sphincter muscles), low spinal anaesthesia (depriving IAS of its parasympathetic supply) or high spinal anaesthesia (depriving IAS of its sympathetic supply)

Culver et al found no change in the peak anal pressure in their study on opossum despite abolishing external sphincter activity with pancuronium bromide and using phentolamine.
(alpha adrenergic antagonist) to abolish the tonic adrenergic activity of IAS. Furthermore, the use of tetrodotoxin, obliterating the tonic neural activity, did not modify the anal canal pressure $^{18}$. These results led them to conclude that the basal tone is IAS is primarily myogenic.

*In vitro* study of porcine IAS by Cook *et al.* revealed that this myogenic tone and spontaneous activity depends on extracellular calcium and flux across the cell membrane. The IAS strips prepared for organ bath study lost the tone and spontaneous activity when placed in calcium-free solution. Moreover, the addition of nifedipine which is an antagonist of L-type calcium channel (main subgroup of Ca channel in smooth muscle cells), also leads to abolished tone in IAS $^{19}$. The calcium channel blockers (CCB) such as diltiazem have been used in an attempt to modulate IAS tone based upon the above characteristics in the patients with the anal fissure and have been reported to have similar efficacy as GTN.

There has been an upsurge in research to understand the molecular mechanisms underlying the basal IAS tone. Several studies have shown activation of Rho kinase (ROCK) by GTP-RhoA to play a significant role in maintaining this basal myogenic IAS tone $^{20, 21}$. IAS relaxation demonstrated in studies as a result of ROCK inhibition $^{22}$ makes it an exciting new therapeutic agent to treat hypertensive IAS disorders such as Hirschsprung’s disease, haemorrhoids and anal fissures.

**Pathology**

The IAS is reported to contribute between 50-85% of the resting anal tone, the remainder being from the vascular anal cushions and the EAS $^{23}$, illustrating IAS’s crucial role in maintaining continence. The IAS disease spectrum comprises of symptoms due to alteration
in pressure and as such can be divided into two sub groups, i.e. low-pressure group and high-pressure group.

1. Low pressure

The low pressure most often results in varying degree of incontinence to different rectal components, i.e. solid stool, liquid/semi-formed stool, gas. The common causes of low pressure are mentioned in Table 1.

a. Obstetric injury

Obstetric anal sphincter injuries during childbirth have long been recognised as a leading cause of faecal incontinence. About 13 - 25% of women report some form of anal incontinence three to six month after vaginal or caesarean delivery \(^{24,25}\) with the prevalence falling to 1 - 6% by 12 months \(^{26,27}\). Patients can suffer a range of symptoms including flatus incontinence, passive soiling, or frank incontinence of stools. Many women also experience faecal urgency which can be quite distressing. The advent of endoanal ultrasound (EAUS) in the late 1980s proved to be a key factor in recognising the obstetric injuries. Studies have reported an increase in detection rates of sphincteric injuries with the use of post-partum EAUS \(^{28,29}\).

The rate of anal sphincter disruption in primiparous women has been reported to be as high as 27 to 35 % and between 4 - 8.5% in multiparous women \(^{30}\). The risk factors include the use of forceps, prolonged second stage of labour, high birth weight and occipito-posterior presentation. The Royal College of Obstetricians and Gynaecologists classify the obstetric sphincter injury from first to the fourth degree with an increasing severity upon moving up
Involvement of IAS occurs in grade 3c (both EAS and IAS torn) and 4 (injury involving EAS, IAS and the anal epithelium).

[Insert Figure 2]

The association of anal sphincter injury and FI has been demonstrated in several studies. In a large study of 500 patients, Mahony et al. found a significant association between IAS injury during childbirth and faecal incontinence and recommended that the presence of an IAS defect should be sought carefully in cases of obstetric anal sphincter injury. Another study showed the fourth-degree tears and the episiotomy to be associated with persistent IAS defect on an ultrasound done 6-12 months postpartum despite repair of the anal sphincter lacerations at the time of delivery.

There is little doubt that obstetric sphincter injuries can have a disastrous effect on patient’s quality of life. A combination of early recognition of these injuries, provision of supportive treatment and the decision about mode of future pregnancies tends to reduce the disease burden.

b. Anorectal Surgery

Anorectal surgical procedures such as haemorrhoidectomy, anal dilatation, fistula surgery, low anterior resection can cause structural and functional damage to the sphincter complex. Evolution of surgical practice has led to a reduction of iatrogenic injury. With increased awareness of sphincter damage, certain procedures are no longer done (Lord’s dilatation) and others are done more cautiously (limited lateral sphincterotomy, haemorrhoidectomy).
**Haemorrhoidectomy**

Different surgical techniques used for haemorrhoidectomy have been shown to cause varying degree of damage to the IAS \textsuperscript{32}. The most recent technique of transanal haemorrhoidal dearterialization (THD) has shown some promising results without affecting the continence but further clinical trials are needed to evaluate its results in the long term. \textsuperscript{33}

**Anal dilatation**

Anal dilatation, used to treat haemorrhoids and anal fissure in the past fell out of favour due to the reports of extensive IAS damage seen on EAUS in two separate studies \textsuperscript{34,35}.

c. **Rectal Prolapse**

Aetiopathogenesis of faecal incontinence in rectal prolapse is multifactorial and poorly understood. However, IAS dysfunction is known to be one of the definitive causal factors of incontinence in this group. In cases of external prolapse, a reduction in both resting and squeeze pressures leading to incontinence has been postulated due to several factors including internal sphincter dilatation, rectal prolapse waves and intermittent activation of the recto-anal inhibitory reflex (RAIR), nerve damage from stretching due to perineal descent, and reduction of the rectal reservoir \textsuperscript{36}.

In contrast, incontinence in the internal prolapse has been speculated to be due to attenuation of the RAIR mechanism. Another possible cause is a reduction in IAS tone as shown in a recent study of 515 patients which found an inverse relationship between resting pressure and the grade of internal prolapse without an effect on squeeze pressure \textsuperscript{37}.
d. Anal penetration

Anal penetration is another factor reported to cause damage to the anal sphincters. A study comparing 40 anoreceptive to 18 non-anoreceptive males by Miles et al. concluded that anal intercourse (AI) was associated with reduced anal canal resting pressure and an increased risk of minor faecal incontinence. Chun et al. demonstrated the same results in their study on 28 males engaging in AI. On further examination with EAUS, they reported thinner anal sphincters in anoreceptive group, albeit not statistically significant, but no disruption of the IAS or EAS was seen. There were no complaints of faecal incontinence by the study subjects.

In contrast to passive AI, unwanted anal penetration was found to be associated with structural internal anal sphincter damage in all the 7 patients who were studied by Engel et al.

e. IAS degeneration

This was first described by a study conducted at St Marks Hospital in which Vaizey et al. identified a manometric and sonographic abnormality in EAUS of 38 patients who had a history of isolated passive soiling. All of the 38 patients had a functionally and structurally normal external anal sphincter along with normal pudendal nerve terminal motor latencies. They were found to have low resting anal pressure in addition to an abnormally thin and poorly defined internal sphincter.
f. Scleroderma

Scleroderma, an autoimmune connective tissue disease affecting blood vessels and collagen production, is reported to have anorectal involvement in 50–70% of patients. Several studies have found low resting anal pressure in these patients, attributing it to the involvement of IAS. With the development of better anorectal imaging modalities, such as EAUS and Endoanal MRI, the research interest moved from measuring physiological parameters towards detecting the morphological involvement of IAS in these patients. Engel et al. were the first to report the IAS atrophy in scleroderma patients followed by other studies confirming the same.

A study from our centre compared scleroderma patients with and without anorectal symptoms. Although one would have expected to see morphological differences in IAS in these two patient subgroups, the study demonstrated that all these patients had thinned and atrophic IAS (on EAUS) without any significant difference in the atrophy scores or IAS thickness between them. The result from this study points towards other possible factors such as functional changes in the sphincter which might be responsible for FI in these patients. This has already been shown to be the case in the oesophageal involvement. The effects of scleroderma on IAS biomechanics remain unexplored and the new technology using impedance planimetry, EndoFLIP, might be able to provide some new information.

g. Radiation toxicity

Electro-magnetic radiation has long been recognised as causing bowel dysfunction. Most of the early studies attributed this to decreased reservoir capacity and compliance of rectum in addition to nervous degeneration. Varma et al. were the first to show a significant reduction in resting pressure and physiological sphincter length in patients following
radiotherapy, thereby suggesting IAS dysfunction \(^{45}\). Since then several other studies reported an increase in FI symptoms and a reduced RP in irradiated patients as compared to patients treated with surgery alone. An association between radiation dose and anorectal dysfunction was reported by Kusunoki et al. who noted patients receiving a high-dose (80 Gy) had lower RPs as compared to those receiving low-dose (30 Gy) or no radiation. De Silva et al. were the first to provide a direct histological evidence of increased collagen deposition and hypertrophy of the myenteric plexus in irradiated IAS \(^{46}\). Lorenzi et al. recently published the first study providing a physiological basis for chemo-radiotherapy (CRT) induced impairment of IAS function in patients treated for rectal cancer. In their organ bath studies, using human IAS, they established that pelvic irradiation not only damaged the intrinsic nerves but also affected the muscular component of the IAS \(^{47}\).

2. High pressure

Low pressure in the anal canal due to the above mentioned pathological disorders usually leads to FI. At the other end of the spectrum are anorectal disorders which are characterised by an abnormally high pressure generated by IAS.

a. Anal Fissure

Anal fissure has long been postulated to be a result of elevated RP in anal canal which eventually leads to ischaemia of the anal lining. Many studies have demonstrated the increase in maximal resting pressure above 90 mmHg to be associated with anal fissure \(^{48}\). Moreover, the gold standard treatment of lateral internal sphincterotomy has been proven to reduce the RP, on manometry, to allow for the healing, thereby providing further evidence for high RP to be the causal factor for anal fissure. The primary cause of high
resting pressure in the first place still remains an enigma, although several theories exist about its increase being secondary to trauma from passing hard stools resulting in spasm, psychological stress and being idiopathic in nature.

**b. Internal sphincter achalasia**

Internal sphincter achalasia is a rarely diagnosed disease of IAS in which it does not relax fully to rectal distension. It presents in a similar way as Hirschprung’s disease with symptoms of constipation and gradual bloating. However, unlike in Hirschprung’s the rectal biopsy shows the ganglion to be present. The pathogenesis is thought to be multifactorial, including the absence of nitrergic innervations, defective innervation of the neuromuscular junction and altered distribution of interstitial cells of Cajal 49.

**Assessment**

The evaluation of patients with anorectal disorders should begin with a detailed clinical assessment. A thorough history helps the clinician gain an insight into the underlying aetiological factors and severity of the disease. A full physical examination including digital rectal examination provides useful information about the resting sphincter tone, integrity of puborectalis sling, anorectal angle and the strength of voluntary contraction 50. Further evaluation comprises assessing the structural and physiological integrity of the anal sphincter muscles as discussed below.

**1. Structural assessment**
The detection of a structural lesion has the highest impact in terms of identifying aetiology and potentially suggesting management options. Several modalities exist to detect morphological defects having their own advantages and limitations as outlined below.

a. Ultrasound

*Endoanal ultrasound (EAUS)*

Anal Endosonography was developed from urology, where the technique was used for transrectal imaging and puncturing of the prostate. The accuracy of EAUS for detecting anal sphincter defects has been demonstrated in several prospective studies that have compared US findings to the results of surgery (sphincteroplasty). In the largest study reported to date, US findings were prospectively compared with operative findings in 44 patients who underwent pelvic floor repair and the endorectal US was found to be 100% sensitive in detecting either IAS or EAS defects in this study population.

Although useful in the detection of internal sphincteric defects, it is limited by inherent poor contrast and does not accurately demonstrate external sphincter due to its echogenicity being frequently similar to that of ischioanal fat.

*Transvaginal ultrasound (TVUS)*

TVUS was developed by Sultan et al. in 1994 in order to obtain more accurate sphincter muscle measurements by avoiding distortion of epithelial structures and compression of sphincters due to the anal probe. They clearly visualized puborectalis, EAS, IAS, anal submucosa and anal cushions and concluded that TVUS allows for accurate imaging of anal sphincters and their defects. Further uses of TVUS for identifying pathologies such as rectal fistulae and perianal sepsis were established by studies from Alexander et al. and
Poen et al. Different authors have reported a varying level of accuracy of TVUS in evaluating the anal sphincters with some reporting it to be equivalent to EAUS while others report it to be inferior to EAUS, having a sensitivity of only 44% and specificity of 96% for detecting IAS defects.

Although the interpretation of TVUS requires more expertise it has a clear advantage of being cheaper than the endoanal probe and of eliminating distortion of anal epithelium. Its use has increased due to the clarity of the sphincter it offers, its ability to demonstrate important landmarks such as anorectal junction and puborectalis sling and the ease of converting it to transperineal approach to evaluate perianal sepsis.

**Transperineal ultrasound (TPUS)**

TPUS was developed in an attempt to improve patient acceptability by being less invasive. There are mixed reports about its utility with some finding it useful to evaluate IAS only while others found it equivalent to EAUS in seeing the whole of the anal canal.

Although having an advantage of being less painful and more acceptable, TPUS has been found to be inferior in comparison to TVUS and EAUS at detecting the incidence of occult anal sphincter damage. This figure is comparable for TVUS and EAUS at 29% whereas for TPUS it is just 7.9%.

**b. Elastography**

Elastography is a new imaging modality based on differences in radiofrequency signals following endogenous/exogenous compression due to different elastic properties of the targeted tissues or organs. In simple words, it is an ultrasound technique which can produce
images based on tissue stiffness. The elastography image usually comprises a red, green and blue colour corresponding to distensible, intermediate and rigid areas respectively in the targeted organ.

In the anorectal region, it identifies the IAS and EAS based on their different elastogram colour distributions. The IAS is seen as mostly red whereas EAS appears to be mostly blue. This is assumed to be due to the different type of musculature, the IAS being a smooth-muscle type possessing more elastic properties than the EAS.

Although current studies have failed to demonstrate any advantage of elastography as compared to conventional EAUS in the majority of the FI patients, one of its potential uses may lie in studying the anal sphincters post pelvic radiation to detect fibrotic changes not seen with the conventional EAUS.

c. **Endoanal MRI**

Endoanal MRI was developed in the early 90s and allows detailed visualization of normal anatomy and pathologic conditions of the anal sphincter. It has been described as the most accurate technique for identifying sphincteric lesions far superior to endoanal ultrasound owing to its multiplanar capability and higher inherent contrast resolution. IAS defects are identified as either IAS discontinuity or as replacement of normal smooth muscle by fibrous tissue with concomitant muscle thinning. It also allows for detection of thinning and atrophy of sphincters and correlates well to findings at the time of surgery and histology of
biopsy specimens. Despite its drawback of being more expensive, it has the potential of preventing unnecessary operations and as such be cost effective in the long run.

2. Physiological assessment

a. Anorectal manometry

Anorectal manometry (ARM) is considered to be the gold standard for defining sphincter function and is the most well established and commonly used technique for investigating anorectal function. A complete assessment of anorectal function involves evaluating the following parameters: (1) anal sphincter resting and squeeze pressures, (2) rectoanal inhibitory reflex, (3) rectal sensation, (4) changes in anal and rectal pressures during attempted defecation, (5) rectal compliance and (6) performance of a balloon expulsion test.

Of these, resting pressure and rectoanal inhibitory reflex are the direct evaluators of IAS function. Maximum resting anal canal tone is widely acknowledged to be a key reflection of IAS function. RAIR reflex, first described by Gowers in 1877, consists of relaxation of IAS in response to rectal distension. This transient relaxation of IAS is well accepted to play a crucial part in maintaining continence. Zbar et al. studied the different phases of RAIR reflex in detail and noted a rapid recovery of RAIR in incontinent patients. Kaur et al. reported significantly greater relaxation of IAS in an incontinent patient as compared to the constipated patients (P=0.001). They also reported consistently progressive increase in IAS relaxation with progressive rectoanal inhibitory reflex in the incontinent group but not in
the constipated patients or in healthy control subjects. Impairment of RAIR secondary to neuropathy in diabetic patients has been suggested in a study by Deen et al. Despite its widespread use, ARM has well-established limitations. One of the main caveats has been that despite decades of use there is still no standardized protocol for performing the test or interpreting its results. Also, there is no consensus regarding normative data presumably due to differences in the manometry probes and study population in addition to the aforementioned factors. Moreover, several authors have reported a lack of reproducibility and its inefficiency to provide precise measurement of anal canal pressures. Another drawback is ARM’s relatively mediocre reflection of anal sphincter function, as demonstrated by a significant overlap in anal canal pressures when comparing healthy individuals with those suffering from faecal incontinence.

b. High-resolution anorectal manometry (HRAM)

High-resolution manometry is a relatively new technique primarily used for physiological studies in the oesophagus where it was found to convey a diagnostic advantage over standard manometric techniques. Subsequently, this technique was adopted to study the physiology of anorectum where it provided an added advantage of simultaneously measuring circumferential pressures throughout the anal canal and rectum. Jones et al. reported a good correlation between ARM and HRAM measurements in their prospective study of 29 patients.

Further advances in the HRAM technique have resulted in 3D HRAM probe which combines the two functionalities of evaluating the physiology and anatomy at the same time. Although this technique has been shown to be reproducible it has failed to demonstrate the
sensitivity and specificity equivalent to EAUS. It was found to have a false negative rate of 14% and false positive rate of 41% in detecting the IAS defects. 63

Despite the fact that HRAM technology provides an improved manometric and topographic analysis, there is much work to be done before it helps unravel the complexities of the anorectal disorders.

c. Endolumenal Functional Lumen Imaging Probe (EndoFLIP)

EndoFLIP is the most contemporary technology investigating luminal physiology. As with HRAM, EndoFLIP was also initially designed to study the gastro-oesophageal junction and later extended to anorectal studies. It is based on the impedance planimetry technique which allows measurements of cross-sectional areas (CSA) in the alimentary tract.

The system comprises a recording unit and a luminal catheter having several electrodes situated in a balloon which gets infused by an electrically conductive fluid. Voltage measurements are made between pairs of electrodes to estimate the CSA at the midpoint between those electrodes.

This novel technique offers the ability to provide real-time images of the function of sphincter function during distension. The main difference between ARM and EndoFLIP is that while the former evaluates the anal canal on the basis of pressure generated in its closed state the latter helps determine the opening pressures of the anal canal or resistance to distension offered by the anal canal. It offers the potential of providing this new information on opening sphincter pressures which will be especially useful in evaluating patients with passive faecal incontinence. EndoFLIP has shown promising results by
outlining the geometric and biomechanical properties of anal canal \cite{64, 65} but needs further studies in order to be developed as a useful tool.

**Treatment options for low pressure**

The initial management starts with lifestyle modification, medications and coping strategies. Failing this, further treatment is chosen according to the cause of IAS dysfunction and can be classified into two main groups: Structural for morphologically damaged IAS and Physiological for morphologically intact but functionally weak IAS.

1. **Initial Management**

   a. **Lifestyle modification**

   This is considered to be the first step in managing FI and starts with the dietary advice in order to promote an ideal stool consistency and predictable bowel movements. In addition, patients should also be encouraged to develop good bowel habits including adopting good toilet posture, avoid straining and emptying bowels after a meal to utilise the gastrocolic response.

   b. **Medications**

   Anti-diarrhoeal medications such as loperamide can be offered to patients with FI once other causes of diarrhoea (such as bowel cancer, laxative abuse etc) have been excluded. Patients who cannot tolerate loperamide can be offered codeine phosphate or co-phenotrope.
c. Coping Strategies

NICE guidelines recommend that patients should be made aware of coping strategies as a part of their initial management. This includes providing information about continence products such as disposable pads, anal plugs, odour control products and disposable gloves. Patients should also be provided information about where to get emotional and psychological support in the form of counselling or psychological therapy where appropriate.

2. Structural management

a. Surgical repair

Direct surgical repair of IAS has been attempted in past but failed to achieve a successful outcome. The small size of IAS makes it difficult for sutures to hold and makes it difficult to achieve satisfactory healing. Two studies looking at patients post repair did not find a significant improvement in postoperative manometric findings. Moreover, sonography revealed a persistent defect in few patients despite repair and the patients failed to achieve full continence. One case series looked at 15 patients who underwent island anoplasty, which involved filling the IAS defect with skin and subcutaneous fat. It reported an improvement in continence score at a median follow-up of 34 months but at the cost of high rate of wound infection (23%).
b. Augmentation techniques

After successful use of bulking agents by urologists to improve bladder neck closure, these were introduced in the treatment of FI due to IAS dysfunction. Although their mechanism of action remains unclear it has been postulated that these agents work due to the mechanical effect of filling a defect or by raising anal cushions thereby causing closure of anal canal. Several studies have been done using various injectable agents. A summary of these studies is presented in Table 2.

Although this technique has demonstrated varying levels of success, apart from few randomised controlled trials of the newer agents like Solesta, Bulkamid and Permacol, most of the evidence base consists of a limited number of case series. A Cochrane review on injectable bulking agents concluded that the number of trials in this field was limited and most of the studies had methodological weaknesses. Moreover, there is a substantial variation in terms of the procedure itself, for instance, use of ultrasound, volume of bulking agent used, number of sites injected etc. Another limitation of note is that there is no long-term follow-up data thereby making it difficult to predict the long-term effectiveness of this procedure.

c. Neosphincters

i. Graciloplasty

This involves perianal musculoplasty using the gracilis muscle which is mobilised from the upper thigh and fixed to the contralateral ischial tuberosity after encircling the anus completely. Application of low-frequency electrical stimulation to fast twitch type II muscle fibres of gracilis muscle transforms them to slow twitching type I fibres which are not easily fatigued, thereby resulting in improved outcomes. The effectiveness of dynamic
graciloplasty in restoring continence has been shown to range between 60 to 80% at follow-ups ranging from 1 to 5 years\textsuperscript{71-73}. The main critique of this approach is its complexity, relatively high rates of complications and surgical revisions associated with it which have been reported as high as 74 and 40\% respectively\textsuperscript{74, 75}. Apart from this, functional failure due to continuing incontinence or anal retention renders this technique less appealing. For these reasons, graciloplasty is infrequently performed at this time\textsuperscript{76}.

ii. Artificial anal sphincters

An artificial anal sphincter specifically designed for managing FI was introduced in 1996 and since then has gained considerable interest around the world. A recent meta-analysis looking at 541 patients, implanted with an artificial anal sphincter, across 21 studies reported an improvement in incontinence rate ranging between 50 \textendash 65\% in addition to a substantial increase in the resting pressure. Another significant improvement was in QOL score, which was observed across all the studies. Table 3 presents the detailed outcome of studies included in the meta-analysis\textsuperscript{77}.

Despite the encouraging results, only a relatively small number of these devices are implanted each year owing to the associated complications and poor long-term results. Surgical revision is common with revision rates increasing with time and reaching above 90\% by 5\textsuperscript{th} year\textsuperscript{77}. An interesting finding was despite an increase in the rate of surgical revision and decrease in the continence with time, the QOL of patients remained high. The commonest causes for revision were device malfunction (36\%), erosion (29\%) and infection
(28%). Evacuatory difficulty was noted to be one of the significant problems amongst studies and it was suggested that there should be a preoperative assessment for outlet obstruction in addition to liberal use of laxatives or enemas postoperatively if required.  

iii. Magnetic band

Magnetic anal sphincter consists of series of magnetic beads interlinked with titanium wire which once implanted, stay closed, preventing episodes of incontinence. When the patient gets an urge to defecate they simply push in a normal defecatory manner and the force generated separates the beads allowing the stool to be evacuated.

A limited amount of studies that exist demonstrate a significant reduction in incontinence score and an improvement in the quality of life. A study comparing it to artificial bowel sphincter found it equally effective in short term. The reported complications include infection, anal pain, rectal bleeding and device separation. This technique still requires further evaluation to determine its long-term effectiveness and understand, in particular, whether fibrosis develops around the implant thereby limiting its effectiveness.

d. Myoblasts

Frudinger et al. have demonstrated that autologous mesenchyme derived myoblasts can be injected into the EAS of 10 female patients whose anal sphincters had been disrupted by obstetric trauma. Short term data has shown an encouraging significant reduction (p<0.001) in Wexner incontinence score, pre and post treatment. Long-term follow-up of this cohort is awaited.
e. Smooth muscle cells

Bioengineered human IAS reconstructs have been successfully developed from human IAS smooth muscle cells. Rattan et al. were able to develop IAS reconstructs which demonstrated a much higher basal tone than seen in previous similar studies. Although the basal tone of these constructs was $1/20^{th}$ of an intact IAS the authors speculated that this might increase after grafting. The reconstructs were shown to respond to different agonists and antagonists in a manner similar to the intact IAS.\(^{80}\)

f. SECCA

First used in Mexico in 1999, this involves administering temperature controlled radiofrequency energy to the anal canal. There is no definite consensus on its mechanism of action but several hypotheses have been put forward including neuromodulation of afferent nerve fibres, collagen deposition, fibrosis and modulation of interstitial Cajal cell function.\(^{81}\)

A review looking at 10 studies of 220 patients concluded that SECCA improved continence for at least 6 months. Moreover, this improvement was sustained in the 39 patients that were followed up for 5 years. The complications included mucosal ulceration, minor rectal bleeding and anal pain all of which were self-limiting.\(^{81}\)

The main advantage of this technique is its minimally invasive nature and relatively low morbidity as compared to injectable bulking agent or SNS. Although it has shown good outcomes in the short-term, larger studies with long-term follow-ups are required to identify the suitable subgroup of patients who will benefit from this technique.
3. Physiological management

a. Biofeedback

Described originally as an “operant conditioning therapy” by Engel et al. in 1974, biofeedback has become an important tool in the management of faecal incontinence. In its present state, it has been described as “complex combination of patient-therapist interaction, patient education and formal or informal advice on a range of related issues”\textsuperscript{82}. Different centres use varying techniques but the three main modalities are - rectal sensitivity training to enable the patient to detect small volumes of stool in order to prevent leakage, strength training to enhance squeeze strength and endurance and co-ordination training to teach the patient to squeeze external sphincter on activation of RAIR reflex. Although different studies have measured varying outcomes measures, the mean success rate has been reported as ranging from 40-100% in the treatment of FI \textsuperscript{83}.

b. Neuromodulation

**Sacral Nerve Stimulation (SNS)**

Sacral nerve stimulator involves surgical placement of an electrode, connected to a pulse generator, against one of the sacral nerve roots (usually S3). Several studies have demonstrated the efficacy of SNS in managing faecal incontinence, as a result of which it has been incorporated in the FI management algorithm.

The mechanism of action of sacral nerve stimulation is likely related to a range of physiological changes. It is hypothesised that stimulation of afferent fibres leads to altered anal and rectal sensation and modification of reflex pathways at the spinal cord level.
Improvement in rectal evacuation may also be a contributing factor, and reduced cortico-anal activity has also been described. With regard to the effect of SNS on IAS, there is no real consensus with few studies showing an increase in resting pressure and others reporting no effect on the IAS tone as shown in table 4. Despite this conundrum, the fact remains that SNS is effective in managing FI in patients with either functional or structural weakness of IAS or a combination of both.

A double-blind crossover study reported a reduction of passive soiling and a decrease in FI episodes in the patient with functionally poor IAS. Similar results were reported for patients with scleroderma, having functionally weak but morphologically intact IAS, who had a decrease in weekly episodes of incontinence with SNS use. SNS has also been reported beneficial in patients with structurally weak IAS. A study from St Mark’s reported a decrease in faecal incontinence episodes per week from a mean (SD) of 9.9 (10.9) to 1.0 (2.4) (p = 0.031), and decrease in soiling episodes per week from 6.1 (1.6) to 1.7 (2.4) (p = 0.031), with use of SNS for patients with IAS disruption.

**Percutaneous Tibial Nerve Stimulation (PTNS)**

Percutaneous Tibial Nerve Stimulation (PTNS) involves stimulating the afferent and efferent fibres of the tibial nerve via a fine gauge needle inserted percutaneously just above and medial to ankle. It obviates the need for a permanently implanted sacral nerve stimulator thereby reducing the associated costs and risk of morbidities associated with SNS device.

Mechanism of action of PTNS is not completely understood but an increase in internal sphincter tone has been postulated as one of them. This was confirmed in a study done by Arroyo et al. where they found a significant increase in the resting pressure of faecally
incontinent patients post PTNS as compared to baseline (51 ± 32 vs 40.9 ± 26.2, p<.001) \(^8\). Apart from improving IAS function, PTNS has been postulated to act by increasing the rectal compliance, inhibiting colorectal motility and also by interfering with the rectal sensory thresholds for defecation. Despite several case series suggesting improvement in FI with PTNS use, a recent RCT did not find a significant clinical benefit of using PTNS over sham electrical stimulation, thereby raising questions about its future use in managing faecal incontinence \(^8\).

**c. Topical therapy**

Several different topical ointments have been studied for the management of FI, phenylephrine being the commonest one. Although it led to an increase in maximum resting anal pressure, not all the studies were able to demonstrate an improvement in incontinence score. Another drug, methoxamine hydrochloride was found to increase the IAS contractions. However, phase II trial failed to demonstrate a significant improvement with different dosing regimens.

As evident from the trials, the search for an effective topical agent is ongoing and one can only hope that future studies will find an effective pharmacological agent.

**Treatment options for high pressure**

**a. Topical therapy**
Topical treatments commonly used to reduce resting anal pressure are Nitroglycerine (GTN) and Diltiazem. A Cochrane review found them to have a successful outcome in 50% cases of anal fissures and being associated with much less adverse effects as compared to surgical treatment. Another newer agent, sildenafil, which is a selective phosphodiesterase 5 (PDE5) inhibitor, has been shown to reduce the IAS tone during in-vivo and in-vitro studies (on human IAS). Tadalafil, another PDE5 inhibitor has also been reported as improving pain during defecation and healing of anal fissure in a small case series. These agents are not currently the part of mainstream treatment options and further trials are awaited to study their long-term effectiveness.

b. Injectable agents

Botulinum toxin, a neurotoxin leads to temporary chemical denervation of motor end plates. When injected into the IAS it results in a reduction of resting anal pressure and an increase in local blood flow thereby promoting healing. This is usually reserved for patients who have not responded to topical therapy. Although earlier studies showed good initial healing (up to 80% of patients) at 6 months later studies showed a fissure recurrence rate of 42% at 48 months follow-up. A recent meta-analysis concluded that botox is equivalent to GTN in efficacy.
A surgical procedure is usually reserved for the patient with chronic anal fissure which has failed to resolve with topical or injectable agents. The procedure of choice is lateral sphincterotomy (LS), which involves division of internal sphincter to reduce the resting anal pressure. It has been shown to have better outcomes than topical agents or botox injection. The main side-effects of LS are urgency, flatus incontinence and mild faecal soiling in early postoperative period. However, this immediate postoperative incontinence is rarely permanent and is usually mild.

**Future Challenges**

Although our knowledge of internal anal sphincter has vastly improved in the last three decades it is still not complete. There is a much better understanding of the physiological working of IAS with effects of sympathetic and parasympathetic innervation becoming clearly defined with the help of numerous studies in this field. However, studies looking at effects of enteric innervation on IAS have only begun in the last decade and still need further work to develop a complete understanding.

The advent of new diagnostic techniques has made it possible to appreciate the function of IAS better. EndoFLIP, in particular, is an exciting novel technology which can help provide the critically missing information in patients with passive soiling. Further studies are required to develop it as a useful diagnostic tool and also to prove its effectiveness. The aim is to treat physiologically phenotype faecally incontinent patients beyond just determining whether sphincters are disrupted or not.
As for treatments, this is an exciting period with the emergence of several promising treatment modalities. These data provide important insights into the role of RhoA/ROCK in the pathophysiology and therapeutic approaches in the rectoanal motility disorders especially affected with hypertensive IAS. However, they also need to be assessed for long-term outcomes before they can be integrated as a definitive part of the FI management algorithm.
References


Table 1: Causes of low resting anal pressure

<table>
<thead>
<tr>
<th>With structural defect</th>
<th>Without structural defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorectal surgery</td>
<td>IAS degeneration</td>
</tr>
<tr>
<td>Obstetric injury</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Rectal Intussusception and Prolapse</td>
<td>Radiation toxicity</td>
</tr>
<tr>
<td>Trauma due to anal penetration</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Studies</td>
<td>Type of study</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Dehli et al.¹</td>
<td>RCT</td>
</tr>
</tbody>
</table>
| Graf et al.²            | RCT           | 206 | NASHA Dx vs Sham                                                               | 12                  | >50% reduction in FI episodes for patients in NASHA Dx group as compared to sham group at 6 months 52% vs 31% (OR: 2.4; 95% CI, 1.2-4.5)  
Significant increase in mean number of incontinence-free days in NASHA Dx group vs. sham group at month 6 (3.1 vs. 1.7, respectively; P=0.0156) | Proctalgia (14%), fever (8%), and rectal hemorrhage (7%) |
<p>| Maeda et al.³           | RCT           | 10  | Bulkamid vs Permacol                                                          | 6                   | No sustained improvement seen beyond 6 weeks as measured by Patients’ clinical self-assessments, Anorectal physiological testing, Incontinence scores or Bowel diary scores | Not reported                                                                                                                                 |
| Siproudhis et al.⁴      | RCT           | 44  | Polydimethylsiloxane (PDMS) vs. saline                                         | 3                   | No significant difference in successful treatment in two groups (23% vs. 27%, respectively, P = 0.73)                                                                 | 18 AEs in PDMS group (including pain, anal inflammation or bleeding) vs. 4 in control group |
| Tjandra et al.⁵          | RCT           | 82  | PTP injection (silicone) with                                                 | 6                   | At 3 months Group A patients achieved &gt;50% improvement in | Minor discomfort at anal injection site                                                                                                                                                             |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratto et al. (^6)</td>
<td>Case series</td>
<td>10</td>
<td>Sphinkeeper™ prosthesis (previously known as Gatekeeper™ prosthesis)</td>
<td>Wexner’s continence score as compared to Group B (69% vs. 40%; (P = 0.014)). 93% of Group A and 92% of Group B had &gt;50% improvement in global quality of life scores (visual analog scale)</td>
</tr>
<tr>
<td>Ratto et al. (^7)</td>
<td>Case series</td>
<td>14</td>
<td>Gatekeeper™ prosthesis (polyacrylonitrile cylinder)</td>
<td>Significant decrease in FI episodes from 7.1 per week at baseline to 1.4, 1.0(3.2) and 0.4(0.6) per week respectively at 1-month, 3-month and last follow-up ((P = 0.002)). CCFIS improved significantly from 12.7(3.3) to 4.1(3.0), 3.9(2.6) and 5.1(3.0) respectively ((P &lt; 0.001)), and Vaizey score from 15.4(3.3) to 7.1(3.9), 4.7(3.0) and 6.9(5.0) respectively ((P = 0.010)).</td>
</tr>
<tr>
<td>Davis et al. (^8)</td>
<td>Case series</td>
<td>18</td>
<td>Carbon coated beads</td>
<td>No statistically significant difference up to 6 months. At 12 months, significant improvement noted in the continence grading ((P=0.003)) and patient satisfaction ((P=0.053)).</td>
</tr>
<tr>
<td>Malouf et al. (^9)</td>
<td>Case series</td>
<td>10</td>
<td>Ultrasound guided silicone injections</td>
<td>At 6 months 70% had no relief of symptoms. No significant change noted in anorectal manometry parameters</td>
</tr>
</tbody>
</table>

\(^6\) Sphinkeeper™ prosthesis (previously known as Gatekeeper™ prosthesis)
\(^7\) Gatekeeper™ prosthesis (polyacrylonitrile cylinder)
\(^8\) Carbon coated beads
\(^9\) Ultrasound guided silicone injections
<table>
<thead>
<tr>
<th>Case Series</th>
<th>Technique</th>
<th>Improvement</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feretis et al.</td>
<td>Microballoons made of silicone</td>
<td>Improvement in mean incontinence score from 16.16 (15-18) to 5 (4-7); (P =0.027)</td>
<td>No significant AEs or serious post-implantation complications</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>Collagen</td>
<td>65% showed marked symptomatic improvement. 12% reported minimal and 18% reported no improvement</td>
<td>Nil reported</td>
</tr>
<tr>
<td>Shafik et al.</td>
<td>Polytetrafluoroethylene</td>
<td>63% improvement in Wexner score post injection</td>
<td>Mild pain</td>
</tr>
<tr>
<td>Shafik et al.</td>
<td>Autologous Fat</td>
<td>85% improvement in Wexner score post injection</td>
<td>Mild pain</td>
</tr>
</tbody>
</table>

**Table 2: Outcomes of augmentation techniques**

<table>
<thead>
<tr>
<th>Reference based on follow-up duration</th>
<th>Patients analysed</th>
<th>Definite explant of device</th>
<th>Total no. of surgical revisions</th>
<th>Solid continence</th>
<th>Liquid continence</th>
<th>Gas continence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2.9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehur et al, 1996</td>
<td>10</td>
<td>3</td>
<td>6</td>
<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Lehur et al, 2000</td>
<td>20</td>
<td>4</td>
<td>10</td>
<td>19</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Savoye et al, 2000</td>
<td>12</td>
<td>0</td>
<td>NA</td>
<td>12</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Devesa et al, 2002</td>
<td>43</td>
<td>10</td>
<td>NA</td>
<td>43</td>
<td>17 in 26</td>
<td>29</td>
</tr>
<tr>
<td>Ortiz et al, 2002</td>
<td>15</td>
<td>7</td>
<td>14</td>
<td>14</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Michot et al, 2003, group 2</td>
<td>19</td>
<td>3</td>
<td>15</td>
<td>19</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Casal et al, 2004</td>
<td>9</td>
<td>1</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Pooled proportion, % (95% CI)</strong></td>
<td><strong>96 (90–98)</strong></td>
<td><strong>71 (59–81)</strong></td>
<td><strong>47 (33–62)</strong></td>
<td></td>
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<tr>
<td>3–4.9 years</td>
<td></td>
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<tr>
<td>Altomare et al, 2004</td>
<td>14</td>
<td>9</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Michot et al, 2010</td>
<td>23</td>
<td>9</td>
<td>11</td>
<td>23</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td><strong>Pooled proportion, % (95% CI)</strong></td>
<td><strong>98 (74–100)</strong></td>
<td><strong>83 (62–93)</strong></td>
<td><strong>51 (36–67)</strong></td>
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<tr>
<td>≥5 years</td>
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<tr>
<td>Christiansen et al, 1999</td>
<td>8</td>
<td>7</td>
<td>13</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Parker et al, 2003, group 1</td>
<td>10</td>
<td>18</td>
<td>NA</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Ruiz Carmona, et al, 2009</td>
<td>9</td>
<td>7</td>
<td>19</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pooled proportion, % (95% CI)</strong></td>
<td><strong>63 (34–85)</strong></td>
<td><strong>45 (27–63)</strong></td>
<td><strong>11 (4–29)</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Table 3: Outcomes of artificial bowel sphincter implantation. Reprinted with permission from Elsevier; Journal of the American College of Surgeons, Volume 217, Issue 4, October 2013, Pages 718–725


Table 4: Effect of neuromodulation on anal sphincter pressures.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Resting Pressure</th>
<th>Squeeze Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sacral Nerve Stimulation Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leroi et al.¹</td>
<td>2001</td>
<td>6</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Rosen et al.²</td>
<td>2001</td>
<td>20</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Kenefick et al.³</td>
<td>2002</td>
<td>15</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Uludag et al.⁴</td>
<td>2002</td>
<td>38</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Matzel et al.⁵</td>
<td>2003</td>
<td>16</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Uludag et al.⁶</td>
<td>2004</td>
<td>75</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Sheldon et al.⁷</td>
<td>2005</td>
<td>10</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Michelsen et al.⁸</td>
<td>2006</td>
<td>29</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Melenhorst et al.⁹</td>
<td>2007</td>
<td>100</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Holzer et al.¹⁰</td>
<td>2007</td>
<td>29</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Munoz-Duyos et al.¹¹</td>
<td>2008</td>
<td>47</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Jarret et al.¹²</td>
<td>2008</td>
<td>8</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Moya et al.¹³</td>
<td>2014</td>
<td>50</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Madbouly et al.¹⁴</td>
<td>2015</td>
<td>24</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Percutaneous Tibial Nerve Stimulation Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>López-Delgado et al.¹⁵</td>
<td>2014</td>
<td>24</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>George et al.¹⁶</td>
<td>2013</td>
<td>30</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Moreira et al.¹⁷</td>
<td>2013</td>
<td>10</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Boyle et al.¹⁸</td>
<td>2010</td>
<td>31</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>de la Portilla et al.¹⁹</td>
<td>2009</td>
<td>16</td>
<td>↔</td>
<td>↑</td>
</tr>
</tbody>
</table>

Figure 2

First Degree Perineal Tear

Second Degree Perineal Tear

Third Degree Perineal Tear

Fourth Degree Perineal Tear
Figure Legends

Fig 1: Anatomy of anal canal; Reprinted by permission from John Wiley and Sons: The Obstetrician & Gynaecologist, Management of obstetric anal sphincter injury, Volume 5, Issue 2, 72-8 (2003)

Fig 2: Classification of obstetric anal sphincter injury; Reprinted by permission from Macmillan Publishers Ltd: The American Journal of Gastroenterology 110, 521-529 (April 2015)