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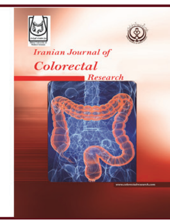

Low Anterior Resection Syndrome: A Review

Ju Yong Cheong*[1,2*]*, PhD;* *Mark Muhlmann*[2]*, MD

[1]*Royal Prince Alfred Hospital, Sydney, Australia.*
[2]*Prince of Wales Hospital, Sydney, Australia*

***Corresponding authors:**
Ju Yong Cheong
Prince of Wales Hospital, Department of Colorectal Surgery, 320-346 Barker St, Randwick NSW 2031, Australia. **Tel:** +61 409 110219;
Email: Juyong.cheong@gmail.com

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Abstract

Context: Low anterior resection syndrome (LARS) is a common debilitating problem faced by patients who underwent low or ultralow anterior resection. The management of LARS is complicated by the fact that our understanding of the pathophysiology of this disease is as yet unclear. In fact, our limitation in understanding is highlighted by the fact that only in 2020 has there been an international consensus on the definition of LARS (LARS international collaborative group).
Evidence Acquisition: A comprehensive review of the current literature on the pathophysiology, risk factors and management of LARS was performed.
Results: In this review, we discuss the suspected pathophysiology of LARS, including damage to anatomy (sphincter, hiatal ligament, conjoint longitudinal ligamaent), loss of physiology (of rectum), and damage to nervous system (damage to hypogastric nerves, denervation of left colon, loss of recto-sigmoid brake). The risk factors for LARS are discussed, including neoadjuvant treatment, TME dissection, rectal stump height, anastomotic leak, as well as the protective role of a pouch formation in reducing the rate of LARS. Management of LARS involves management of symptoms, and management of underlying neurophysiology. The non operative measures include dietary restrictions, medications to reduce motility, pelvic floor exercises, colonic irrigations. Interventional approaches includes sacral nerve stimulation (SNS), and when bowel function becomes too debilitating a stoma may be created.
Conclusion: LARS is a significant and debilitating disorder. It has complex pathophysiology and there are some definite risk factors. Management involves non-operative and operative approaches, trans-anal irrigation and sacral nerve stimulation showing promise.

Keywords: Low anterior resection syndrome, Rectal cancer, Pathophysiology, Management

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Introduction/Definition

In the last three decades, there have been developments in the management of low rectal cancer, including the introduction of sphincter-saving surgery, total mesorectal excision (TME), and neo-adjuvant radiotherapy. Such developments have led to improvements in survival, thereby shifting the focus to improving the bowel function and quality of life of patients (1).

The low anterior resection syndrome (LARS) has recently undergone a change in definition. The previous definition of "disordered bowel function after rectal resection, leading to a detriment in quality of life" (2) was updated by an international consensus in 2020. The LARS International Collaborative Group, involving a patient group, colorectal surgeons, and other healthcare professionals (73), after a rigorous process including a Delphi survey, face-to-face consultation, and online consultation, issued a 2020 consensus statement on the definition of LARS. This definition encompasses a patient with a history of low anterior resection (LAR) who develops at least one (of eight) symptoms, and at least one (of eight) consequences (1).

The eight symptoms include:

1. Variable, unpredictable bowel function
2. Altered stool consistency
3. Increased stool frequency as compared with preoperative stool frequency.
4. Repeated painful stools: pain on urge, on passing a bowel motion, and/or after passing a bowel motion.
5. Emptying difficulties: difficulty emptying the bowel for any reason; a feeling that the bowel is not empty after passing a bowel motion; the need to return to the toilet multiple times to empty the bowel.
6. Urgency: the need to rush to the toilet to defecate and/or the inability to delay passing a bowel movement.
7. Incontinence: the unintended passage of a large volume of fecal material.
8. Soiling: the involuntary passage of a small amount of stool onto clothing.

The eight consequences include:

1. Toilet dependence
2. Preoccupation with bowel function
3. Dissatisfaction with bowels
4. Strategies and compromises
5. Impact on mental and emotional wellbeing
6. Impact on social and daily activities
7. Impact on relationship and intimacy
8. Impact on roles, commitments, and responsibilities.

The prevalence of LARS is very high. A 2018 meta-analysis examined the prevalence of LARS using the LARS score (2012 definition of LARS) based on 11 studies with 4007 patients. Following LAR, major LARS (defined by a score of 30-42) had a prevalence of 41% (95% CI: 34-48%), with a range of 17.8-56%. Minor LARS (score of 21-29) was found in 24%, with a range of 17-50% (3).

Pathophysiology of LARS

The pathophysiology of LARS is multifactorial, involving disruption of anatomy, physiology, and nervous system function.

Damage to Anal Sphincter

The internal anal sphincter is responsible for 55-75% of the resting anal tone. Direct damage can occur during an intersphincteric dissection or following the insertion of a circular stapler (ECS, EEA). A randomized controlled trial in 2000 examined patients undergoing sigmoid colectomy (no dissection beyond the sacral promontory) and compared the effect of circular stapling devices versus biofragmentable anastomotic rings (BAR). In the circular stapling devices group (n=18), preoperative and postoperative anorectal manometry showed a reduction in mean resting anal pressure (84.8→63.1). Endoanal ultrasound showed significantly greater internal anal sphincter fragmentation in the circular stapling group relative to the BAR group (P=0.046) (4). A 1998 study examined 39 consecutive patients undergoing LAR by endoanal ultrasound preoperatively and postoperatively at 3, 6, 9, 12, and 24 months, demonstrating that 18% of patients developed internal anal sphincter injury after LAR (5).

Damage to Hiatal Ligament and Conjoint Longitudinal Muscle

The uppermost part of the anus is surrounded by a fascia called the 'hiatal ligament'. The hiatal ligament is connected to the fascia on the pelvic surface of the levator muscle. With defaecation, the pubococcygeus and iliococcygeus muscles contract, which, through the effect on the hiatal ligament, leads to the opening of the anal canal. Damage to the hiatal ligament has been suggested to contribute to functional damage of the anal canal (6). Anatomically, the internal sphincter is derived from the inner circular rectal muscle. The outer longitudinal muscle of the rectum continues below as the conjoint longitudinal muscle, which penetrates the external anal sphincter to reach the perineum. The contraction of the conjoint longitudinal muscle (along with the contraction of the posterior rectococcygeus muscle) leads to the shortening of the anal canal during defecation. During LAR, the conjoint longitudinal muscle may be damaged, especially when dissecting circumferentially around the anorectal junction near the pelvic floor (6).

Loss of Rectum's Reservoir Function

The rectum acts as a reservoir but remains empty at most times. Defecation is preceded by propagated bursts of contraction from the sigmoid colon, which propel feces into the rectum. This rectal accumulation leads to relaxation of the internal anal sphincter via the recto-anal inhibitory reflex. Tightening of the external sphincter and pelvic floor muscles can temporarily override the urge to defecate. The rectum also regularly contracts, propelling the feces retrograde, thereby keeping the volume low in the rectum and suppressing the urge to defecate. Rectal distension by feces also leads to brief reflex contraction of the external sphincter (recto-anal contractile reflex) mediated by pelvic splanchnic nerves and pudendal nerves, thereby preventing accidental incontinence (7). Thus, the loss of the rectum itself and the loss of its innervation leads to the loss of these functions.

Damage to Branches of Inferior Hypogastric Plexus During TME:

The TME procedure can lead to damage to nerves of the rectal wall and internal anal sphincter. The inferior hypogastric plexus is a mixture of sympathetic (from superior hypogastric plexus via hypogastric nerves), parasympathetic (from pelvic splanchnic nerves), and afferent fibers (from rectum and internal anal sphincter). The inferior hypogastric plexus gives branches to the rectum, which travel just below the peritoneal reflection, and branches to the internal anal sphincter, which run along the fascia of the levator muscles (and enter the internal sphincter at the level of the dentate line at the directions of 2-3 and 9-10 o'clock). These branches can be damaged by TME, and TME is a recognized risk factor for LARS (6).

Denervation of Left Colon (Loss of Sympathetic Tone)

Electrophysiologically, the transverse colon has a high-frequency dominant range and is phase-locked. In comparison, the descending colon has a high degree of inhibitory sympathetic tone. During LAR, the left colon is mobilized, the splenic flexure is brought down and the inferior mesenteric artery (IMA) is transected, leading to denervation of the left colon. A 2008 Korean study demonstrated that in rats, this mobilization and extrinsic autonomic denervation caused an increase in the motility of the distal colon secondary to the destruction of the inhibitory sympathetic innervations (alpha-adrenergic pathway). The authors postulated that LARS symptoms may be partially explained by the increased motility of the left colon (8).

High Division of IMA, Resulting in Neo-rectal Spasticity

Nerve damage from the high division of the IMA leads to spasticity of the neorectum, resulting in a sense of incomplete evacuation (9). High division of the IMA (as compared to low division preserving left colic branch) is associated with larger segmental denervation of the sigmoid colon. A 2005 Japanese study examined 76 patients undergoing LAR. The high IMA division group had spastic waves in the neo-rectum in 58.3% of cases, as compared to 20% in the low IMA division group ($P<0.05$). Spasticity of the neorectum was significantly correlated with urgency, multiple evacuations, and major soiling ($P<0.01$). Thus, high division of the IMA and autonomic denervation of a larger region of the neo-rectum may be a contributing factor in the pathophysiology of LARS.

In keeping with the idea of autonomic denervation, a 2013 study compared patients with major LARS and patients with no LARS after TME with no neo-adjuvant radiotherapy (10). Rectal stimulation and anorectal physiology studies showed that whilst there was no difference in biomechanical and sensory properties of the anal canal or neorectum between the two groups, the group with major LARS had a higher rise in the neo-rectal pressure during distension post-prandially as compared to the fasting state; this was not observed in the no LARS group after eating. Hence, the authors suggested that abnormal neo-rectal motility in response to eating may contribute to LARS. In fact, the authors found that many patients with major LARS describe a severe urge to defecate and fragmentation in the first hours after eating. Notably, the study found that a meal of 1991 kJ (476 kcal) induced an increase in neo-rectal pressure in the major LARS group, whereas pressure was unchanged in the no LARS group.

Loss of Rectosigmoid Brake

The loss of the rectosigmoid brake is a contributor to LARS (11). The colon has a number of motions. One is segmental contraction, which 'chops and mixes' the fecal contents. Another is mass propagating waves, which propel feces from the proximal colon toward the distal colon and rectum. This mass propagating movement usually occurs after a meal. However, not all mass propagating waves lead to defaecation due to the rectosigmoid brake. This is because during these waves, whilst the proximal colon is highly active in propagating the feces, the distal sigmoid and rectum are not active. In fact, the rectum and sigmoid send retrograde contractions, so that the feces that arrive at the rectum and sigmoid colon are pushed back again to the proximal colon, where they can be 'chopped and mixed' again. When this rectosigmoid brake is lost due to denervation of the descending/sigmoid colon or rectum, all mass propagating waves will lead to filling of the rectum, and the urge to evacuate the rectum occurs. This leads to the LARS symptoms of urgency and frequency.

Risk Factors for LARS

Neo-adjuvant Radiotherapy, Rectal Remnant Height <4 cm

A 2018 meta-analysis based on 4007 patients undergoing LARS found 'major LARS' (LARS score) in 41% of patients undergoing LAR. Of the 11 studies, 8 studies identified radiotherapy (adjuvant or neoadjuvant) as a risk factor for 'major LARS'. 6 of 11 studies identified rectal remnant height as a significant risk factor for major LARS (12). One study also found having defunctioning ileostomy for longer than 6 months was associated with a 3.7-fold risk of LARS ($P=0.03$) (13).

A 2015 study examined the relationship between neoadjuvant chemoradiotherapy (CRT) and length of the rectal remnant (as measured by postoperative MRI scan) and their impact on LARS in 125 patients. When patients did not receive neoadjuvant-CRT, the rectal stump length had a significant impact on the development of major LARS; those with <4 cm rectal stump length developed major LARS in 46% of cases versus 10% if the rectal stump was more than 4 cm long (P<0.0001). Long-course chemoradiotherapy (irrespective of rectal stump length) was a significant risk factor for major LARS (OR: 3.5). In other words, when patients received neoadjuvant-CRT, it did not matter whether the rectal stump was more or less than 4 cm long (P=0.892) (14).

Adjuvant Radiotherapy

A 2017 study by Jimenez-Gomez based on 190 patients found on multivariate analysis that preoperative radiotherapy (OR: 4.33, 95% CI: 2.03-9.27) and postoperative radiotherapy (OR: 9.52, 95% CI: 1.74-52.24) were significant risk factors for major LARS (P=0.0003). TME, as compared to partial mesorectal excision, was also another risk factor for major LARS on multivariate analysis (OR: 2.18, 95% CI: 1.02-4.65, P=0.043) (15).

Anastomotic Leak

A study by Hallbook in 1996 compared 19 patients with anastomotic leak after LAR with 19 matched patients who did not develop anastomotic leaks. The anastomotic leaks healed without strictures. The group of patients who developed anastomotic leaks had double the frequency of bowel motion (4 vs 2, P=0.02) after a median follow-up of 30 months. Neorectal compliance and distension were also significantly lower in the anastomotic leak group, with lower volume at a distension pressure of 40 cmH2O and decreased compliance at sensation of filling, at urge, and at maximum tolerated volume (16).

A similar study by Nesbakken in 2001 compared 11 patients with anastomotic leaks (no residual strictures) after LAR with 11 matched patients who did not develop anastomotic leaks at 12-48 months after defunctioning stoma closure. The group with anastomotic leakage had significantly lower maximum tolerable volume in the neo-rectum (120 ml vs 180 ml, P=0.04) and significantly less feeling of complete evacuation (P=0.02) (17).

The Protective Nature of Pouch Formation

There are many techniques for anastomosis during LAR. A 2015 meta-analysis compared reconstruction options for LAR on the functional outcome and quality of life (18). Straight end to end, side to end, colonic J-pouch colo-rectal/colo-anal, and transverse coloplasty were compared. 21 trials with 1636 patients were included in the meta-analysis. In the comparison of straight colo-anal anastomosis versus colonic J pouch, colonic J-pouch showed significantly less stool frequency (mean difference of 2.85 [1.09-4.61], P=0.001) within 8 months of surgery, with persistently less stool frequency at 8-18 months after surgery (mean difference of 1.22 [0.25-2.20], P=0.014). Straight colo-anal anastomosis had more than twice the chance of incomplete defecation as compared to colonic J-pouch within 8 months of surgery (odds ratio of 2.32 [1.02-5.28], P=0.044). Patients with straight colo-anal anastomosis were also more than four times likely to require anti-diarrheal medications at 8-18 months after surgery compared with patients who had colonic J-pouch (odds ratio: 4.83 [1.74-13.4], P=0.002). This meta-analysis did not include any comparison between straight colo-anal vs. side to end or coloplasty. Thus, based on this 2015 meta-analysis, the only valid conclusion is that the colonic J pouch appears to provide superior function compared with straight colo-anal anastomosis.

Since this 2015 meta-analysis, there have been multiple trials comparing various pouch techniques. In 2019, a multi-center, international, randomized controlled trial compared functional outcomes after colonic J-pouch (80 patients) versus side to end anastomosis (87 patients) (19) using the fecal incontinence severity index (FISI) and a new questionnaire created for this study. The FISI score was similar between the groups at baseline (a higher FISI score indicates worse bowel function). However, at six months, the FISI score doubled for both J-pouch and side to end groups, before dropping at 12 and 24 months for both groups. There was no difference between the two groups. The new bowel function questionnaire also did not show any difference between the two groups at all mentioned time points.

A 2019 Swiss randomized controlled trial involving 15 hospitals, and 336 patients undergoing LAR were randomized to straight colo-anal, side to end, and colon-J pouch anastomosis (20). The composite evacuation score (involves the use of medication to evacuate, difficulties in emptying, digitation to evacuate, returning to evacuate, feeling of incomplete evacuation, straining to evacuate, and time needed to evacuate) did not show any significant differences at 12 months after the three types of anastomosis. Furthermore, the composite incontinence score (involves warning before passing motion, ability to differentiate between gas from feces, ability to defer evacuation, wearing a pad during the day, wearing a pad at night, incontinence of gas, incontinence of loose stool, incontinence of feces) also showed no difference among the three anastomotic approaches.

Thus, there is no definitive evidence that one reservoir technique is superior to another, except that a reservoir formation (J pouch) appears to provide superior function as compared to a straight coloanal anastomosis.

Measuring LARS

LARS Score

Whilst there are a few scoring systems that have been used for measuring LARS, the most commonly used and validated scoring system is the Low Anterior Resection Syndrome Score (LARS score) introduced in 2012. The LARS scoring system was developed based on the Danish Colorectal Cancer Group Database. The LARS score is an easy-to-use, validity-tested scoring system with high sensitivity (72.54%) and specificity (82.52%) (21).

The LARS scoring system is comprised of five questions:

1. Do you ever have occasions when you cannot control your flatus (wind)?

a. No, never	0
b. Yes, less than once per week	4
c. Yes, at least once per week	7

2. Do you ever have any accidental leakage of liquid stool?

a. No, never	0
b. Yes, less than once per week	3
c. Yes, at least once per week	3

3. How often do you open your bowels?

a. >7 times / 24 hours	4
b. 4-7 times / 24 hours	2
c. 1-3 times / 24 hours	0
d. Less than once / 24 hours	5

4. Do you ever have to open your bowels again within one hour of the last bowel opening?

a. Never	0
b. Yes, less than once per week	9
c. Yes, at least once per week	11

5. Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

a. Never	0
b. Yes, less than once per week	11
c. Yes, at least once per week	16

Out of a total score of 42, a score of 0-20 is interpreted as 'no LARS', 21-29 as 'minor LARS', and 30-42 as 'major LARS'.

Score numbers are nonlinear in their increase, meaning the LARS score has been developed to better reflect the patient's 'subjective bother' from LARS. The authors calculated that the relationship between the frequency of occurrence of bothersome symptoms and the 'subjective bother' is not linear. Thereby, by better reflecting the patient's symptoms, it is more indicative of the impact on quality of life (21).

MSKCC-BFI Score

Another scoring system is the Bowel Function Instrument (BFI) developed by the Memorial Sloan Kettering Cancer Center. It consists of 18 questions, asking patients to recall a four-week time frame. These 14 questions are grouped into 3 subscales: diet, urgency/soilage, and frequency. The total score ranges from 18-90, with 90 representing the best bowel function. It is based on a meticulous design and a comprehensive evaluation of bowel dysfunction (22). However, this has not been used as frequently as the LARS score. One problem with the BFI is that it is excessively comprehensive and complex for clinical use as its calculation and interpretation are time-consuming (21).

A 2015 paper described the strengths and weaknesses of various questionnaires and scoring systems for measuring LARS (23). Several well-known fecal incontinence scores can be used (and have been used in the past) to evaluate incontinence in LARS patients. These include the Wexner Score (24), St Marks's score (25), and the FISI score (26). The Wexner score is the most widely used instrument, though the FISI is the most methodologically rigorous scale. Whilst they are good for measuring incontinence, they have limitations in 'painting the full picture of LARS' (23). For a comprehensive evaluation of LARS, the review recommends the use of the MSKCC-BFI scoring system. As stated above, the MSKCC-BFI is better able to assess the symptoms as well as impacts on the patient, such as diet limitation and pad wearing. However, the LARS score is much more practical (only five questions as compared to 18, with subscales). The author concludes that one instrument should not preclude the use of another, and a combination of questionnaires and scoring systems should sometimes be used (e.g., Wexner score in combination with LARS score).

The LARS International Collaborative Group in 2020 released an international consensus definition of LARS. After the consensus on what the definition is and what the priorities are, a 'new LARS scoring' system is expected to be created soon.

Management of LARS

The management of LARS involves addressing both the symptoms and underlying neurophysiology. Non-operative measures include dietary restrictions, medications to reduce motility, pelvic floor exercises, and colonic irrigations. Interventional approaches include sacral nerve stimulation (SNS), and, when bowel function becomes too debilitating, a stoma may be created.

Dietary Management

Dietary measures include avoiding food that causes stool softening (caffeine, citrus fruits, spicy food, alcohol) and fiber supplements (6). A randomized clinical trial examined the effect of various dietary fibers on fecal incontinence (27). This trial however excluded patients who had "gastrointestinal tract altered by surgery", meaning that LARS patients do not meet the criteria. The study compared placebo, carboxymethylcellulose, gum Arabic, and psyllium fibers. The psyllium fibers significantly reduced fecal incontinence frequency as compared to placebo (2.5 vs 5.5 episodes per week). The study found that all fibers increased the total wet/dry weight of feces; however, psyllium increased the total (residual, undigested) fiber in the feces, leading to gel formation. Whilst dietary fiber supplement is recommended for fecal incontinence, there is no strong evidence behind their effectiveness in the management of LARS (6).

Medications

Medications such as loperamide can be used to reduce colonic motility. There is some evidence also that loperamide increases the internal anal sphincter tone. A 1989 study examined 19 patients who required ileoanal anastomosis (28). Among them, 9 patients had intact anal sphincter function and 10 had impaired sphincter function. After one day of loperamide (16 mg), the median number of stools was reduced in both groups, as well as the fecal weight. In the 9 patients with intact anal sphincter function, the resting anal sphincter pressure increased from 80 to 95 cm H_2O ($P<0.05$). Loperamide induces irregular segmental contraction by selective stimulation of circular muscles and by disturbing the coordinated contraction of intestinal muscles, thereby increasing the intestinal transit time and leading to greater absorption of water and electrolytes. Loperamide also stimulates the internal anal sphincter, leading to an increase in resting pressure.

To address the spastic hypermotility of the neo-rectum, serotonin antagonists may be used. A 2014 study examined 25 patients with 'uncontrollable urgency and fecal soiling' after operations who were given one month of therapy with the $5HT_3$ antagonist ramosetron (29). All measures of incontinence (Wexner incontinence score), urgency severity, and the number of defecation improved significantly after one month of therapy with ramosetron.

Pelvic Floor Rehabilitation

A 2014 systematic review of 5 studies with 321 patients examined the efficacy of pelvic floor rehabilitation in improving functional outcomes after LAR (30). Of the five included studies, two studies showed significant improvements in the Wexner incontinence score, one study showed a significant improvement in the modified Cleveland incontinence score, and one study showed an improved FACT-C score after pelvic floor rehabilitation. Due to the heterogeneity of the studies and the limited quality of the studies, a meta-analysis could not be performed. The systematic review concluded that pelvic floor rehabilitation should not be recommended routinely for all patients who undergo LAR, but should be reserved for patients with fecal incontinence or LARS, as they may benefit the most.

Trans-anal Colonic Irrigation

Trans-anal colonic irrigation has been recently appraised. A 2018 study examined 27 patients who had major LARS (score >30) and had failed other conservative methods (diet, loperamide, and pelvic floor rehabilitation) (31). Transanal irrigation was performed using the Peristeen system (Coloplast, Humblebaek, Denmark) with up to 1500 ml (median 450 ml) of lukewarm tapwater irrigation, 3-4 times per week for 6 months. The median number of daily bowel movements decreased from 7 at the start to 1 at 6 months (end of TAI), but rose to 4 at 9 months (3 months after TAI). The LARS score fell from a median of 35 at the start to 12.2 at 6 months (end of TAI); however, after ceasing TAI, it rose again to 27 (3 months after TAI ceased, $P<0.0001$).

A 2009 study examined 30 patients with fecal incontinence after LAR for rectal cancer (32). The TAI system employed was the Biotrol Irrimatic pump (Braun), using 500 ml of water daily at body temperature. Patients in this study had severe incontinence (mean William incontinence score of 4.4 out of 5; score 5 indicates frequent incontinence to solid stool), and patients had incontinence postoperatively for a long time (mean time between LAR and TAI was 3.1 years). Of the 21 out of 30 patients who had persisted with TAI, the incontinence improved significantly with William's incontinence score falling from 4.5 to 1.7 ($P<0.0001$). Notably, 57% (12 patients) became continent (pseudo), 14% only had incontinence to flatus and 29% (6 patients) were incontinent only to liquid stools.

In a 2017 study, a qualitative analysis was performed on 15 patients with LARS scores of >20 who undertook TAI using the Peristeen system (33). At six months, the LARS score fell from 35.9 to 17.7. Quality of life assessment of the 11 patients who completed the TAI and answered the questionnaire reported a positive outcome, with some patients describing it as life-changing, and all 11 patients asserted that they would highly recommend it to anyone with LARS.

A 2011 study examined 14 patients with LARS who failed to improve 9 months after diet control, loperamide, and anal plug, along with one patient for whom SNS had failed. The patients were treated with 29 months (median) of TAI. After TAI, the number of defecations decreased from 8 to 1 per day ($P<0.001$). Defaecation at night decreased from 3 to 0 ($P<0.0001$), and the Cleveland incontinence score decreased from 17 to 5 ($P<0.01$). Furthermore, the SF-36 quality of life assessment showed significant mental improvement (34).

The mechanism of TAI is uncertain; however, it has been suggested that regular management of bowel function through irrigation could have a rehabilitative effect on colonic motility. Therefore, one study suggested that TAI should always be done according to a constant schedule at the same hour of the day, with the same time interval between the irrigations, without missing sessions (31).

Sacral Nerve Stimulation (SNS)

Since its introduction in 1995, SNS has established itself as a potential method of management of fecal incontinence resistant to conservative management. On an intention to treat basis, SNS has a median success rate for fecal incontinence of between 54-63% (35). SNS has also been used in disordered defaecations, including slow transit constipation and rectal evacuatory dysfunction. Interestingly, it is a paradox that SNS is effective for both fecal incontinence and chronic constipation. A 2014 systematic review of both 62 clinical studies and 9 experimental animal-based studies confirmed the effects of SNS on colonic (motor & sensory), rectal, and anal function, as well as its effect on the central nervous system (35). With colonic motility, SNS has been found to cause: (1) a significant increase in retrograde movements during defecation, (2) an increase in the number of distal colon retrograde propagating contractile sequences, and, in patients with slow transit constipation, (3) a significant reduction in delayed whole gut transit, (4) an increase in total antegrade pressure sequence frequency throughout the colon, and (5) an increased frequency of high amplitude pressure sequences and pressure sequences that propagate more than 30 cm along the bowel, leading to improvement in constipation symptoms with a reduction in laxative use. In the rectum, SNS has been found to cause: (1) decrease in the frequency of motor complexes; (2) inhibition of spontaneous motility complexes after meals and on awakening; (3) no change in rectal wall tension or compliance; (4) 'normalization of neo-rectal sensation' (patients with hyposensitivity developed reduced sensory threshold sensitivity, i.e., increased sensitivity; patients with hypersensitivity developed increased sensory threshold, i.e., reduced sensitivity); (5) the neurotransmitter Substance P was reduced following SNS, indicating evidence of neuroplasticity; (6) in both the rectal and anal mucosa and smooth muscles, the expression of neuronal and induced nitric oxide synthesis was increased; and (7) reduced paracellular permeability. SNS has been found to have the following effects on the anus: (1) increase in voluntary anal squeeze pressure, (2) increase in resting anal pressure, and (3) hypertrophy of the external anal sphincter. The cortical effect of SNS has been examined using transcranial magnetic stimulation, PET scan, and cortical evoked potentials. Notably, a reduction in cortico-anal excitability and cortical representation has been found, indicating that SNS results in inhibition of the motor cortex to the external anal sphincter (cortico-anal) pathway. An animal study suggested that SNS may initiate a 'long-term potentiation-like effect in the somatosensory cortex, leading to improved awareness of the anorectum'. The meta-analysis concluded that the effect of SNS on anorectal function appears to occur at the pelvic afferent or central level. SNS of the S2-4 nerves stimulates somatic fibers from the pudendal nerves, afferent sensory fibers from the anal sphincter/pelvic floor, and autonomic fibers. Activation of these afferent fibers leads to 'modification of ascending supraspinal control of defecation'. "The continuous low-level stimulation of somatic afferents, as proposed in the Gates Theory, inhibits activation of spinobulbar pathways, thereby reducing descending inhibition of sphincter function and rectal contractility via Onuf's nucleus" (35).

In 2019, a meta-analysis with 10 studies examined the use of SNS for LARS (36). The studies included were very small, ranging from 1 to 16 patients, with a total of 95 patients. All studies were either case series or prospective cohort studies. Seven studies assessed changes in incontinence scores (Wexner score), while three examined LARS score changes. The mean reduction in the Wexner score was 11.23 ($P<0.00001$); however, the authors noted a significantly high level of heterogeneity. The three studies that used the LARS score also showed a significant reduction in the LARS score with a mean difference of 17.87 ($P<0.00001$). However, every one of these studies showed a significant improvement in either the Wexner score or LARS score after SNS implantation, which is indicative of publication bias. Also, indications for permanent SNS insertion varied widely from 'subjective improvement in symptoms' to '>50% improvement in continence', '>70% reduction in incontinence', and 'improvement of incontinence'. Thus, based on this most recent meta-analysis, it is too early to conclude that SNS implantation results in significant improvement in LARS.

Currently, in MD Anderson, there is a trial underway examination the effect of SNS on LARS: 'Sacral Nerve Stimulation in treating LARS or fecal incontinence in patients with locally advanced rectal cancer or other pelvic cancer - the RESTORE study' (NCT04066894). The first cohort's inclusion criteria include patients who are 18 years or older, T1-4 (with or without neoadjuvant radiotherapy), N+/-, with self-reported fecal incontinence or LARS with failed conservative management. The study is expected to be completed by 2025 (37-42).

Conclusion

LARS is a significant and debilitating disorder. There has been a recent new definition created for LARS; however, it makes one wonder whether the definition has been made too broad as whilst it is very sensitive, it may lack specificity. It is yet to be seen whether this will impact not only the management of patients but also the conduction of future studies. After the new consensus definition, we await a new scoring system. In the meantime, the LARS score is the most commonly used system. Management involves non-operative methods (diet, loperamide, and serotonin inhibitors), pelvic floor rehabilitation, and trans-anal irrigation. Evidence for SNS is not high level, and whilst there may be significant publication bias, the studies appear to indicate an improvement in outcome. Randomized controlled trials are needed to assess SNS.

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