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Systematic review and meta-analysis of randomized clinical trials on the treatment of low anterior resection syndrome

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ABSTRACT

Background: We conducted a systematic review of randomized clinical trials on treating low anterior resection syndrome to help inform current practice.
Methods: This Preferred Reporting Items for Systematic Reviews and Meta-Analyses–compliant systematic review of randomized clinical trials involved different treatments for low anterior resection syndrome. The risk of bias 2 tool was used to assess the risk of bias. The main outcomes were improvement in low anterior resection syndrome after treatment assessed by change in low anterior resection syndrome, fecal incontinence scores, and adverse treatment effects.
Results: After an initial screening of 1,286 studies, 7 randomized clinical trials were included. Sample sizes ranged between 12 to 104 patients. Posterior tibial nerve stimulation was the most frequently assessed treatment in 3 randomized clinical trials. The weighted mean difference between posterior tibial nerve stimulation and medical treatment or sham therapy in follow-up low anterior resection syndrome score (−3.31, $P = .157$) was insignificant. Transanal irrigation reduced major low anterior resection syndrome symptoms by 61.5% compared with 28.6% after posterior tibial nerve stimulation with a significantly lower 6-month follow-up low anterior resection syndrome score. Pelvic floor training achieved better improvement in low anterior resection syndrome than standard care (47.8% vs 21.3%) at 6 months, but this was not maintained at 12 months (40.0% vs 34.9%). Ramosetron was associated with a greater short-term improvement in major low anterior resection syndrome (23% vs 8%) and a lower low anterior resection syndrome score (29.5 vs 34.6) at 4-weeks follow-up than Kegels or Sitz baths. No significant improvement in bowel function was noted after probiotics use as probiotics and placebo had similar follow-up low anterior resection syndrome scores (33.3 vs 36).
Conclusion: Transanal irrigation was associated with improvement in low anterior resection syndrome according to 2 trials, and ramosetron showed promising short-term results in one trial. Posterior tibial nerve stimulation had a marginal benefit compared with standard care. In contrast, pelvic floor training was associated with short-term symptomatic improvement, and probiotics showed no tangible improvement in low anterior resection syndrome symptoms. Firm conclusions cannot be drawn due to the small number of trials published.

Introduction

Low anterior resection syndrome (LARS) is a common consequence of surgical resection of cancers of the middle or low third of the rectum. In fact, the prevalence of LARS widely varies between 17.8% and 74%.[1] Low anterior resection syndrome entails a constellation of symptoms that include fecal incontinence (FI), frequency or urgency of stools, loose stools, tenesmus, and

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sensation of incomplete emptying.[2] Low anterior resection syndrome is assessed by the LARS score that includes the cardinal symptoms of LARS, which are incontinence for flatus or liquid stools, frequency, clustering, and urgency. Low anterior resection syndrome can then be classified according to the severity of symptoms as major LARS (score 30–42) and minor LARS (score 21-29).[3] The negative impact of LARS, particularly major LARS, on patients' quality of life has been described as severe to the extent that some patients prefer a permanent stoma to avoid LARS symptoms.[4]

The exact pathophysiology of LARS is not yet clear. The widely accepted theory attributes LARS to the reduction in the inherent reservoir capacity and compliance of the rectum after proctectomy.[5] Another theory assumes the type of anastomosis to play a role in the development of LARS. Therefore, several alternative anastomotic techniques have been suggested, including colonic J-pouch-anastomosis, side-to-end anal anastomosis, and transverse coloplasty pouch.[2,6] Moreover, other factors such as diverting stoma, time to stoma closure, and time since closure may also influence bowel function after LAR.

The treatment of LARS is challenging and suboptimal. Different methods for treating LARS have been assessed, including dietary modification and pharmacologic treatment, pelvic floor rehabilitation, bowel irrigation, neuromodulation, and defunctioning stoma.[7] The multitude of treatment options for LARS attests to the lack of consensus on its optimal treatment. There is a paucity of level I evidence on the efficacy of the treatments of LARS as most studies are observational and noncontrolled. This systematic review aimed to inform the current practice of LARS management by reviewing the current level I evidence on the treatment of LARS as reported in randomized clinical trials to provide insight on treatments that showed significant merit and need to be further examined in multicenter randomized trials.

Methods

Registration and reporting

This systematic review and meta-analysis was reported in adherence to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2020).[8] A priori registration of the protocol of this systematic review in the prospective register of systematic reviews was conducted (CRD42022375889). There were no deviations from the registered protocol. This study was not submitted for Institutional Review Board review and/or approval due to the nature of the study in that no patient data was accessed and/or reviewed.

Literature search

Two authors (S.E, Z.G.) conducted an independent systematic search of the literature looking for randomized clinical trials (RCTs) that compared treatments of low anterior resection syndrome (LARS). The articles retrieved were cross-checked among the investigators, and conflicts were resolved by mutual agreement. The literature search and article selection process was under the senior author's supervision (S.D.W).

Electronic databases, including PubMed and Scopus, were searched from their inception through October 2022. A snowball search was performed by searching the reference section of the articles retrieved in the initial search. Furthermore, the PubMed function “related articles” was activated to look for further eligible RCTs.

We excluded duplicate reports and conference abstracts without full text. Then, the remaining articles were screened by title and/or abstract, followed by full-text screening. One of the 2 authors (S.E., S.M.) reviewed the articles' full text to ascertain their inclusion eligibility. The senior author (S.D.W.) reviewed the search results and final lists of articles before approving them.

Search keywords

The following keywords were used in the database search: “low anterior resection,” “syndrome,” “LARS,” “fecal incontinence,” “urgency,” “frequency,” “bowel dysfunction,” “resection,” “total mesorectal excision,” “proctectomy,” “TME,” “rectal cancer,” “rectal carcinoma,” “treatment,” and “outcome.”

The following syntax combination was used for the literature search: (low anterior resection syndrome or LARS or bowel dysfunction or FI) and (total mesorectal excision or TME or proctectomy) and (rectal cancer or rectal carcinoma) and (treatment or management).

Article selection criteria

Only English RCTs comparing $\geq$2 treatments or 1 active treatment and a placebo for LARS after proctectomy were included. We excluded nonrandomized cohort studies, case reports, case series, animal studies, editorials, previous reviews, and meta-analyses. The most recent and complete RCT was only included.

The following PICO criteria were used for assessment when reviewing overlapping RCTs that included the same cohort of patients within similar periods meant for inclusion:

P (Patients): Patients with LARS after proctecomy.

I (Intervention): Any active treatment of LARS.

C (Comparator): Any active treatment, standard care, or placebo and/or sham treatment.

O (Outcome): Improvement in LARS assessed by a change in LARS and FI scores.

Assessment of risk of bias

Two authors (S.E, Z.G.) assessed the risk of bias in the studies using the Risk of Bias 2 tool for assessing RCTs.[9] Any conflicts of interpretation of the results were addressed by mutual consensus.

Data extraction

Two authors extracted the following information from each study into an Excel sheet template (Microsoft, Inc):

- Authors, duration, country, and design of the study
- Total number of patients and numbers in each group
- Type of treatment of LARS
- Percent improvement in LARS symptoms
- Change in LARS and FI scores after treatment
- Follow-up duration in months

Outcomes

The primary outcome of this review was the improvement in LARS after treatment measured by the percentage of patients who had significant symptom improvement as assessed by change in LARS score. The secondary outcomes included the reduction in FI score and adverse effects of treatment.

Statistical analysis

Statistical analyses were performed using EZR (version 1.55, Jichi Medical University, Shimotsuke, Japan) and R software (version 4.1.2; R Foundation for Statistical Computing). A pairwise meta-analysis of the weighted mean difference between

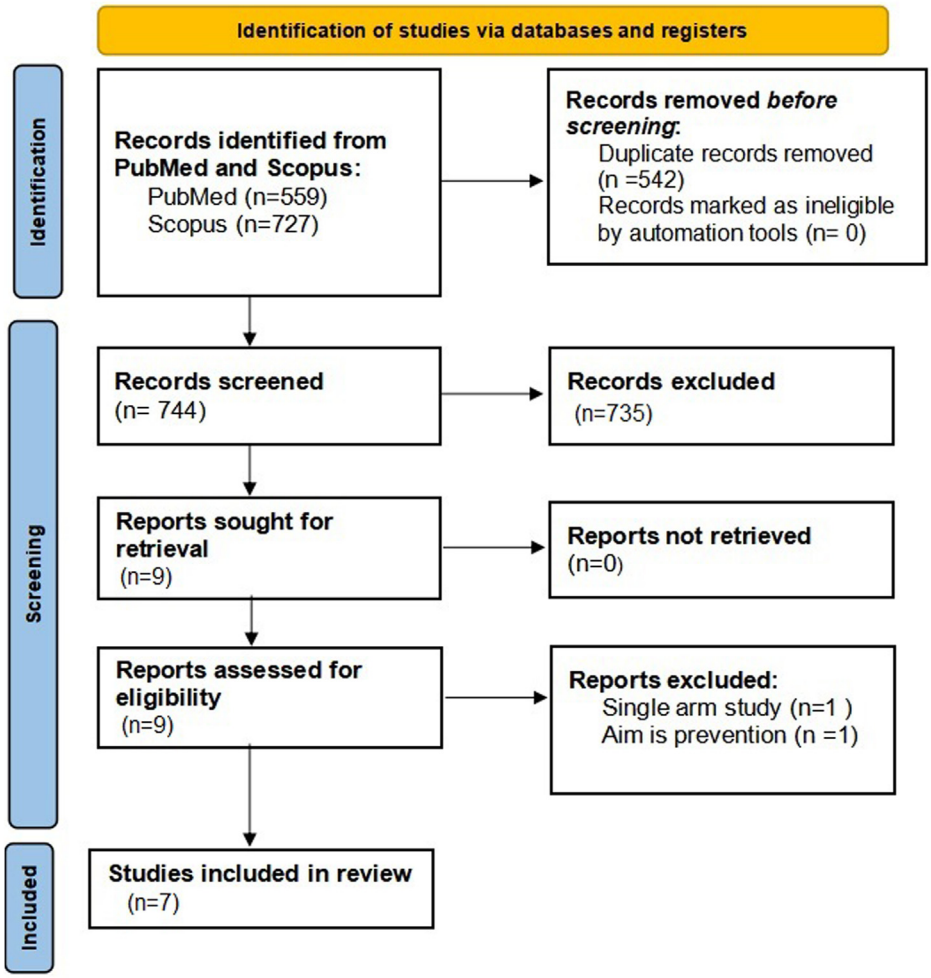

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for study inclusion.

treatments was conducted in the LARS score and incontinence score. Statistical heterogeneity was assessed using the *P* value of the Cochrane Q test and the Inconsistency (I^2) statistics (low if I^2 <25%, moderate if I^2 = 25%–75%, and high if I^2 >75%). The fixed-effect model was used when there was no significant statistical heterogeneity; otherwise, the random-effect model was used.

Results

Characteristics of studies

After an initial screening of 1286 studies, 7 RCTs[10–16] were included in this systematic review; the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart is illustrated in Figure 1. The studies were published between 2020 and 2022. Five trials[10,12,14–16] were conducted in European counties and 2 in South Korea.[11,13] The sample size ranged across the trials between 12 and 104 patients, and the median age ranged between 58.8 and 68 years. The trials mainly included patients with major LARS with average baseline LARS scores between 35 and 36.4. Three trials[12,14,15] compared posterior tibial nerve stimulation (PTNS) with either conservative treatment, sham stimulation, or transanal irrigation (TAI), one trial[16] compared TAI with conservative treatment, one trial[10] compared pelvic floor muscle training with standard care, another trial[11] compared the 5-HT3 receptor antagonist ramosetron with conservative treatment, and another[13] compared probiotics therapy with placebo. The average follow-up of the trials ranged between 3 weeks and 12 months (Table I). According to the Risk of Bias 2 tool, 2 studies had a low risk of bias, 3 had some concern of bias, and 2 had a high risk of bias (Table II).

Pelvic floor training

In a multicenter trial, Asnong et al[10] compared pelvic floor muscle training with standard care in patients with at least minor LARS after total mesorectal excision for rectal cancer. Although pelvic floor training achieved better improvement in LARS at 6 months than standard care (47.8% vs 21.3%), this difference was not maintained at 12 months of follow-up (40.0% vs 34.9%). The mean LARS scores (29.4 vs 29.7) and COREFO score (27.1 vs 28.2) were similar among the 2 groups at 12 months.

Ramosetron

In a large RCT of 100 male patients, Ryoo et al[11] found the use of ramosetron to be associated with a greater improvement in major LARS (23% vs 8%) and a lower LARS score (29.5 vs 34.6) at 4 weeks of follow-up compared with Kegel maneuver and Sitz baths. Minor adverse effects of ramosetron were noted in 5 patients, and there were no serious adverse effects.

Table I
Characteristics of the trials included

Study	Country	Duration	Compared groups	Number	Male	Follow-up
Pieniowski et al 2022[16]	Sweden	May 2016–November 2019	Transanal irrigation vs conservative treatment	45	25	12 mo
Asnong et al, 2022[10]	Belgium	January 2017–January 2021	Pelvic floor muscle training vs standard care	104	71	12 mo
Ryoo et al, 2021[11]	Korea	July 2017–December 2018	Ramosetron vs conservative	100	100	1 mo
Marinello et al, 2021[12]	Spain	September 2016–July 2018	Posterior tibial nerve stimulation vs sham	46	27	12 mo
Yoon et al, 2021[13]	Korea	June 2016–March 2018	Probiotics vs placebo	36	23	3 wk
Cuicchi et al, 2020[14]	Italy	January 2015–October 2015	Posterior tibial nerve stimulation and medical treatment vs medical treatment alone	12	7	12 mo
Enriquez-Navascues et al, 2020[15]	Spain	May 2017–February 2018	Posterior tibial nerve stimulation vs transanal irrigation	27	17	6 mo

Table II
Results of quality assessment of randomized trials using ROB-2 tool

Study	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported result	Overall risk
Pieniowski et al[16]	Low	Some concern	Low	Some concern	Low	Some concern
Asnong et al, 2022[10]	Some concern	Some concern	Low	Low	Some concern	Some concern
Ryoo et al, 2021[11]	Low	Some concern	Low	Low	Some concern	Some concern
Marinello et al, 2021[12]	Low	Low	High	Low	Low	High
Yoon et al, 2021[13]	Low	Low	Low	Low	Low	Low
Cuicchi et al, 2020[14]	Low	Low	Low	Low	Low	Low
Enriquez-Navascues et al, 2020[15]	Some concern	High	Some concern	Low	Low	High

ROB-2, Risk of Bias 2.

Probiotics

In a small trial comprising 36 patients, Yoon et al[13] showed no significant impact of using probiotics on improving bowel function after ileostomy reversal. Probiotics and placebo had similar Memorial Sloan-Kettering Cancer Center scores (56.2 vs 55) and LARS scores (33.3 vs 36) at the 3-week follow-up.

Posterior tibial nerve stimulation

In a triple-blinded trial on 46 patients, Marinello et al[12] found patients who received PTNS had more reduction in LARS score (15.7% vs 6.6%) and lower LARS score (30.7 vs 33.9) and St Marks score (12.5 vs 15.7) than patients who received sham stimulation at 1-year follow-up. In a double-blinded RCT, Cuicchi et al[14] found that adding PTNS to the medical treatment of LARS significantly decreased the percentage of major LARS by 83.3% compared with 17% after medical treatment only. The LARS score (28.2 vs 31.8) and the FI severity index (17.2 vs 36.7) were significantly lower when PTNS was added to medical treatment.

Meta-analysis of the outcome of PTNS versus medical treatment or sham therapy reported in the 2 trials[12,14] showed that the weighted mean differences in the follow-up LARS score (−3.31, 95% CI, −7.91, 1.28, $P = .157$, $I^2 = 0$; Figure 2) and follow-up FI score (−8.65, 95% CI, −23.72, 6.42, $P = .261$, $I^2 = 64\%$; Figure 3) were not statistically significant.

Transanal irrigation

Enriquez-Navascues et al[15] conducted an open-label RCT on 27 patients and reported that TAI managed to reduce major LARS symptoms by 61.5% compared with 28.6% after PTNS with a significantly lower follow-up LARS score (12 vs 30) and Vaizey score (6 vs 9) at 6 months of follow-up. Pieniowski et al[16] compared TAI with conservative treatment of LARS that included bulk-forming medications, loperamide, and basic dietary advice. Twenty-two patients had TAI, and 23 received conservative treatment. After 12 months of follow-up, the mean LARS score (22.9 vs 32.4; $P = .002$) and Cleveland Clinic Florida FI score (6.4 vs 9.2; $P = .05$) were lower in the TAI group than in the control group. Transanal irrigation was also associated with a higher quality of life score.

The outcomes of the treatments of LARS, as reported in the studies, are summarized in Table III. Figure 4 illustrates the follow-up LARS scores in the treatment and control groups in the studies reviewed.

Discussion

The present systematic review included only RCTs to demonstrate the current level-I evidence on the treatment of LARS. Seven RCTs were found, all published within the past 3 years. Posterior tibial nerve stimulation was the most commonly assessed treatment of LARS in the reviewed RCTs. Posterior tibial nerve stimulation aims to achieve an indirect modulation of the sacral nerve via stimulation of the posterior tibial nerve. Although sacral nerve stimulation (SNS) is commonly used for treating LARS,[17] we could not find RCTs assessing its effect, highlighting that the evidence on SNS use in LARS is based only on observational studies.[18–20] Two trials compared PTNS with medical treatment or sham stimulation, and in both trials, PTNS improved LARS and incontinence scores that were not noted in the control group. However, a meta-analysis of both trials showed no significant difference in the mean follow-up LARS scores between PTNS and the control group. Although 2 previous pilot studies[17,21] reported promising outcomes of PTNS in LARS, several limitations to both studies include the small number of patients, heterogeneity in radiotherapy administered and level of the anastomosis, and short follow-up.

Conversely, one randomized trial[15] showed that TAI was more effective than PTNS. Transanal irrigation has been shown to be beneficial in treating LARS,[22] whereas another randomized trial[16] also concluded that TAI reduces symptoms of LARS and improves quality of life more than conservative treatment. Furthermore,

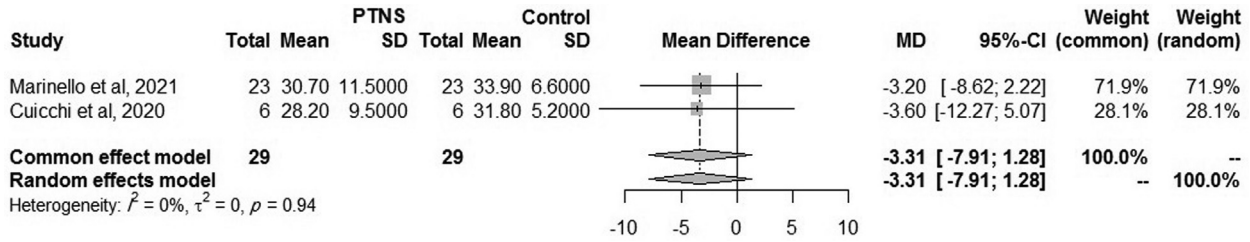

Figure 2. Forest plot depicting the weighted mean difference in the low anterior resection syndrome score between posterior tibial nerve stimulation and control group. *MD*, mean difference; *PTNS*, posterior tibial nerve stimulation.

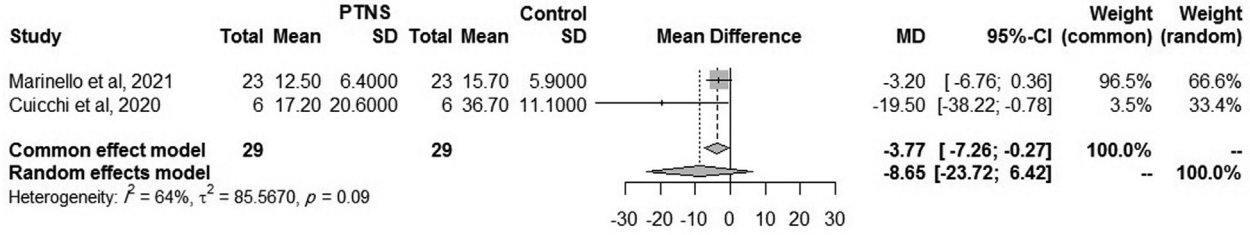

Figure 3. Forest plot depicting the weighted mean difference in fecal incontinence score between posterior tibial nerve stimulation and control group. *MD*, mean difference; *PTNS*, posterior tibial nerve stimulation.

Rosen et al[23] showed that prophylactic TAI could be used to prevent symptoms of LARS after rectal resection. The number of bowel movements during the day was still lower 12 months after discontinuing TAI compared with only supportive treatment. It has been implied that doing TAI regularly may improve colonic motility because of the mechanical effect of a high volume of water irrigating the colon and stimulating its motility.[24] Transanal irrigation was associated with the best outcomes among all treatments reviewed as the mean follow-up LARS score after TAI ranged between 12 to 22.9, lower than the LARS scores after all other treatments, which ranged between 29.4 to 33.3. Perhaps TAI should be the first attempted treatment in patients with LARS because it's simple and affordable.

One promising medication for LARS is ramosetron. Ramosetron was shown to improve symptoms of irritable bowel syndrome and was noted to have higher affinity and selectivity than other drugs.[25] These characteristics make ramosetron not only effective in the treatment of LARS but also safe. One trial[11] examined the utility of ramosetron in LARS and showed a remarkable improvement in LARS at 4 weeks compared with Kegel exercise and Sitz baths. However, limitations such as including male patients only, short follow-up, and lack of placebo control should be noted when interpreting the trial results.

Pelvic floor training managed to improve symptoms in 40% of patients with LARS at 12 months.[10] However, this improvement was comparable to the control group's (35%). Asnong et al[10] noted that the therapeutic effect of pelvic floor training was significantly better than the control group at 4 and 6 months. Yet, this superior effect was not maintained on longer follow-ups. The limited effect of pelvic floor training on LARS symptoms explained by the authors is that it addresses only some aspects that contribute to the multifactorial pathophysiology of LARS, including anatomical, neurological, physiological, and psychological factors. The authors recommended providing pelvic floor training for all patients with LARS symptoms for 3 months, yet additional evidence is needed to support this recommendation.

Another proposed treatment for LARS is probiotics.[26] Probiotics are a popular treatment for functional bowel disorders, namely irritable bowel syndrome, that aims to modulate the gut microbiota.[27] Probiotics can also alleviate bowel symptoms resembling LARS in patients with inflammatory bowel disease.[28] To examine the effect of probiotics on LARS, Yoon et al[13] compared the probiotic lactobacillus plantarum to a placebo in 36 patients with LARS. The follow-up LARS score after probiotics was similar to that in the placebo group, indicating a lack of a true benefit of probiotics in relieving LARS symptoms. Nonetheless, the lack of benefit of probiotics may be attributable to 2 main factors: the short treatment period and the use of a single bacterial strain. As the authors stated, "it is unclear how long it takes to colonize Lactobacillus plantarum in the human gut after treatment and whether colonization is sustainable." Furthermore, it has been shown that using multistrain and multispecies probiotics would achieve synergistic results and better outcomes than single-strain probiotics.[29]

The main message of the current review was to highlight the difficulty of treating LARS despite the different methods used. Low anterior resection syndrome can negatively impact a patient's quality of life after rectal cancer resection.[4] This impaired quality of life is attested to by the fact that some patients opt to have a permanent colostomy because of the severe LARS symptoms. Among the treatments reviewed in this study, TAI represents a minimally invasive treatment option for LARS that would be well accepted by the patients. Transanal irrigation has been recognized as an effective treatment for bowel dysfunction and related symptoms of constipation and FI that can be performed by the person with bowel dysfunction, and necessarily by a health care professional.[30]

Perhaps because the origin of LARS is multifaceted, treatment should also be multimodal. Combining more than one treatment method, such as PTNS with TAI and pelvic floor training, may have a synergistic effect and confer better improvement in LARS symptoms. The bowel rehabilitation program has been devised as a promising stepwise approach for treating LARS. The bowel rehabilitation program comprises 5 steps of escalating treatments in which the first step is medical management, the second step includes pelvic floor physiotherapy, biofeedback, and TAI, the third step is SNS, the fourth step includes percutaneous endoscopic cecostomy and anterograde enema, and the last step is definitive colostomy.[31]

Table III
Outcomes of compared treatments of LARS

Study	Group 1				Group 2			
	Number	Treatment	Follow-up LARS score	Follow-up FI score	Number	Treatment	Follow-up LARS score	Follow-up FI score
Pieniowski et al[16]	22	Transanal irrigation	22.9	6.4 (Wexner)	23	Conservative treatment	32.4	9.2 (Wexner)
Asnong et al, 2022[10]	50	Pelvic floor training	29.40 ± 9.69	27.1 ±16.9 (COREFO)	54	Standard care	29.70 ± 9.09	28.2 ± 15.1 m (COREFO)
Ryoo et al, 2021[11]	48	Ramosetron	29.56 ± 9.3	NR	50	Kegel maneuver and Sitz bat	34.6 ± 7.6	NR
Yoon et al, 2021[13]	19	Probiotics	33.3 ± 7.6	NR	17	Placebo	36 ± 5.3	NR
Marinello et al, 2021[12]	23	PTNS	30.7 ± 11.5	12.5 (St Marks)	23	Sham	33.9 ± 6.6	15.7 (St Marks)
Cuicchi et al, 2020[14]	6	PTNS + medical	28.2 ± 9.5	17.2 ± 20.6 (Fisi)	6	Medical treatment	31.8 ± 5.2	36.7 ± 11.1 (Fisi)
Enriquez-Navascues et al, 2020[15]	14	PTNS	30 ± 2.3	9 ± 0.8 (Vaizey)	14	Transanal irrigation	12 ± 4.1	6 ± 0.8 (Vaizey)

FI, fecal incontinence; *LARS*, low anterior resection syndrome; *NR*, not reported; *PTNS*, posterior tibial nerve stimulation.

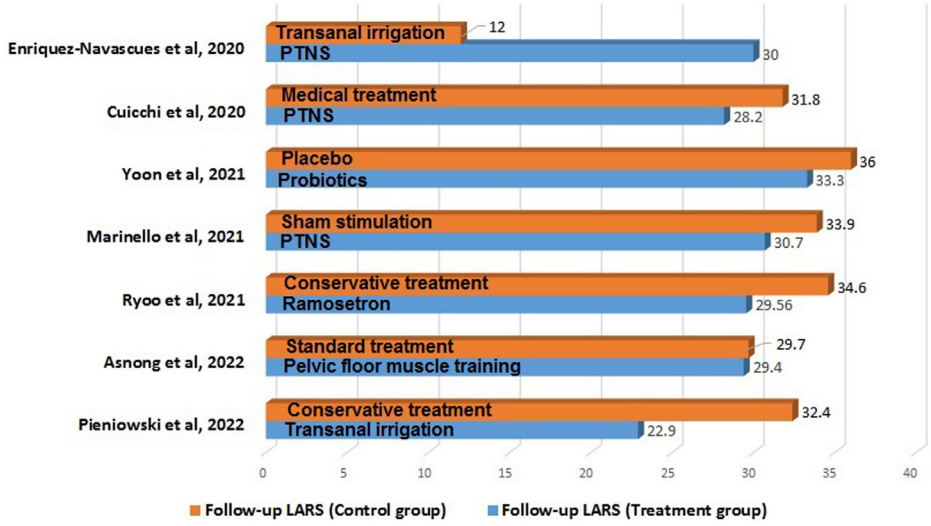

Figure 4. Follow-up low anterior resection syndrome scores in the treatment and control groups in the trials reviewed. *LARS*, low anterior resection syndrome; *PTNS*, posterior tibial nerve stimulation.

The limitations of this systematic review include the small number of studies reviewed and the heterogeneous nature of the interventions examined for treating LARS. The studies that investigated PTNS compared it with conservative treatment; this is an unclear term because the magnitude and amount of conservative treatment could vary, which may be a problem when studying the effect of different treatments on LARS.

In conclusion, based on moderate-quality level I evidence, TAI was associated with improvement in LARS according to 2 trials, and ramosetron showed promising short-term results in 1 trial. Posterior tibial nerve stimulation had a marginal benefit compared with standard care. In contrast, pelvic floor training was associated with short-term symptomatic improvement, and probiotics showed no tangible improvement in LARS symptoms. Firm conclusions cannot be drawn due to the small number of trials published.

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Conflict of interest/Disclosure Statement

Dr Wexner reports receiving consulting fees from ARC/Corvus, Astellas, Baxter, Becton Dickinson, GI Supply, ICON Language Services, Intuitive Surgical, Leading BioSciences, Livsmed, Medtronic, Olympus Surgical, Stryker, and Takeda and receiving royalties from Intuitive Surgical and Karl Storz Endoscopy America.

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