Systematic Review/Meta-analysis

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Perioperative bowel regimens following posterior spinal fusions for adolescent idiopathic scoliosis: a systematic review

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Background: Bowel morbidity after posterior spinal fusions (PSFs) for adolescent idiopathic scoliosis (AIS) delays the advancement of postoperative oral diet and discharge. This systematic review aims to investigate the effectiveness of perioperative bowel regimens in reducing length of stay and postoperative bowel morbidity in these patients.

Materials and methods: We systematically searched MEDLINE, Embase, Cochrane, SPORTDiscus, and CINAHL for articles reporting on clinical results of PSFs for AIS patients. Demographic data, mean operative time and estimated blood loss, length of stay, time to first flatus and/or bowel movement, first oral intake, and postoperative pain scores were extracted from the selected studies.

Results: Six articles (n = 468 patients) met the final inclusion criteria. Only one study, which assessed oral methylnaltrexone, reported a significant reduction in the mean hospital length of stay (0.60 days, $P < 0.05$) and postoperative abdominal distension (17% versus 40%, $P < 0.05$); however, it was also the only study to report a significantly increased mean operative time (38.9 min, $P = 0.03$) and estimated blood loss (111.1 mL, $P = 0.05$) compared to the treatment group. Time to flatus, regular diet, postoperative opioid consumption, and pain scores did not differ significantly in any of the reported studies.

Conclusion: There is limited evidence to demonstrate any specific perioperative bowel regimen will decrease postpreparative bowel morbidity and/or length of stay. While not a treatment in isolation, oral methylnaltrexone may be a safe and effective adjunct to standard postoperative bowel regimens and may have a better patient tolerance profile.

Keywords: adolescent idiopathic scoliosis, bowel morbidity, perioperative bowel regimen, posterior instrumented fusion

Introduction

Adolescent idiopathic scoliosis (AIS) is the most common type of pediatric scoliosis[1]. Ten-year outcome studies have shown that spinal fusion surgery for AIS leads to substantially better patient-reported outcome measures, curve correction, and quality of life when compared to unoperated AIS patients[2]. Effective pain control, management of opioid-related side effects, and delayed mobilization are only a few of the perioperative difficulties associated with surgical correction of AIS. This potentially leads to elevated morbidity, increasing length of hospital stays, and a delayed return to normal functioning[3]. Recent evidence has shown that the average length of stay for a patient undergoing posterior spinal fusion (PSF) for AIS is as high as 5–6 days[4]. Bowel morbidity, such as abdominal pain and constipation, after PSFs greatly delays the advancement of postoperative oral diet and discharge of AIS patients[5,6].

In turn, the recent trend in postoperative care of AIS patients is the implementation of enhanced recovery after surgery (ERAS) protocols[7]. ERAS protocols tend to initiate an oral diet as soon as possible to improve bowel function and shorten the length of hospitalization. While bowel movement before discharge is not a requisite of most ERAS protocols, the associated perioperative discomfort can delay mobility targets for safe discharge.

It is known that gastrointestinal (GI) concerns affect more than half of AIS patients following PSFs, in turn limiting the effectiveness of an early oral diet[8–10].Therefore, greater attention needs to be paid to effective and safe bowel regimens to reduce negative postoperative GI symptoms. Most existing evidence focuses on the use of chewing gum as a treatment. A recent systematic review and meta-analysis showed that chewing gum does not significantly affect bowel morbidity or length of stay for AIS patients following PSFs[11]. However, different perioperative bowel regimen adjuncts

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have demonstrated promising results[12,13]. These different adjuncts can potentially enhance recovery by minimizing bowel complications and/or reducing hospital stays; therefore, understanding the effects of various adjuncts can lead to tailored interventions that optimize induvial outcomes and overall satisfaction during the recovery process.

This study aims to provide a systematic review of the literature and investigate the effectiveness of perioperative bowel regimen adjuncts in reducing length of stay and postoperative bowel morbidity in AIS patients undergoing PSFs.

Materials and methods

We followed the protocol outlined in the Cochrane Handbook for Systematic Reviews of Interventions[14]. We report our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[15].

Systematic search

With the help of a medical librarian, a thorough search plan was implemented. Adhering to PRISMA guidelines, the systematic search strategy was conducted using MEDLINE®, Embase®, CENTRAL®, SPORTDiscus®, and CINAHL® electronic databases. Details of the search strategy can be found in Supplemental Digital Content, Appendix 1 (http://links.lww.com/MS9/A692). Reference lists of relevant studies were screened to identify additional published studies. All identified records from the electronic search were downloaded and imported into Covidence systematic review software. Our study protocol was registered with PROSPERO with the identifier # CRD42024515792.

Inclusion/exclusion criteria

Inclusion and exclusion criteria were defined and agreed upon by all authors. Our systematic review employed the following inclusion criteria: patients < 18 years of age, diagnosis of AIS, and studies with a comparative arm of the outcomes of a perioperative bowel regimen adjunct for AIS patients who underwent PSFs. The inclusion of our study dates was up until 29 Feb 2024.

Articles that met any of the following exclusion criteria were excluded from the systematic review: non-English language articles, treatment or control arm of the trial comprised <10 patients, studies lacking a comparative arm, studies including neuromuscular or syndromic scoliosis, cadaveric studies, revision surgery, case reports, review articles, experimental studies, conference abstracts, comments, and editorials.

Article screening

Duplicate articles were removed from the systematic search results via Covidence. The remaining titles and abstracts were independently screened by two authors (LB and AA) using the previously established inclusion and exclusion criteria. Outstanding discrepancies were resolved via the study's senior author. The full texts of the articles were then reviewed. All remaining full-text articles that met criteria were included in the systematic review.

Data extraction and quality appraisal

Data extraction was performed from the included studies. Contingent on their availability, the following data and outcomes were recorded: first author, publication year, the number of subjects, age, gender distribution, mean operative time, mean estimated blood loss, BMI, length of stay, time to first flatus and/or bowel movement, first oral intake, postoperative abdominal pain scores, and postoperative nausea scores. Given the potential heterogeneity of outcomes and the limited number of studies available on this topic, a meta-analysis was not performed. Assessment of the risk of bias in each study was done using the Methodological Index for Non-randomized Studies (MINORS)[16] for the two retrospective cohort studies and the Cochrane risk-of-bias tool[17] for the randomized controlled trials (RCTs). Following the approach of previous studies[18], a MINORS score of < 14 was considered poor quality, 15–22 moderate quality, and 23–24 good quality.

Statistical analysis

We calculated interobserver agreement for the assessments of study eligibility using the Cohen κ coefficient and interpreted the κ values according to Landis and Koch[19].

Results

Systematic search and article screening

The systematic search yielded 517 total articles with 145 duplicate titles removed (Fig. 1). The remaining 372 articles were screened by titles and abstracts, with 365 excluded. The remaining seven articles were then assessed for eligibility based on a full-text review. One additional study was excluded following a full-text review for failure to include our target patient population[20]. A total of six articles were included in the review. Interobserver agreement between the reviewers for study eligibility was excellent ($\kappa = 0.89$).

Of the six included articles, three were RCTs assessing the utility of including chewing gum as a post-operative bowel regimen adjunct[21–23]. One RCT assessed the use of a preoperative bowel preparation to no preoperative bowel intervention[13], and two non-randomized studies specifically assessed postoperative bowel regimen adjuncts[12,24]. No funding was received for any of the studies.

Risk of bias

Both retrospective cohort studies scored 18/24 on MINORS, indicating a moderate risk of bias (Table 1). Given the nature of the studies, all three RCTs using gum as an intervention had unblinded outcome assessors (participants). Therefore, there is potential for some bias concerning patient-reported outcomes such as abdominal pain and nausea scores (Figs. 2, 3). Only one included study, Smith *et al* (2013), demonstrated an overall low risk of bias across all measured domains.

Study demographics

Characteristics of the included studies are summarized in Table 2. A total of 468 patients with AIS undergoing PSF were included in this review. The mean age of the participants was 14.5 ± 1.2 years, and 331 (81%) were female in five trials. One included study did not report the mean age, age range, or sex distribution[13].

In Jennings *et al* (2015) [Gum 1], 42 (51%) patients were randomized to chew sugar-free gum for 15–30 minutes starting on the first postoperative day until discharge as compared to 41

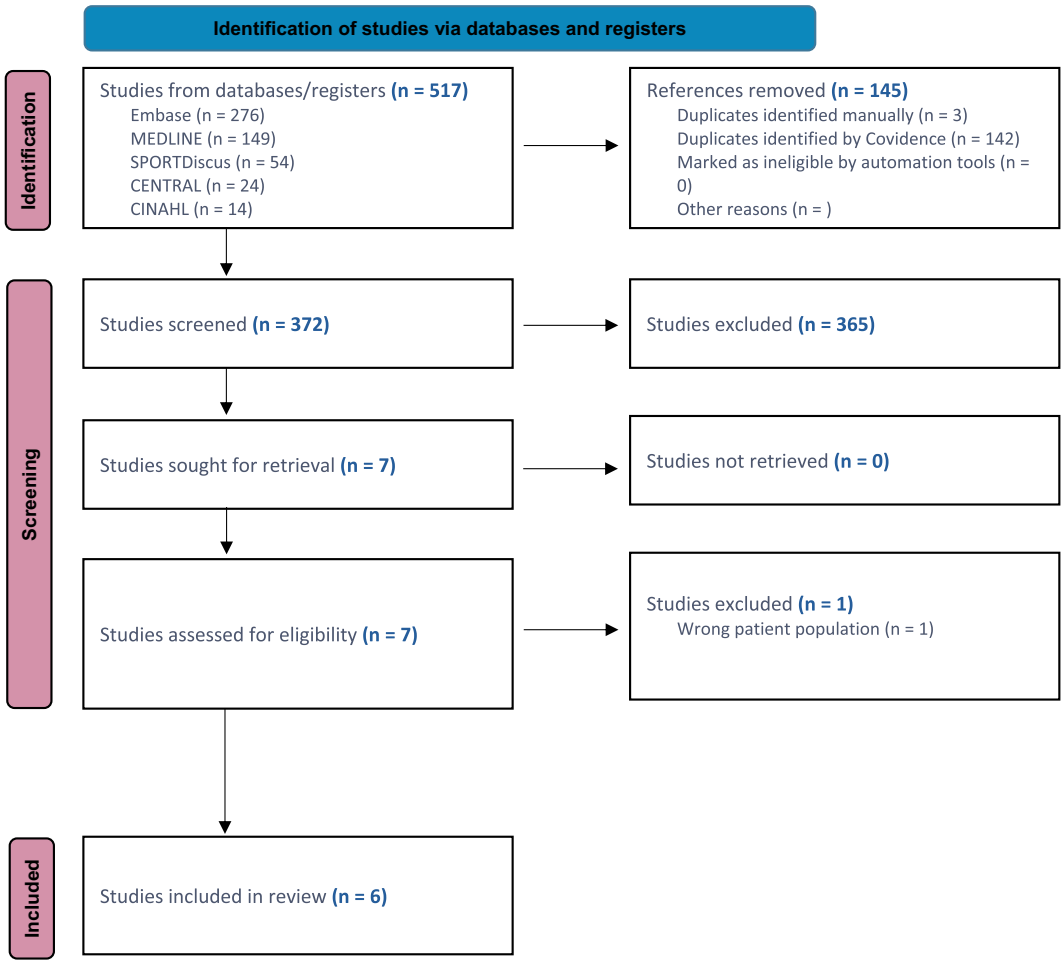

Figure 1. PRISMA flow diagram.

(49%) given no gum postoperatively. In Chan *et al* (2017) [Gum 2] and Meng *et al* (2018) [Gum 3] studies, 93 patients were randomly assigned to sugar-free chewing gums for 30 minutes, three times a day for three days postoperatively versus 92 patients given no treatment postoperatively.

Smith *et al* (2013) reported an RCT assessing a preoperative bowel preparation with 30 patients randomized to receive polyethylene glycol 3350 the night before surgery compared to 30 patients who received no preoperative bowel preparation. Five patients were excluded from the study because of incomplete data, which left 27 patients (49%) in the treatment group and 28 (51%) patients in the control arm.

Lin *et al* (2021) compared 52 patients who had received postoperative weight-based oral methylnaltrexone to 52 case-matched controls. Rhodes *et al* (2016) describe two separate postoperative bowel regimen adjuncts where 20 patients received 17 g of polyethylene glycol 3350 (PEG) mixed in eight ounces of a clear liquid of the patient's preference compared to 16 patients who received 30 mL of mineral oil (MO) mixed in pudding and ice cream.

Interventions

Gum chewing[21-23]

All 3 gum studies assessed the mean operation duration (min), estimated blood loss (mL), and levels fused and found no significant difference between the intervention and control groups (Table 3). Gum 1 found that postoperative chewing gum led to a significant reduction in the average time to first bowel movement

Table 1

Risk of bias and quality assessment using the methodological index for non-randomized studies (MINORS) criteria

Study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss of follow up less than 5%	Prospective calculation of the study size	Additional criteria for comparative studies				Total
									An adequate control group	Contemporary group	Baseline equivalent of groups	Adequate statistical analysis	
Lin, 2021	2	2	0	2	0	2	2	0	2	2	2	2	18
Rhodes, 2016	2	2	0	2	0	2	2	0	2	2	2	2	18

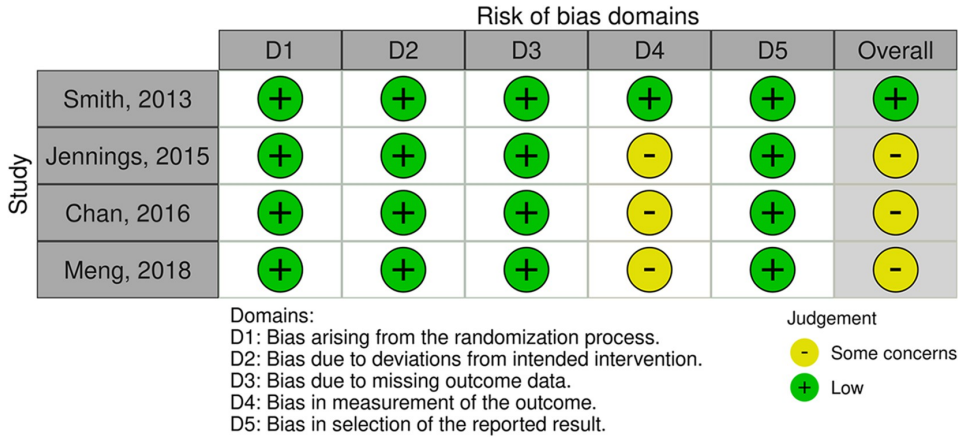

Figure 2. Appraisal of the risk of bias of the included trials using the Cochrane risk-of-bias tool (randomized controlled trials).

(30.9 hours, $P = 0.04$); however, Gum 2 and Gum 3 found no significant difference. Gum 3 reported significantly reduced 24-hour abdominal pain scores (0.9, $P = 0.027$); however, this difference did not remain at the 48- and 72-hour mark. Gum 1 and Gum 2 found no significant difference in postoperative abdominal pain scores when comparing between similar time intervals. Additionally, none of the gum studies found any significant difference with regard to length of stay (LOS), time to flatus, postoperative nausea scores, or scheduled and/or as-needed bowel medications. Furthermore, only Gum 2 and Gum 3 reported on time to solids, time to liquids, and patient-controlled analgesia opioid use and found no significant difference between groups. Gum 2 was the only gum study to report on abdominal distension and found no significant difference between groups.

Oral methylnaltrexone[12]

When assessing operative parameters, Lin *et al* (2021) found that the control group had significantly greater mean operative time (38.9 min, $P = 0.03$) and estimated blood loss (111.1 mL, $P = 0.05$) compared to the treatment group (Table 3). Lin *et al* (2021) was also the only study to find that a postoperative bowel regimen adjunct (oral methylnaltrexone) resulted in a significant reduction in the mean hospital LOS (3.09 versus 3.69 days, $P < 0.05$) (Table 4). They also found that oral methylnaltrexone led to a significantly greater percentage of patients having a bowel movement by postoperative day two compared to the control group (59% versus 30%, $P < 0.005$) as well as significantly decreased postoperative abdominal distention (17% versus 40%, $P < 0.05$). However, they did not find any significant difference between groups with regard to morphine equivalent usage postoperatively, the average maximum FACES pain scale, or scheduled and/or as-needed bowel medications.

Polyethylene glycol 3350 (PEG) versus mineral oil (MO)[24]

Rhodes *et al* (2016) found no significant difference when comparing PEG and MO with regard to patient LOS, time to first bowel movement, time to regular diet, morphine equivalent usage postoperatively, or scheduled and/or as-needed bowel medications.

Preoperative PEG[13]

Smith *et al* (2013) found no significant difference for LOS between groups. However, they did find that a preoperative bowel prep led to a significant reduction in the average time to first bowel movement (3.96 versus 4.64 days, $P = 0.03$) as well as a significant decrease in the mean postoperative weight gain (2.65 versus 3.75 lbs, $P = 0.016$). They also reported a statistically significant decrease in the mean number of postoperative bowel

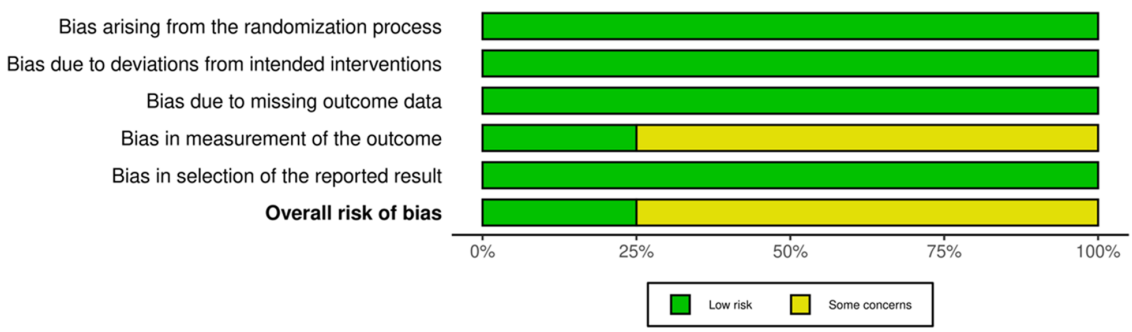

Figure 3. Risk of bias assessment.

Table 2

Baseline characteristics of included studies

First author (name, year)	Study period	Country	Study design, LoE	Mean age, yr	% female	Intervention group	Control group
Lin, 2021	May 2011–July 2019	US	RC, III	14	77	Weight-based daily PO methylnaltrexone, before breakfast, starting on POD1 ($n = 52$) (weight < 38 kg = 150 mg; between 38 and < 62 kg = 300 mg; ≥ 62 kg = 450 mg)	No postoperative treatment ($n = 52$)
Meng, 2018 (Gum 3)	March 2016–June 2017	China	RCT, II	13	80	Chewed sugarless gum for 20–30 minutes at 8:00, 12:00, and 18:00 from POD1 to POD3 ($n = 63$)	No postoperative treatment ($n = 62$)
Chan, 2017 (Gum 2)	January 2016–June 2016	Malaysia	RCT, I	16	85	Chewed gum for ~30 minutes every 4 to 6 hours from 2 hours postoperation to POD3 ($n = 30$)	No postoperative treatment ($n = 30$)
Rhodes, 2016	June–May (year not specified)	US	RC, III	14	83	7 g of PEG mixed in 8 ounces of a clear liquid of the patient's preference starting on POD2 ($n = 20$)	30 mL of MO mixed in pudding and ice cream starting on POD2 ($n = 16$)
Jennings, 2015 (Gum 1)	July 2009–July 2013	US	RCT, II	14	83	Chewed gum for 15–30 minutes 5 times a day beginning on POD1 ($n = 42$)	No postoperative treatment ($n = 41$)
Smith, 2013	June 2007–July 2009	US	RCT, II	NR	NR	Preoperative bowel preparation using NuLytley, beginning the night before surgery ($n = 27$)	No preoperative bowel preparation ($n = 28$)

LoE, level of evidence; NR, not reported; RC, retrospective cohort; RCT, randomized controlled trial; POD, postoperative day; PEG = polyethylene glycol 3350; MO = mineral oil.

medications (4.31 versus 7.11, $P = 0.023$) but did note no significant difference in the number of suppositories or enemas used between groups.

Discussion

Results of our systematic review show that there is a paucity of literature supporting any given perioperative bowel regimen adjuncts to decrease postoperative bowel morbidity and/or length of stay in AIS patients undergoing PSFs. The use of chewing gum to simulate oral intake and induce bowel movement by stimulating salivary and pancreatic secretions and the cephalic-vagal response is well-known[25–27]. In our systematic review, Gum 1–3 found that chewing gum does not have a significant effect on postoperative abdominal pain, nausea, or hospital stays after PSFs. These findings were confirmed by a meta-analysis done by Tong *et al* (2023) that analyzed these three papers[11]. Nonetheless, many ERAS protocols continue to advise the use of chewing gum to speed up bowel recovery following GI, urological, transperitoneal vascular, obstetric, and gynecologic surgeries[7,28–32]. Within the framework of current ERAS protocols, emphasis is placed on early discharge; however, postoperative bowel management is imperative to prevent discomfort and potential emergency room re-presentation if not adequately addressed for these patients. Future investigations may enhance these results to warrant consideration of incorporation into modified ERAS protocols.

Opioid-induced constipation (OIC) is known to play a significant role in postoperative GI issues following surgery. This mechanism is well-understood as opioids activate mu-opioid receptors in the GI tract, which in turn result in decreased peristalsis and subsequent constipation[33,34]. Unfortunately, the literature has shown that around half of patients with OIC are unsuccessfully treated by traditional laxatives and stool softeners[35]. In turn, more aggressive treatments such as suppositories and enemas tend to be used for patients with OIC which can negatively affect a pediatric patient's hospital experience and increase their length of stay[8]. Lin *et al* (2021) carried out a novel investigation in the pediatric population; however, there is evidence in adult studies showing similar results with methylnaltrexone in the treatment of OIC[33,34]. Despite these promising results, this study reported a significantly higher average operative time in the control group compared to the treatment group, which can in turn bias length of stay, bowel function, and abdominal distension.

Smith *et al* (2013) happened to be the only included study to look at preoperative bowel preparation. The study did show a difference in the number of bowel medications required and the number of days to the first bowel movement when

Table 3

Mean estimated blood loss (EBL), operative duration, and levels fused

First author (name, year)	EBL (mL)			Operative duration (min)			Levels fused		
	I	C	P value	I	C	P value	I	C	P value
Lin, 2021	340.3 ± 170.3	451.4 ± 240.9	**0.05**	230.1 ± 80.5	269.0 ± 95.3	**0.03**	11.8 ± 1.7	11.3 ± 3.3	0.35
Meng, 2018	887.1 ± 93.3	909.3 ± 84.3	0.16	223.9 ± 31.8	218.9 ± 32.1	0.38	10.1 ± 2.1	10.2 ± 1.9	0.85
Chan, 2017	1009.7 ± 581.0	933.4 ± 552.2	0.60	153.8 ± 48.9	157.7 ± 47.7	0.75	9.7 ± 2.3	9.9 ± 2.3	0.82
Jennings, 2015	1037 ± 973.1	885 ± 471.2	0.37	258 ± 47.3	270 ± 57.1	0.28	10.26 ± 1.93	10.31 ± 2.00	0.90

I = intervention group; C = control group; NR = not reported.

Table 4
Postoperative outcomes

First author (name, year)	LOS			Time to first BM			Time to flatus			Time to regular diet			Postoperative opioid consumption			Postoperative pain scores			Postoperative abdominal distension/weight difference			Postoperative PRN GI medications		
	I	C	*P*-value	I	C	*P*-value	I	C	*P*-value	I	C	*P*-value	I	C	*P*-value	I	C	*P*-value	I	C	*P*-value	I	C	*P*-value
Lin, 2021	3.09 ± 0.66 (d)	3.69 ± 0.80 (d)	**< 0.05**	59% (by POD2)	30% (by POD2)	**< 0.05**	NR	NR	NR	NR	NR	NR	0.86 ± 0.37 (per hour)	0.77 ± 0.26 (per hour)	0.18	5.8 ± 1.7 (FACES)	6 ± 1.7 (FACES)	0.39	17% (abdominal distension)	40% (abdominal distension)	**< 0.05**	44%	50%	0.43
Meng, 2018	7.1 ± 1.5 (d)	7.0 ± 1.4 (d)	0.954	128.4 ± 44.3 (h)	136.2 ± 41.5 (h)	0.307	59.9 ± 23.1 (h)	53.6 ± 17.2	0.09	30.6 ± 9.9 (h)	32.3 ± 12.5 (h)	0.406	258.1 ± 24.4 (mcg PCA morphine by POD2)	261.5 ± (24.4 mcg PCA by POD2)	0.445	4.2 ± 1.7 (POD1 abdominal pain score)	5.1 ± 2.6 (POD1 abdominal pain score)	**0.027**	NR	NR	NR	NR	NR	NR
Chan, 2017	74:12 ± 10:43 (h:m)	69:34 ± 6:22 (h:m)	0.052	115:29 ± 31:04 (h:m)	113:08 ± 39:57 (h:m)	0.814	36:47 ± 15:47 (h:m)	35:03 ± 16:15 (h:m)	0.684	28:00 ± 10:05 (h:m)	30:18 ± 9:45 (h:m)	0.391	29.4 ± 24.2 (mg PCA morphine by POD2)	31.5 ± 17.9 (mg PCA morphine by POD2)	0.583	3.1 ± 2.3 (POD2 abdominal pain score)	2.5 ± 2.5 (POD2 abdominal pain score)	0.396	70.7 ± 8.3 (cm by POD2)	71.2 ± 8.5 (cm by POD2)	0.816	NR	NR	NR
Rhodes, 2016	122.5 (h)	123.8 (h)	NS	10% (before discharge)	25% (before discharge)	0.374	NR	NR	NR	48.8	57.4	NS	1.87	2.2	NS	NR	NR	NR	NR	NR	NR	2 (1-3)	2 (1.25-3)	NS
Jennings, 2015	4.4 ± 0.8 (d)	4.5 ± 0.8 (d)	0.54	145.9 ± 63.1 (h)	176.8 ± 71.7 (h)	**0.04**	55.2 ± 19.6 (h)	62.3 ± 21.0 (h)	0.12	NR	NR	NR	NR	NR	NR	2.8 ± 2.5 (POD2 abdominal pain score)	3.7 ± 2.3 (Pod2 abdominal pain score)	0.08	NR	NR	NR	2.3 ± 3.6	2.3 ± 2.5	0.99
Smith, 2013	6.00 ± 0.96 (d)	6.29 ± 1.01	0.288	3.96 ± 1.32 (d)	4.64 ± 0.91 (d)	**0.03**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2.65 ± 1.44 (lbs)	3.75 ± 1.79 (lbs)	**0.016**	4.31 ± 3.33	7.11 ± 5.20	**0.023**

I = intervention group; C = control group; NR = not reported; NS = not significant; LOS = length of stay; BM = bowel movement; GI = gastrointestinal; POD = postoperative day; h = hours; d = days; cm = centimeter; lbs = pounds.

comparing the two groups. However, in its entirety, this study did not demonstrate a significant reduction in bowel morbidity or hospital length of stay for AIS patients receiving bowel preparation before PSF surgery. Also, the authors noted that most of the patients described bowel preparation as an unlikable process. Previous research has similarly demonstrated that bowel preparations intended for adult usage are ineffective when used on pediatric patients, primarily due to the unpleasant taste of the solution and/or the high volume needed[36]. Furthermore, studies have shown that PEG-based solutions have very poor compliance in the pediatric population[36,37]. Therefore, given the lack of a significant decrease in bowel morbidity or length of stay in conjunction with potential poor compliance, preoperative bowel regimens do not appear to be an effective option for AIS patients undergoing PSFs.

Finally, Rhodes *et al* (2016) compared two postoperative bowel regimens. PEG has been found to be favored over MO for functional constipation; however, the same is not as well documented for postoperative ileus. Both medications are administered orally, and therefore, a lack of appetite or nausea may lead to poor compliance or reduced dose intake[38,39]. However, Rhodes *et al* (2016) reported that no significant differences were found in this study comparing PEG and MO in the prophylaxis of postoperative constipation. Similarly, a recent ERAS study on AIS patients undergoing PSF demonstrated that prophylactic postoperative laxatives do not significantly affect the time to first bowel movement[40].

This review is not without limitations. The moderate risk of bias associated with unblinded nature of most of the studies can affect the results. Non-blinded assessments can exaggerate treatment effects, with subjective outcomes like pain being particularly vulnerable. This bias can lead to overestimation of benefits in a study, affecting the reliability of findings and potentially skewing clinical decision-making. Also, the inclusion of diverse interventions may increase heterogeneity, complicating the interpretation of their effectiveness and making it challenging to draw definitive conclusions about their role in AIS management.

Conclusion

There is limited evidence to demonstrate any specific perioperative bowel regimen adjuncts will decrease postpreparative bowel morbidity and/or length of stay in AIS patients undergoing PSFs. While not a treatment in isolation, oral methylnaltrexone may be a safe and effective adjunct to standard postoperative bowel regimens and may have a better patient tolerance profile but requires further extensive research to draw definitive conclusions. As of now, available evidence does not help determine the optimal management strategy in terms of bowel regimens after surgery in AIS. As ERAS protocols continue to develop, large multicenter randomized investigations are warranted to determine the optimal perioperative bowel regimen for these patients.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author's contribution

Conception and design: L.R.B., A.A.P., A.I., P.T.; administrative support: K.M., S.S., P.R., D.B., T.C., P.T.; provision of study materials: K.M., S.S., P.R., D.B., T.C., P.T.; collection and assembly of data: L.R.B., A.A.P., A.I., P.T.; data analysis and interpretation: L.R.B., A.A.P., A.I., P.T.; manuscript writing: all authors; final approval of manuscript: all authors.

Conflicts of interest disclosure

All the authors declare to have no conflicts of interest relevant to this study.

Research registration unique identifying number (UIN)

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Guarantor

Lee Benaroch.

Provenance and peer review

Not invited.

Data availability statement

Available upon request.

Level of evidence

Level III – Systematic Review.

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