Systematic review

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Preoperative bowel stimulation prior to ileostomy closure to restore bowel function more quickly and improve postoperative outcomes: a systematic review

T. Rombey*, I. G. Panagiotopoulou†, D. Hind‡ and N. S. Fearnhead†

*The School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK, †Cambridge University Hospitals NHS Foundation Trust, Addenbrookes Hospital, Cambridge, UK, and ‡Sheffield Clinical Trials Research Unit, University of Sheffield, Sheffield, UK

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Abstract

Aim Closure of a diverting ileostomy following restorative surgery is often associated with significant short-term morbidity and variable long-term bowel function. The aim of this systematic review was to investigate if preoperative stimulation of the defunctioned bowel restores bowel function more quickly after ileostomy closure and improves postoperative outcomes when compared with standard preoperative care.

Method MEDLINE, Embase, CENTRAL, Google Scholar and ClinicalTrials.gov were searched for studies evaluating preoperative bowel stimulation in patients with a temporary ileostomy after low anterior resection or ileal pouch–anal anastomosis, regardless of their design, publication type or language. Study selection, data extraction and study assessment were performed by one reviewer and verified by another. Study results were synthesized narratively. The GRADE approach was used to assess the quality of evidence.

Results Eight studies involving a total of 267 participants were included. The studies had a moderate to high risk of bias and were of varying methodological quality. Preoperative stimulation of the defunctioned bowel reduced the time to postoperative restoration of bowel function and the length of hospital stay when compared with standard preoperative care. Other functional outcomes and postoperative complication rates were similar to those of standard preoperative care. The overall quality of evidence was very low.

Conclusion Despite these promising early results, there is insufficient high-quality evidence to recommend routine implementation of preoperative bowel stimulation in clinical practice. Nevertheless, there is no evidence suggesting that the intervention worsens outcomes or is unsafe, paving the way for rigorous assessment of effectiveness, acceptability and cost-effectiveness within the context of well-designed clinical trials.

Keywords Preoperative bowel stimulation, ileostomy closure, low anterior resection, ileoanal pouch anastomosis, rectal cancer, ulcerative colitis

Introduction

A temporary ileostomy is usually performed to divert the faecal stream above a low rectal, coloanal or ileoanal pouch anastomosis with the intention of mitigating the serious complication of anastomotic leakage [1].

The most frequent indications for temporary ileostomy are low anterior resection (LAR) for rectal cancer and restorative proctocolectomy with ileoanal pouch anastomosis (IPAA) for ulcerative colitis [2,3]. In England, more than 8500 patients are diagnosed with rectal cancer each year [4]. More than half undergo a major resection; 83% of these have a temporary stoma that is closed within 18 months in only 65% of patients [4]. Approximately 6500 patients per year are diagnosed with ulcerative colitis in the United Kingdom [5], of whom 10–30% undergo surgery within 10 years after their diagnosis [6]. IPAA is the most common restorative procedure after colectomy for ulcerative colitis in the UK [7,8]. In England, a temporary ileostomy is performed in 81% of patients at the time of pouch surgery [9]. A study from Germany found that the ileostomy is subsequently closed in 86% of patients [10], although many centres are now advocating ileoanal pouch surgery without temporary diversion by focusing on proactive management of early septic complications [11].

Correspondence to: Tanja Rombey, The School of Health and Related Research (ScHARR), University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK.
E-mail: trombey@web.de

Living with an ileostomy significantly affects quality of life [12,13] and is associated with significant morbidity, such as dehydration, acute kidney injury and impaired long-term renal function [14–16]. Ileostomy closure is associated with a mortality rate of less than 1% [3,17–19], but 20% of patients experience complications, including small bowel obstruction, wound sepsis, ileus, anastomotic leakage, fistula, perforation, abscess, bleeding or hernia [3,17–19]. Even after successful ileostomy closure, most patients with ileoanal pouches experience diarrhoea, faecal incontinence or nocturnal bowel movements [20], while those who have had rectal cancer surgery often experience symptoms of anterior resection syndrome, such as frequent and urgent bowel movements, faecal incontinence or evacuatory dysfunction [21].

In patients without complications related to the index surgery, one means of reducing ileostomy-associated morbidity would be to close the temporary ileostomy early (within a few weeks) [22]. The EASY trial demonstrated that very early closure (within 13 days of the index procedure) is associated with fewer overall complications [23], although paradoxically there was no reported effect on quality of life. [24].

In patients who undergo delayed ileostomy closure, it is possible that preoperative stimulation of the defunctioned colon may be beneficial. The rationale for this is that it may reverse the microbial dysbiosis and villous atrophy observed in defunctioned bowel [25,26], as these factors impair absorptive capacity [27]. Alteration in the microbiome of diverted bowel has been well-studied with *Clostridium difficile* infection, a recognized complication of ileostomy closure [28]. Defunctioned bowel also undergoes luminal shrinkage, with some loss of motility [27], contractility and smooth muscle strength [26], all of which may contribute to the high complication rates following reversal [29]. Stimulation of defunctioned bowel with saline or diluted ileostomy output was found to improve ileal absorption and motility in an early study [27]; the authors concluded that it 'would likely hasten adaptation to the (ileostomy) closure'.

The aim of this systematic review was to determine whether or not preoperative bowel stimulation improves postoperative outcomes and reduces complications after ileostomy closure in patients with a temporary ileostomy after LAR or IPAA when compared with standard preoperative care.

Method

Protocol and registration

The review was registered in PROSPERO (CRD42018095127) and was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions [30]. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31].

Eligibility criteria

Studies were included regardless of their design, publication year, language, type or status if they:

1 included patients with a temporary ileostomy after LAR or IPAA;
2 compared preoperative bowel stimulation (defined as preoperative intervention involving the instillation of substances through the efferent limb of the stoma with standard preoperative care (as defined by the study authors);
3 had measured and reported results for at least one of the review's outcomes.

The primary outcome was time to restoration of bowel function, which was subdivided into four factors: times to tolerance of liquids, tolerance of solid food, passing flatus and passing stool. The secondary outcomes were other functional outcomes, for example stool frequency, further patient-relevant outcomes, postoperative length of stay (LOS) and complications.

Literature search

MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar and ClinicalTrials.gov were searched for eligible studies (see Data S1 in the online Supporting Information for the full search strategy). No limits, such as language restrictions, were applied. The date of the last search was 23 October 2018.

In addition, annual meeting abstracts of the Association of Coloproctology of Great Britain and Ireland, the American Society of Colon and Rectal Surgeons and the European Society of Coloproctology were screened and experts in the field of coloproctology, including authors of the included studies, were contacted via email to identify further eligible studies.

Study selection and data collection process

One reviewer (TR) performed the searches and imported all records into EndNote. After removal of duplicates, the reviewer screened the titles and abstracts of all remaining unique records and, if potentially relevant, their full-texts. Another reviewer (IP) independently screened a randomly generated 10% sample in the same way to verify the first reviewer's accuracy. Discrepancies were resolved by discussion until consensus

was reached. As the level of agreement between the reviewers was 93.5% after title and abstract screening and 100% after full-text screening, a second review for the remaining records was deemed unnecessary.

Data were collected and extracted directly into the results tables by one reviewer (TR) and verified by another reviewer (IP). Discrepancies were resolved by discussion until consensus was reached. In case of ambiguities or missing key information, the corresponding authors were contacted via email where possible. For a list of all data items see Data S2.

Risk of bias in individual studies

The risk of bias of randomized controlled trials (RCTs) was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [30] and the risk of bias in nonrandomized studies (NRS) with the 'Risk Of Bias In Nonrandomized Studies – of Interventions' (ROBINS-I) tool [32]. The methodological quality of case reports was assessed with the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports [33]. The assessment was performed by one reviewer (TR) and was verified by another reviewer (DH). Discrepancies were resolved by discussion until consensus was reached.

Synthesis of results

A meta-analysis was not performed, as it is not appropriate to combine results of RCTs and NRS [34] and the literature search failed to identify enough (i.e. two or more) RCTs that were sufficiently methodologically and clinically homogeneous.

Therefore, the results of all studies were synthesized narratively for each of the prespecified outcomes if reported by at least one study. Timing and effect measures as defined by the study authors were used. Studies were subgrouped into those that concerned LAR or IPAA as variation in their results through clinical and methodological heterogeneity was anticipated.

Risk of bias across studies

The risk of bias was not formally assessed as fewer than 10 studies were included in our analysis [30].

Additional analyses

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence for each of the predefined outcomes [35]. Grading was performed by one reviewer (TR), who followed the GRADE handbook [36], and verified by the remaining authors.

Results

Search and study selection

The systematic literature search and study selection process are presented in a PRISMA flow diagram [31] (Fig. 1). We included seven published studies from three bibliographic databases [37–43] and an ongoing study identified from ClinicalTrials.gov [44], for which the corresponding author provided results of an interim analysis that had been presented at the 22nd National Meeting of the Spanish Association Foundation of Coloproctology in Bilbao, Spain on 9 May 2018.

We also identified a study protocol and a trial abstract for two ongoing RCTs for which no results were available. They were both registered in ClinicalTrials.gov (NCT02559635 [45] and NCT02751736 [46]) and investigate preoperative bowel stimulation with saline [45] and probiotics [46], respectively, in patients with a temporary ileostomy after LAR.

Study and patient characteristics

A detailed overview of the study and patient characteristics can be found in Table 1. Of the eight included studies, five were comparative studies, with two RCTs [38,43] and three NRS [39,42,44], and three were case reports [37,40,41]. Two studies were registered in ClinicalTrials.gov (NCT01881594 [38] and NCT03424447 [44]). Information on the funding source was available for two studies [39,44], and on ethics approval for all comparative studies [38,42–44] except one [39].

The number of included patients ranged from one (in the three case reports) to 100. In four studies the included patients had a temporary ileostomy after IPAA [39,40,42,43], and in four studies after LAR [37,38,41,44]. Mean patient age ranged from 26 to 65 years, which can be explained by the different age of onset of the diseases. About 60% of all patients were men.

Description of the intervention

In five studies, preoperative bowel stimulation was performed once daily with physiological saline [37,38,41,43,44]. In one study saline was used [43] in combination with a thickening agent. One study used a solution of liquid diet [39], one used an isosmolar solution consisting of saline and sucrose [42] and one used an ileostomy connector allowing faeces from the

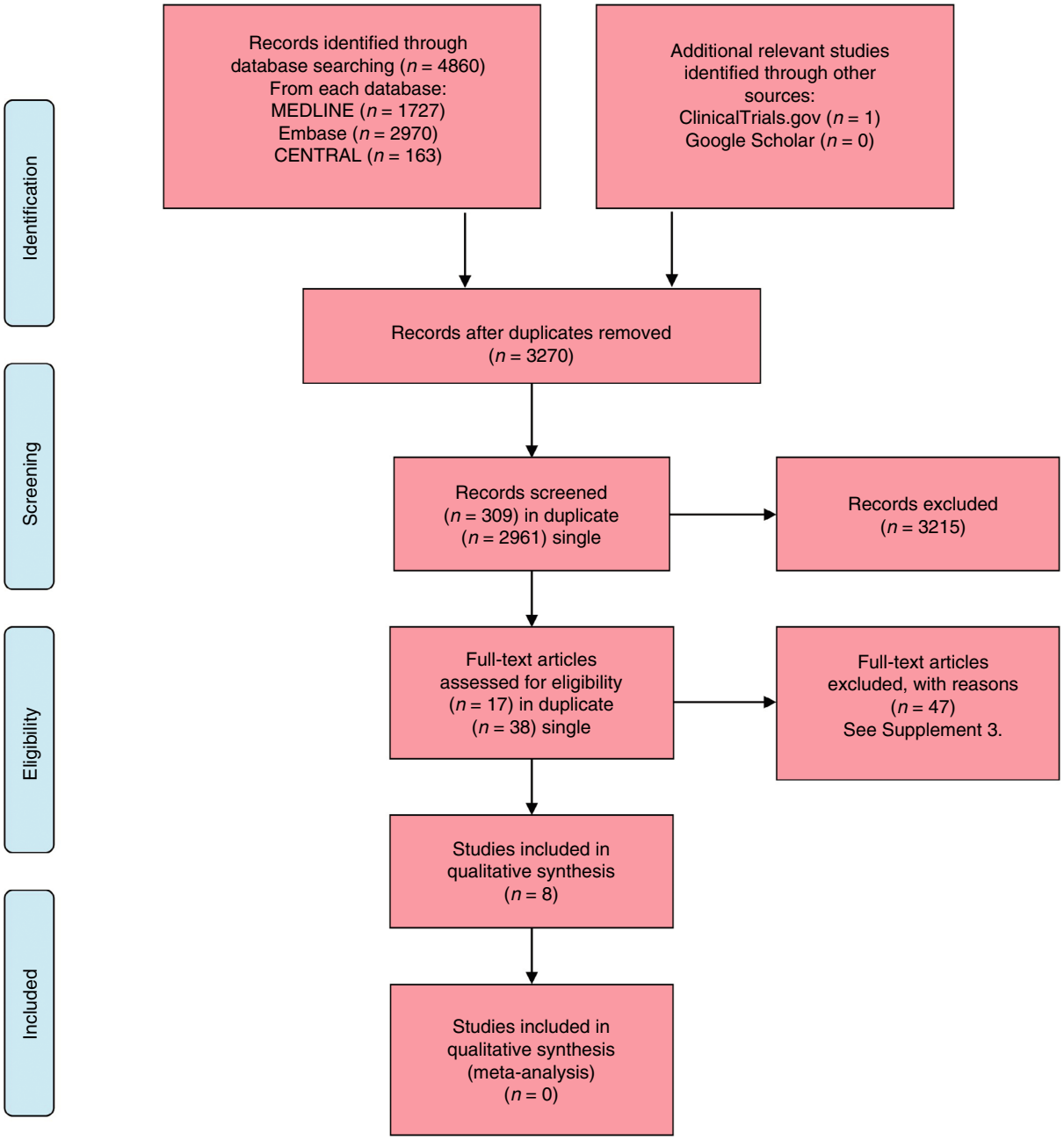

Figure 1 PRISMA flow diagram.

patient's proximal ileum to travel into the efferent limb [40]. The volumes used ranged from 50 to 500 ml per stimulation. Administration of saline was via a syringe [37,38] or catheter [39,41,43,44]. The overall duration of the intervention ranged from 2 weeks to 3 months before ileostomy closure. The intervention was usually performed in an outpatient setting or at home. In three studies [41,43,44], Kegel exercises were performed as a co-intervention in both study groups to strengthen the pelvic floor muscles. For more details see Table 2.

Risk of bias and methodological quality of included studies

A detailed overview of the included risk of bias or methodological quality can be found in Data S4. Of the two RCTs, one was judged as having a low risk of bias in the majority of domains of the Cochrane risk of bias tool [38] while the other RCT had a high risk of bias in most domains [43]. All NRS were judged as having a high overall risk of bias with the ROBINS-I

Table 1 Study and patient characteristics.

Study ID	Study design and publication type	Country of origin, setting	Study duration*	Total no. of participants	Participants IG *vs* CG	Diagnoses, index surgery	Mean age (years)	Proportion of men
Abrisqueta *et al.* (2013) [37]	Case report, published article	Spain, teaching hospital	Aug 2011–Jan 2012	*n* = 1	Not applicable	Rectal cancer, LAR	62	100%
Abrisqueta *et al.* (2014) [38]	RCT, published article	Spain, teaching hospital	Jun 2011 – Jul 2013	*n* = 70	*n* = 35 *vs* *n* = 35	Rectal cancer, LAR	63 *vs* 65	83% *vs* 69%
Kuster *et al.* (1993) [39]	NRS, published article	USA, general hospital	Sept 1989–not reported	*n* = 34	*n* = 24 *vs* *n* = 10	Ulcerative colitis, IPAA	Not reported	Not reported
Maeda *et al.* (1995) [40]	Case report, published article	Japan, general hospital	Aug 1991–Jan 1992	*n* = 1	Not applicable	Ulcerative colitis, IPAA	26	100%
Menéndez *et al.* (2013) [41]	Case report, published article	Spain, general hospital	Jul 2012–Feb 2013	*n* = 1	Not applicable	Rectal cancer, LAR	55	0%
Miedema *et al.* (1998) [42]	NRS, published article	USA, teaching hospital	Not reported	*n* = 13	*n* = 6 *vs* *n* = 7	Ulcerative colitis, IPAA	33 *vs* 39	100% *vs* 86%
Thomas *et al.* (1996) [43]	NRS, published article	USA, teaching hospital	Dec 1991–Feb 1994	*n* = 47†	*n* = 24 *vs* *n* = 23	Ulcerative colitis, IPAA	42 *vs* 37	8% *vs* 57%
Vázquez-Melero *et al.* (2018) [44]	NRS‡, conference presentation	Spain, teaching hospital	Nov 2014–Apr 2017§	*n* = 100	*n* = 50 *vs* *n* = 50	Colorectal cancer¶, LAR	64 *vs* 65	56% *vs* 62%

CG, control group; IG, intervention group; IPAA, ileal pouch–anal anastomosis; LAR, low anterior resection; NRS, nonrandomized study; RCT, randomized controlled trial.
*For case reports: from index surgery to ileostomy closure.
†Number of analysed participants (two participants withdrew and nine had incomplete data).
‡Interim analysis.
§Historical control group: May 2009–Jan 2014.
¶In 85% of the patients.

tool [39,42,44]. Two case reports met most of the eight items from the JBI Critical Appraisal Checklist for Case Reports [37,41], but the third case report only met two [40].

Synthesis of results

Results for each of the review outcomes are presented in Table 3. The measurement tool or method, length of follow-up and number and timing of outcome measurements was only reported in one RCT, in which the primary outcome was stool frequency [43]. The measurement tool was a record filled in by patients each day over 3 months [43]. The professional role of the person who measured the outcome was reported in two studies, where it was the operating surgeon [38,44].

Time to restoration of bowel function

Five studies, which included a total of 185 patients, reported results regarding the review's primary outcome [37,38,41,42,44]. The three comparative studies [38,42,44] found that preoperative bowel stimulation reduced the time to restoration of bowel function when compared with standard preoperative care. The reduction was statistically significant with regard to the mean time to tolerance of solid food [38,44]. The mean time to passing flatus or stool was significantly lower in two out of three studies [38,44], but the mean time to tolerance of liquids did not significantly differ between the intervention and control groups in the two studies reporting this outcome [42,44]. The results of the case reports matched the results of the comparative studies [37,41].

Table 2 Description of intervention and comparison.

Study ID	Substance	Dose	Frequency	Administration	Duration	Delivery setting	Co-intervention	Comparison
Abrisqueta *et al.* (2013) [37]	Physiological saline + thickening agent	500 ml	Once daily	Via 100-ml syringe	2 weeks	Unclear	None	Not applicable
Abrisqueta *et al.* (2014) [38]	Physiological saline + thickening agent	500 ml	Once daily	Via 100-ml syringe	2 weeks	Outpatient	None	No stimulation
Kuster *et al.* (1993) [39]	Solution of liquid diet and water	First 50 ml, increased to 250 ml	Twice daily	Via catheter	2 months	Unclear	None	No stimulation
Maeda *et al.* (1995) [40]	Faecal liquid from the patient's proximal ileum	Not specified	First 6 h, then 8, 9, 10, 11, 12, 24 h a day	Via ileostomy connector	3 months	Outpatient	None	Not applicable
Menéndez *et al.* (2013) [41]	Warm saline + thickening agent	First 300 ml, increased to 500 ml	Weekly, in the last week once daily	Via urinary catheter	3 weeks	Hospital	Kegel exercises	Not applicable
Miedema *et al.* (1998) [42]	Isosmolar solution of saline and sucrose	100 ml	Twice daily	Via urinary catheter	6 weeks	Outpatient	None	No stimulation
Thomas *et al.* (1996) [43]	Physiological saline	First 120 ml, increased to 300 ml	Once daily	Via urinary catheter	4 weeks	Outpatient	Kegel exercises	Kegel exercises only
Vázquez-Melero *et al.* (2018) [44]	Physiological saline with bowel cleansing + thickening agent	500 ml	Once daily	Via urinary catheter	2–3 weeks	Outpatient/at home	Kegel exercises	Kegel exercises only

Other functional outcomes

Four studies comprising 95 patients reported results regarding postoperative stool frequency [39,40,42,43]. One comparative study found that the average stool frequency in the stimulation group was less than half of that in the control group 10 days and 1 month postoperatively [39]. In contrast, two comparative studies did not observe a difference between the intervention and the control group 5 days [42] or 7 days postoperatively [43]. In the case report of a patient with an ileoanal pouch who underwent bowel stimulation with an ileostomy connector [40], the daily frequency of stools within the first 24 h after ileostomy closure was 6.5 times and therefore slightly less than in the comparative studies. Two case reports reported results regarding the onset of intestinal peristalsis [37,41], which were similar.

Postoperative length of stay

Five studies comprising 185 participants reported results for postoperative LOS [37,38,41,42,44]. Preoperative bowel stimulation significantly reduced the mean postoperative LOS in two comparative studies [38,44], by 2.1 and by 2.6 days, respectively. However, the mean postoperative LOS was about 5 days higher in the NRS [44] than in the RCT [38]. There was no statistically significant difference between the intervention and the control group in the other comparative study [42]. In the two case reports [37,41], the postoperative LOS was of 2 and 4 days, respectively, which is consistent with the RCT result [38].

Further patient-relevant outcomes

Two comparative studies reported information regarding participants' compliance with the intervention [43,44], which overall seemed to be adequate. In addition to that, a RCT found that fewer nasogastric tubes were required for patients with postoperative ileus in the intervention group [38]. A NRS stated that no patient experienced significant faecal incontinence after closure [42] and another NRS noted subjectively that 'patients who used instillations had noticeably less discomfort, less perianal skin irritation, good nocturnal rest, better continence and a feeling of well-being and confidence' [39].

Complications

Four studies including 218 participants reported results on complications [37,38,43,44]. One RCT found that the rate of postoperative ileus was significantly lower (3% *vs* 20%) with preoperative bowel stimulation [38]. Rates of other postoperative complications were also found to be lower, but this difference was not statistically significant [38]. Similarly, the rate of postoperative ileus and of wound infections were lower in the intervention group of a NRS, but neither of these differences were statistically significant [44]. Another RCT found that the average number of episodes of nocturnal

Table 3 Study results by outcome.

	Index surgery LAR				Index surgery IPAA			
Study ID	Abrisqueta *et al.* (2013) [37]	Abrisqueta *et al.* (2014) [38]	Menéndez *et al.* (2013) [41]	Vázquez-Melero *et al.* (2018) [44]	Kuster *et al.* (1993) [39]	Maeda *et al.* (1995) [40]	Miedema *et al.* (1998) [42]	Thomas *et al.* (1996) [43]
Primary outcome								
Mean time to:								
Tolerance of liquids	Within the first 24 h	–	Oral tolerance on second postoperative day‡	1.7 ± 0.9 *vs* 3.0 ± 3.1 days	–	–	2.8 ± 0.3 *vs* 4.6 ± 0.8 days	–
Tolerance of solid food	–	1 (1–3) *vs* 2.6 (1–17) days*		3.5 ± 1.3 *vs* 5.6 ± 3.5 days*	–	–	–	–
Passing flatus	–	1.1 (1–2) *vs* 2.9 (1–18) days*,†	1 day§	–	–	–	–	–
Passing stool	–			3 days§	2.3 ± 1.1 *vs* 3.5 ± 3.4 days*	–	–	3.7 ± 0.6 *vs* 4.1 ± 0.6 days –
Secondary outcomes								
Other functional outcomes	Intestinal peristalsis began 12 h after surgery	–	Intestinal peristalsis began 24 h after surgery	–	Stool frequency per day during the first 10 days: 8.5 *vs* 18.2 After 1 month: 5.1 *vs* 11.3 After 12 months: 4.2 *vs* 4.0	Stool frequency during the first 24 h: 6.5	Motility index¶ and stool frequency of did not differ between the groups	Stool frequency during week 1: 8.7 *vs* 8.8 times per day
Length of postoperative hospital stay	2 days	Mean 2.5 ± 1.0 *vs* 4.6 ± 2.8 days*	4 days§	7.3 ± 2.6 *vs* 9.9 ± 5.1 days*	–	–	Median 6 *vs* 7 days	–
Further patient-relevant outcomes	–	Nasogastric tubes required in 0 *vs* 3 patients with postop. ileus	–	Contentment among patients	Better continence and less urgency to defaecate in stimulated group	–	No patient experienced significant incontinence	Compliance with intervention: 84% (range 23–100%)
Postoperative complication rates	Discharged without any complications	Postoperative ileus**: 3 *vs* 20%*,other postoperative complications: 9 *vs* 11%	–	Postoperative ileus: 8 *vs* 16%, wound infection: 12 *vs* 20%	–	–	–	Episodes of nocturnal leakage month 1: 7.7 ± 2.1 *vs* 3.5 ± 6.9, month 2: 6.3 ± 14.2 *vs* 2.6 ± 5.3, month 3: 3.2 ± 6.6 *vs* 6.2 ± 9.9

± Indicates standard deviation of a mean value, () indicates the range.
– Indicates that the outcome was not reported.
*Indicates statistical significance ($P < 0.05$).
†The study did not differentiate between flatus and stool.
‡The study did not differentiate between tolerance to liquids and solid food.
§Information obtained via personal communication with Pablo Menéndez on 6 March 2018.
¶Defined as: $\log_e$ [(sum of the amplitudes × number of contractions) + 1].
**Defined as 'intolerance to oral food' in the absence of clinical and radiological data of mechanical obstruction (abdominal pain, muscular guarding, and slight dilation of the small bowel) for more than 72 h, or the need for a nasogastric tube' (p. 1393).

leakage was higher in the intervention group in the first two postoperative months but lower in the third postoperative month [43]. There were no postoperative complications in the only case report reporting information for that outcome [37]. No study reported any major complications of the intervention itself.

Certainty of evidence

The certainty of the evidence from the eight included studies (Data S5) was judged to be very low for all outcomes as there was a serious risk of bias and imprecision. Furthermore, publication bias was strongly

suspected as there was a large time gap of 15 years between the publication of the first four [39,40,42,43] and the last four studies [37,38,41,44].

Discussion

Main results

This systematic review included eight studies that involved a total of 267 patients with a temporary ileostomy after LAR or IPAA. The studies had a moderate to high risk of bias and were of varying methodological quality.

Preoperative bowel stimulation appears to have a favourable effect on the primary outcome of time to restoration of bowel function. The intervention also seems to reduce postoperative LOS, probably because of the reduction in the time to restoration of bowel function. There is currently insufficient evidence that preclosure bowel stimulation improves other patient-relevant outcomes, such as the daily stool frequency after ileostomy closure. Overall, preoperative bowel stimulation seems to have similar postoperative complication rates as standard preoperative care, although one RCT showed a significant reduction in the incidence of postoperative ileus.

The interventions used in the studies included in this review may minimize or reverse some consequences of diversion, and so have intuitive appeal when designing interventions to improve patient outcomes around a procedure with significant associated morbidity [3,19].

Limitations

The major limitation of this review is the need to combine two different patient groups who commonly have diverting ileostomies (those having LAR for rectal cancer and those having IPAA for ulcerative colitis) to obtain sufficient studies to assess the effectiveness of efferent limb stimulation. Although based on a small number of eligible studies with a moderate to high risk of bias, this review is an appropriate basis for research prioritization. However, caution must be exercised in using these results to change clinical practice.

Implications for practice and further research

Since the strength of evidence was judged to be very low for each outcome it remains unclear if the relative benefits of preoperative bowel stimulation outweigh its relative costs. Thus, the review's results currently do not justify the implementation of preoperative bowel stimulation as a routine procedure.

However, there is no evidence that the interventions described worsen postoperative outcomes or increase complication rates. Hence, these and alternative efferent limb interventions, including probiotic instillation [47] or faecal microbial transplantation [48], should be further investigated, preferably in multicentre RCTs. These should also collect cost-effectiveness data and test different interventions for both efficacy and acceptability. To this end, it might be more efficient and ethical to apply a multi-arm multi-stage efficient modern trial design instead of performing numerous traditional RCTs [49].

Conclusion

In summary, there currently is insufficient evidence to conclude that preoperative bowel stimulation restores bowel function after ileostomy closure faster and improves postoperative outcomes when compared to standard care. Nonetheless, the results of this review suggest that it merits further investigation.

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Author contributions

TR performed the systematic literature search, study selection, data collection, study assessment and analysis and drafted the manuscript. IP verified the study selection and data collection, and critically revised the manuscript. DH conceptualized the review, verified the study assessment and critically revised the manuscript. NF conceptualized the review, interpreted the results and critically revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

All authors declare that they have no conflicts of interest.Accepted Article online 9 April 2019

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Full electronic search strategy.
Data S2. Data items.
Data S3. Excluded records after full-text assessment with main reason.
Data S4. Risk of bias/methodological quality assessment.
Data S5. GRADE evidence profile.