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Systematic Review

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

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Abstract (250/250 words)

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 after ileostomy closure faster and improves postoperative outcomes when compared to 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 was performed by one reviewer and verified by another. Study results were synthesised narratively. The GRADE approach was used to assess 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 time to postoperative restoration of bowel function and length of hospital stay when compared to standard preoperative care. Other functional outcomes and postoperative complication rates were similar to those of standard preoperative care. 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.

What does this paper add to the literature?

This is the first systematic review on preoperative bowel stimulation before ileostomy closure. Preoperative bowel stimulation appears to be safe and potentially more effective than standard preoperative care. This paves the way for well-designed clinical trials in a poorly studied area of colorectal surgery with potential for significant patient benefit.

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 leak [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 8,500 patients are diagnosed with rectal cancer each year [4]. More than half undergo a major resection of whom 83% have a temporary stoma that is closed within 18 months in only 65% of patients [4]. Approximately 6,500 patients per year are diagnosed with ulcerative colitis in the United Kingdom (UK) [5], of whom 10 to 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 the patients at the time of pouch surgery [9]. A study from Germany found that the ileostomy is subsequently closed in 86% of the patients [10], although many centres are now advocating ileoanal pouch surgery without temporary diversion by focussing on proactive management of early septic complications [11].

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 recognised 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], in which 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 to standard preoperative care.

Methods

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) [31].

Eligibility criteria

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

- included patients with a temporary ileostomy after LAR or IPAA,
- compared preoperative bowel stimulation (defined as preoperative intervention involving the instillation of substances through the efferent limb of the stoma to standard preoperative care (as defined by the study authors), and

- 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, e.g. 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 Supplement 1 for the full search strategy). No limits, such as language restrictions, were applied. Date of last search was 23/10/2018.

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 was deemed unnecessary for the remaining records.

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 Supplement 2.

Risk of bias in individual studies

Risk of bias of RCTs was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [30] and risk of bias of non-randomised studies (NRS) with the 'Risk Of Bias In Non-randomised Studies - of Interventions' (ROBINS-I) tool [32]. 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 synthesised narratively for each of the pre-specified 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 underwent 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] (Figure 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 randomised controlled trials (RCTs) for which no results were available. They were both registered in ClinicalTrias.gov (NCT02559635 [45] and NCT02751736 [46]) and investigate preoperative bowel stimulation in patients with a temporary ileostomy after LAR with saline [45] and probiotics [46] respectively.

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 age ranged from 26 to 65 years, which can be explained by the different onset of the diseases. About 60% of all patients were male.

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~~ one used an ileostomy connector allowing faeces from the patient's proximal ileum to travel into the efferent limb [40]. Volumes used ranged from 50 to 500ml per stimulation. Administration of saline was via syringe [37, 38] or ~~-~~catheter [39, 41, 43, 44]. The overall duration of the intervention ranged from two weeks to three 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 can be found in Supplement 4. Of the two RCTs, one was judged as having 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 of them [43]. All NRS were judged as having a high overall risk of bias with the ROBINS-I 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 measurement was only reported inone RCT, in which the primary outcome was stool frequency [43]. The measurement tool was a record filled in by the patients each day over three 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 comprised 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 to standard preoperative care. The reduction was statistically significant with regards 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 case reports' results matched the comparative studies' results [37, 41].

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 one month postoperatively [39]. In contrast, two comparative studies did not observe a difference between the intervention and the control group five days [42] or

seven 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 hours-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 five 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 two and four days, respectively, which is consistent with the RCT result [38].

Further patient relevant outcomes

Two comparative studies reported information regarding the participants' compliance with the intervention [43, 44], which overall seemed to be adequate. In addition to that, an 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 an NRS, but neither of these differences were statistically significant [44]. Another RCT found that the average number of episodes

of nocturnal 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 (Supplement 5) 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 between the publication of the first four [39, 40, 42, 43] and the last four studies [37, 38, 41, 44] of 15 years.

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 review's primary outcome, 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 pre-closure bowel stimulation improves other patient-relevant outcomes, such as the daily frequency of stools 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 minimise 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 have sufficient studies to assess the

effectiveness of efferent limb stimulation. Although based on a small number of eligible studies ~~and~~ with a moderate to high risk of bias, this review is an appropriate basis for research prioritisation. 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 is currently insufficient evidence to conclude that preoperative bowel stimulation restores bowel function after ileostomy closure and no evidence to suggest that it improves postoperative outcomes. . Nonetheless, the results of this review suggest 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 conceptualised the review, verified the study assessment and critically revised the manuscript. NF

conceptualised the review, interpreted the results and critically revised the manuscript.

All authors have read and approved the final manuscript.

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References

1. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann Surg* 2007; **246:** 207-14.
2. Kaidar-Person O, Person B, Wexner SD. Complications of construction and closure of temporary loop ileostomy. *J Am Coll Surg* 2005; **201:** 759-73.
3. Chow A, Tilney HS, Paraskeva P, Jeyarajah S, Zacharakis E, Purkayastha S. The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases. *Int J Colorectal Dis* 2009; **24:** 711-23.
4. Boyle J, Braun M, Eaves E, Hill J, Kuryba A, Roe A, et al. National Bowel Cancer Audit: Annual Report 2017 (Version 2). London: Healthcare Quality Improvement Partnership Ltd, 2017.
5. Ulcerative colitis: management (Clinical guideline 166). London: National Institute for Health and Care Excellence (NICE), 2013.
6. Worley GHT, Fearnhead NS, Brown SR, Acheson AG, Lee MJ, Faiz OD. Review of current practice and outcomes following ileoanal pouch surgery: lessons learned from the Ileoanal Pouch Registry and the 2017 Ileoanal Pouch Report. *Colorectal Dis* 2018; **20:** 913-22.
7. Hwang JM, Varma MG. Surgery for inflammatory bowel disease. *World J Gastroenterol* 2008; **14:** 2678-90.
8. Scoglio D, Ahmed Ali U, Fichera A. Surgical treatment of ulcerative colitis: Ileorectal vs ileal pouch-anal anastomosis. *World J Gastroenterol* 2014; **20:** 13211-8.
9. Brown SR, Faiz OD, Fearnhead NS, Kinsman R, Walton PKH. Ileoanal Pouch Report 2017. London: Association of Coloprotoctology of Great Britain and Ireland, 2017.
10. Wibmer AG, Kroesen AJ, Gröne J, Slavova N, Weinhold A, Buhr HJ, et al. Predictors of permanent ileostomy after restorative proctocolectomy. *Br J Surg* 2010; **97:** 1561-6.
11. Sahami S, Buskens CJ, Fadok TY, Tanis PJ, de Buck van Overstraeten A, Wolthuis AM, et al. Defunctioning Ileostomy is not Associated with Reduced Leakage in Proctocolectomy and Ileal Pouch Anastomosis Surgeries for IBD. *J Crohn's Colitis* 2016; **10:** 779-85.
12. Neuman HB, Patil S, Fuzesi S, Wong WD, Weiser MR, Guillem JG, et al. Impact of a temporary stoma on the quality of life of rectal cancer patients undergoing treatment. *Ann Surg Oncol* 2011; **18:** 1397-403.
13. Herrle F, Sandra-Petrescu F, Weiss C, Post S, Runkel N, Kienle P. Quality of Life and Timing of Stoma Closure in Patients With Rectal Cancer Undergoing Low Anterior Resection With Diverting Stoma: A Multicenter Longitudinal Observational Study. *Dis Colon Rectum* 2016; **59:** 281-90.
14. Beck-Kaltenbach N, Voigt K, Rumstadt B. Renal impairment caused by temporary loop ileostomy. *Int J Colorectal Dis* 2011; **26:** 623-6.
15. Gessler B, Haglind E, Angenete E. A temporary loop ileostomy affects renal function. *Int J Colorectal Dis* 2014; **29:** 1131-5.
16. Woods R, Fielding A, Moosvi SR, Wharton R, Shaikh I, Hernon J, et al. Ileostomy is associated with chronically impaired renal function after rectal cancer surgery. *Colorectal dis* 2017; **19 (Supplement 2):** 32.

17. van Westreenen HL, Visser A, Tanis PJ, Bemelman WA. Morbidity related to defunctioning ileostomy closure after ileal pouch-anal anastomosis and low colonic anastomosis. *Int J Colorectal Dis* 2012; **27:** 49-54.
18. Sharma A, Deeb AP, Rickles AS, Iannuzzi JC, Monson JRT, Fleming FJ. Closure of defunctioning loop ileostomy is associated with considerable morbidity. *Colorectal dis* 2013; **15:** 458-62.
19. Mennigen R, Sewald W, Senninger N, Rijcken E. Morbidity of loop ileostomy closure after restorative proctocolectomy for ulcerative colitis and familial adenomatous polyposis: a systematic review. *J Gastrointest Surg* 2014; **18:** 2192-200.
20. Andersson T, Lunde OC, Johnson E, Moum T, Nesbakken A. Long-term functional outcome and quality of life after restorative proctocolectomy with ileo-anal anastomosis for colitis. *Colorectal dis* 2011; **13:** 431-7.
21. Bryant CLC, Lunniss PJ, Knowles CH, Thaha MA, Chan CLH. Anterior resection syndrome. *Lancet Oncol* 2012; **13:** e403-e8.
22. Farag S, Sajid M, Rehman S, Miles T, Baig M, Sains P. Early versus delayed closure of loop defunctioning ileostomy in patients undergoing distal colorectal resections: An integrated systematic review and meta-analysis of published randomized, controlled trials. *Colorectal dis* 2017; **19 (Supplement 2):** 8.
23. Danielsen AK, Park J, Jansen JE, Bock D, Skullman S, Wedin A, et al. Early Closure of a Temporary Ileostomy in Patients With Rectal Cancer: A Multicenter Randomized Controlled Trial. *Ann Surg* 2017; **265:** 284-90.
24. Park J, Danielsen AK, Angenete E, Bock D, Marinez AC, Haglind E, et al. Quality of life in a randomized trial of early closure of temporary ileostomy after rectal resection for cancer (EASY trial). *Br J Surg* 2018; **105:** 244-51.
25. Beamish EL, Johnson J, Shaw EJ, Scott NA, Bhowmick A, Rigby RJ. Loop ileostomy-mediated fecal stream diversion is associated with microbial dysbiosis. *Gut Microbes* 2017; **8:** 467-78.
26. Williams L, Armstrong MJ, Finan P, Sagar P, Burke D. The effect of faecal diversion on human ileum. *Gut* 2007; **56:** 796-801.
27. Miedema BW, Karlstrom L, Hanson RB, Johnson GP, Kelly KA. Absorption and Motility of the Bypassed Human Ileum. *Dis Colon Rectum* 1990; **33:** 829-35.
28. Harries RL, Ansell J, Codd RJ, Williams GL. A systematic review of Clostridium difficile infection following reversal of ileostomy. *Colorectal dis* 2017; **19:** 881-7.
29. Williams LA, Sagar PM, Finan PJ, Burke D. The outcome of loop ileostomy closure: a prospective study. *Colorectal dis* 2008; **10:** 460-4.
30. Higgins JPT, Green S (eds).Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updatedMarch 2011]. London: The Cochrane Collaboration, 2011. http://handbook.cochrane.org (accessed October 2018).
31. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed)* 2009; **339:** b2535.
32. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical research ed)* 2016; **355:**i4919.
33. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (eds). Joanna Briggs Institute Reviewer's Manual.The Joanna Briggs Institute, 2017. https://reviewersmanual.joannabriggs.org/ (accessed October 2018).
34. Wille-Jørgensen P, Renehan AG. Systematic reviews and meta-analyses in coloproctology: interpretation and potential pitfalls. *Colorectal dis* 2008; **10:** 21-32.
35. Grade Working Group. Grading quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2004; **328:** 1490.

36. Schünemann H, Brożek J, Guyatt G, Oxman A (eds). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed October 2018).
37. Abrisqueta J, Abellan I, Frutos MD, Lujan J, Parrilla P. Afferent loop stimulation prior to ileostomy closure. *Cir Esp* 2013; **91:** 50-2.
38. Abrisqueta J, Abellan I, Lujan J, Hernandez Q, Parrilla P. Stimulation of the efferent limb before ileostomy closure: a randomized clinical trial. *Dis Colon Rectum* 2014; **57:** 1391-6.
39. Kuster GGR, Andree G. Attempts to aid the adaptation of pelvic pouch before temporary ileostomy closure. *Dis Colon Rectum* 1993; **36:** 1022-5.
40. Maeda K, Hashimoto M, Koh J, Yamamoto O, Hosoda Y, Morikawa Y. The use of an ileostomy connector to diminish the frequency of defecation prior to ileostomy closure in patients with a pelvic pouch. *Surg Today* 1995; **25:** 657-61.
41. Menéndez P, Garcia A, Lozano E, Pelaez R. Effectiveness of afferent loop stimulation prior to ileostomy closure. *Cir Esp* 2013; **91:** 547-8.
42. Miedema BW, Kohler L, Smith CD, Phillips SF, Kelly KA. Preoperative perfusion of bypassed ileum does not improve postoperative function. *Dig Dis Sci* 1998; **43:** 429-35.
43. Thomas DS, Beck SL, Dayton MT, Kirchhoff KT. Evaluation of scheduled J-pouch irrigations on decreasing stool frequency after ileoanal pull-through and ileostomy closure. *J Wound Ostomy Continence Nurs* 1996; **23:** 261-8.
44. Vázquez-Melero A, Loizate Totoricaguena A, García Alonso P. ClinicalTrials.gov Identifier: NCT03424447. Stimulation of the Efferent Loop Before Loop Ileostomy Closure. **Vol. 2018**. U.S. National Library of Medicine, Bethesda (Maryland), 2018.
45. Garfinkle R, Trabulsi N, Morin N, Phang T, Liberman S, Feldman L, et al. Study protocol evaluating the use of bowel stimulation before loop ileostomy closure to reduce postoperative ileus: a multicenter randomized controlled trial. *Colorectal dis* 2017; **19:** 1024-9.
46. Kang SI, Oh HK, Kim MJ, Son IT, Kim DW, Kang SB. The effect of probiotics (CJLP243) on bowel function restoration after ileostomy closure in patients with rectal cancer: A pilot randomised controlled trial. *Colorectal dis* 2016; **18 (Supplement 1):** 127.
47. Stephens JH, Hewett PJ. Clinical trial assessing VSL#3 for the treatment of anterior resection syndrome. *ANZ J Surg* 2012; **82:** 420-7.
48. Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. *Aliment Pharmacol Ther* 2017; **46:** 479-93.
49. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med* 2017; **377:** 62-70.

Table 1: Study and patient characteristics.

Study ID	Study design, Publication type	Country of origin, setting	Study duration[a]	Participants in total	Participants IG vs CG	Diagnoses, index surgery	Mean age in years	Proportion of men
Abrisqueta 2013 [37]	Case report, Published article	Spain, Teaching hospital	Aug 2011 – Jan 2012	n = 1	Not applicable	Rectal cancer, LAR	62	100%
Abrisqueta 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 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 1995 [40]	Case report, Published article	Japan, General hospital	Aug 1991 – Jan 1992	n = 1	Not applicable	Ulcerative colitis, IPAA	26	100%
Menéndez 2013 [41]	Case report, Published article	Spain, General hospital	Jul 2012 – Feb 2013	n = 1	Not applicable	Rectal cancer, LAR	55	0%
Miedema 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 1996 [43]	NRS, Published article	USA, Teaching hospital	Dec 1991 – Feb 1994	n = 47[b]	n = 24 vs n = 23	Ulcerative colitis, IPAA	42 vs 37	8% vs 57%
Vázquez-Melero 2018 [44]	NRS[c], Conference presentation	Spain, Teaching hospital	Nov 2014 – Apr 2017[d]	n = 100	n = 50 vs n = 50	Colorectal cancer[e], LAR	64 vs 65	56% vs 62%

Explanations:

a. For case reports: From index surgery to ileostomy closure.

b. Number of analysed participants (two participants withdrew and nine had incomplete data)

c. Interim analysis.

d. Historical control group: May 2009 – Jan 2014.

e. In 85% of the patients.

Abbreviations: CG, control group; IG, intervention group; IPAA, ileal pouch-anal anastomosis; LAR, low anterior resection; NRS, non-randomised study; RCT, randomized controlled trial, USA, United States of America.

Table 2: Description of intervention and comparison.

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

Table 3: Study results by outcome.

	Study ID	Index surgery LAR				Index surgery IPAA			
		Abrisqueta 2013 [37]	**Abrisqueta 2014 [38]**	**Menéndez 2013 [41]**	**Vázquez-Melero 2018 [44]**	**Kuster 1993 [39]**	**Maeda 1995 [40]**	**Miedema 1998 [42]**	**Thomas 1996 [43]**
Primary outcome	Tolerance of liquids	Mean time to: Within the first 24h	-	Oral tolerance on second postoperative day[b]	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*,[a]	1 day[c]	-	-	-	-	-
	Passing stool	-		3 days[c]	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 12h after surgery	-	Intestinal peristalsis began 24h after surgery	-	Stool frequency per day during the first 10 days: 8.5 vs 18.2 After one month: 5.1 vs 11.3 After twelve months: 4.2 vs 4.0	Stool frequency during the first 24 hours: 6.5	Motility index[d] 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[c]	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 defecate in stimulated group	-	No patient experienced significant incontinence	Compliance with intervention: 84% (range 23 to 100%)
Postoperative complication rates	Discharged without any complications	Postoperative ileus[e]: 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

Explanations:

a. The study did not differentiate between flatus and stool.

b. The study did not differentiate between tolerance to liquids and solid food.

c. Information obtained via personal communication with Pablo Menéndez on 6 March 2018.

d. Defined as: $\log_e$ [(sum of the amplitudes x number of contractions) + 1]

e. 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 hours, or the need for a nasogastric tube” (p. 1393).

* indicates statistical significance ($p < 0.05$).

± indicates standard deviation of a mean value, () indicate the range.

- indicates that the outcome was not reported.

Figure 1: PRISMA flow diagram