Noninvasive vagus nerve stimulation to reduce ileus after major colorectal surgery: early development study

Stephen J. Chapman1 | Jack A. Helliwell1 | Maureen Naylor2 | Cerys Tassinari3 | Neil Corrigan3 | David G. Jayne1

Abstract

Aim: Vagus nerve stimulation has emerged as a plausible intervention to reduce ileus after surgery. An early development study was undertaken with the aim of exploring the feasibility of self-administered, noninvasive vagus nerve stimulation (nVNS) after major colorectal surgery.

Method: A parallel-group, randomized controlled trial was undertaken between 1 January 2018 and 31 August 2019. Forty patients undergoing colorectal surgery for malignancy were allocated equally to Sham and Active stimulation groups. Electrical vagus nerve stimulation was self-administered bilaterally over the cervical surface landmarks for 5 days before and after surgery. Outcomes of interest were postoperative complications and adverse events measured using the Clavien–Dindo scale, treatment compliance, device usability according to the Systems Usability Scale (SUS) and clinical measures of bowel recovery.

Results: Forty patients were randomized and one withdrew, leaving 39 for analysis. Postoperative complications occurred in 9/19 (47.4%) participants receiving Sham and 11/20 (55.0%) receiving Active stimulation and were mostly minor. Compliance with treatment before surgery was 4.7 ± 0.9 days out of 5 days in the Sham group and 4.7 ± 1.1 in the Active group. Compliance with treatment after surgery was 4.1 ± 1.1 and 4.4 ± 1.5, respectively. Participants considered the intervention to be ‘acceptable’ according to the SUS. The most prominent differences in bowel recovery were days to first flatus (2.35 ± 1.32 vs 1.65 ± 0.88) and tolerance of solid diet (2.18 ± 2.21 vs 1.75 ± 0.91) for Sham and Active groups, respectively.

Conclusion: This study supports the safety, treatment compliance and usability of self-administered nVNS in patients undergoing major colorectal surgery.

KEYWORDS
ileus, noninvasive vagus nerve stimulation, surgery, vagus nerve
### INTRODUCTION

Ileus occurs in 10%–20% of patients undergoing elective colorectal surgery [1]. It is a distressing condition characterized by abdominal distension, persistent vomiting and delayed faecal elimination after surgery. For patients, this prolongs the length of hospital stay and increases the risk of serious complications such as pneumonia and venous thromboembolic events [2]. For healthcare systems, it increases costs by up to 71%, particularly those associated with nursing care, laboratory investigations and medications [3]. In light of this, ileus is recognized as a research priority by the Association of Coloproctology of Great Britain and Ireland [4].

The mechanism of ileus is multifactorial, with most evidence pointing towards opioid- and inflammatory-induced dysfunction of intestinal transit [5]. In the last 20 years, a number of interventions to prevent ileus and its sequelae have been explored but few have led to meaningful patient benefit. The most promising have included strategies to rationalize opioid-based analgesia (such as mu-receptor antagonists) and to moderate the postoperative inflammatory response (such as enhanced recovery protocols) [6]. Recently, electrical stimulation of the vagus nerve has been proposed as a new intervention. In preclinical models, vagus nerve stimulation accelerates the recovery of bowel function by activating a cholinergic anti-inflammatory pathway in the gut. This inhibits the expression of proinflammatory mediators by intestinal macrophages, which occurs in response to intestinal handling and leads to dysfunction of intestinal smooth muscle [7,8]. This mechanism has been translated into early human studies, where invasive stimulation during surgery has shown to reduce markers of systemic inflammation [9]. There are a number of challenges for implementing invasive stimulation, however, including increased operative risk and a limited opportunity to perform stimulation during surgery, so a different approach is required.

Noninvasive vagus nerve stimulation (nVNS) involves electrical stimulation of the vagus nerve at its cervical surface landmark. This may reduce the risk of serious complications such as neurovascular injury and may preclude the need for longer procedures with greater risk. The aim of this study was to explore the safety, treatment compliance and usability of nVNS when self-administered by patients before and after major colorectal surgery.

### METHOD

#### Ethics and governance

Research ethics approval for the study was obtained from the North East – Tyne & Wear South Ethics Committee (17/NE/0091) on 24 April 2017. All patients provided informed, written consent prior to enrolment. The study was prospectively registered on the ISRCTN registry (ISRCTN10693903) on 18 October 2017. The manuscript is reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist [10].

#### Study design

A parallel-group, double-blinded, randomized controlled trial was undertaken between 1 January 2018 and 31 August 2019. This was an IDEAL Stage 2a development study, focussing on safety and early feasibility [11]. Participants were randomized equally to Sham and Active stimulation groups. There were no changes to the study design apart from an extension to the recruitment end date (31 January 2019 extended to 31 August 2019).

#### Participants

All potential participants were identified from multidisciplinary team meetings and approached in an outpatient setting. Adults with suspected or confirmed colorectal cancer due to undergo elective, minimally invasive (laparoscopic or robotic) colorectal resection were eligible to take part. The following exclusion criteria applied: inflammatory bowel disease, major cardiac disease (including previous myocardial infarction, congestive heart failure, atrial fibrillation/flutter, second- or third-order atrioventricular block), cerebrovascular disease (previous transient ischaemic attack or cerebrovascular accident), seizures in the last 5 years, previous vagotomy at any location, preoperative therapeutic radiotherapy, or regular prescription of medication known to mediate the normal physiological immune response (such as disease-modifying antirheumatic drugs).

#### Study setting

The study was undertaken at a single tertiary referral centre (the John Goligher Colorectal Unit, St James’s University Hospital, Leeds, UK). Treatment decisions were made by a multidisciplinary team of surgeons, oncologists and radiologists. Participants underwent surgery within a guideline-compliant enhanced recovery programme [12]. Preoperatively, this includes screening for anaemia, prophylactic antibiotics, prevention of nausea and minimal fasting. Intraoperatively, it includes principles of physiological normalization and short-acting anaesthesia. Anaesthetic protocols were not
standardized for the study. Postoperatively, it includes principles of multimodal analgesia, early oral intake and early mobilization.

**Interventions**

The nVNS was performed using the GammaCore® device (electroCore Inc.). This is a class IIa, noninvasive device which is CE marked for the treatment of gastric motility disorders. The device delivers an electrical impulse via two stainless steel electrodes mounted on a hand-held apparatus. The intensity of stimulation is self-adjustable and can be titrated to user comfort. Active devices deliver a 5 kHz sine wave burst lasting for 1 ms (five sine waves per 200 μs) repeated every 40 ms (peak voltage 24 V, peak output current 60 mA). Sham devices deliver a low-frequency (0.1 Hz) biphasic direct current impulse (amplitude 0–28 V through 15kΩ ± 10%) that is designed to be perceptible but subtherapeutic for stimulating the vagus nerve [13]. Participants received training from the investigator prior to use. The procedure involved application of conducting gel, self-adjustment of the stimulation intensity to the maximum tolerated level and placement of the device on the surface landmark of the cervical vagus nerve (carotid pulsation). Twice daily stimulation was performed for 120 s across the landmarks of both vagus nerves for 5 days prior to surgery and 5 days after.

**Outcomes and measures**

Safety outcomes included the incidence of complications within 30 days after surgery measured using the Clavien–Dindo scale (minor, grades I–II; major, grades III–V) and the incidence of treatment-related adverse events [14]. Each participant was assigned a single grade corresponding to the highest recorded complication. Early feasibility outcomes included self-reported compliance to the stimulation schedule and device usability measured using the modified System Usability Scale (SUS) [15]. The overall output of the SUS generates an arbitrary score out of 100, where 0–64 is considered ‘not acceptable’, 65–84 ‘acceptable’, and 85–100 ‘excellent’ (Appendix S1 in the Supporting Information). Clinical outcomes were days until first flatus, stool and tolerance of solid diet. These were expressed individually and then collapsed into composite measures of GI–2 (time to first stool and tolerance of solid diet) and GI–3 (time to first flatus or stool, and tolerance of solid diet), as reported previously [16]. The need for nasogastric tube intubation, parenteral nutrition and postoperative morphine consumption between days 0 and 3 (expressed as oral morphine equivalent values) were explored descriptively.

**Randomization and blinding**

Participants were randomized equally (1:1) to Sham and Active device groups, stratified by type of surgery (right-sided and left-sided). An independent statistician generated the randomization list with random permuted blocks. Randomization was performed by a research assistant who was not involved in confirming eligibility or consent. The same assistant prepared devices for allocation to participants by the investigator. Participants and the investigator (outcome assessor) were blinded to the allocation until completion of the study. All devices were identical in appearance, weight, visual feedback and user application.

**Sample size and statistics**

As an early development study, no formal hypothesis testing across the study groups was planned. A sample of 40 participants was considered sufficient to explore safety and early feasibility in order to justify and provide direction for future research. Data were expressed as means with standard deviation, medians with interquartile ranges.
(IQRs) or rates, as appropriate. Two populations were defined: the ‘safety population’, involving all consenting participants, and the ‘feasibility population’, involving consenting participants with exclusions in the event of reoperation or death occurring prior to completion of the intervention schedule. All comparisons were expressed descriptively and analyses were performed using IBM SPSS 22 (IBM Corp.).

Public involvement

A patient representative joined the study management team to help guide its design and delivery. In particular, their involvement helped to shape the design of patient-facing materials and training activities relating to the device. They continue to be involved in the conduct and interpretation of findings within a wider programme of research.

RESULTS

Participant flow

Between 1 January 2018 and 31 August 2019, a total of 297 patients were screened for eligibility and 72 met all criteria for inclusion. Forty participants agreed to take part and were randomized, including 19 to the sham device and 21 to the active device. A single participant in the Active group withdrew consent after randomization, leaving 39 participants in the trial safety population. A further two patients required reoperation prior to completing the intervention schedule, leaving 37 participants in the trial feasibility population. The type of surgery performed differed from the original stratification in three patients (Figure 1).

Participant and procedure characteristics

Overall, 20/39 (51.3%) participants were male and the median age was 68 years (IQR 61.5–76 years). The average body mass index was 28.8 ± 4.5 kg/m² and a single participant reported being a current smoker. Differences in participant characteristics between Sham and Active groups are shown in Table 1. Most procedures began laparoscopically (n = 36/39; 92.3%), with 3/39 (7.7%) requiring conversion to open surgery. The average duration of surgery was 191 ± 61 min and most resected specimens had a histologically confirmed T-stage of 2 or 3 (n = 22/39; 56.4%). Differences in procedure and pathology characteristics are shown in Table 2.

Device safety

In the safety population, 9/19 (47.4%) participants in the Sham group and 11/20 (55.0%) in the Active group experienced at least one postoperative complication. The majority of these were minor (Sham, n = 7/9, 77.8%; Active, n = 10/11, 90.1%). The incidence of specific complications was similar across both groups, with a small preponderance of pneumonia [n = 3 (15.8%) vs n = 1 (5.0%)] and surgical site infection [n = 3 (15.8%) vs (0.0%)] in the Sham group. There was a single case of unplanned hospital readmission and a single case of death recorded within 30 days of surgery in the Sham group. Treatment-related adverse events were infrequent and nonserious, with a single case of stimulation-site pain recorded in both Sham and Active groups. In both cases, this required no further intervention (Table 3).

| TABLE 1  |
|-----------|
| Participant characteristics          | Sham device (n = 19) | Active device (n = 20) |
| Age (years)‡ | 72 (60–80)       | 68 (62–73)        |
| Sex        |                  |
| Female     | 9 (47.4%)        | 10 (50.0%)        |
| Male       | 10 (52.6%)       | 10 (50.0%)        |
| BMI (kg/m²) | 28.9 ± 4.7   | 28.7 ± 4.5        |
| Current smoker | 0 (0.0%)     | 1 (5.0%)         |
| ASA classification |          |                  |
| 1          | 4 (21.1%)       | 3 (15.0%)        |
| 2          | 10 (52.6%)      | 15 (75.0%)       |
| 3          | 5 (26.3%)       | 2 (10.0%)        |
| 4–5        | 0 (0.0%)        | 0 (0.0%)         |
| Previous abdominal surgery |          |                  |
| History of chronic kidney disease | 1 (5.3%) | 0 (0.0%)         |
| History of COPD | 1 (5.3%) | 2 (10.0%)        |
| History of diabetes mellitus |            |                  |
| Diet/tablet controlled | 4 (21.1%) | 1 (5.0%)         |
| Insulin controlled | 1 (5.3%) | 1 (5.0%)         |
| History of ischaemic heart disease | 2 (10.5%) | 1 (5.0%)        |
| History of peripheral vascular disease | 0 (0.0%) | 0 (0.0%)        |
| Preoperative opioid use | 0 (0.0%) | 1 (5.0%)         |
| Preoperative haemoglobin level (g/L) | 125 ± 22 | 128 ± 18        |
| Preoperative albumin level (g/L)‡ | 36 ± 5.9 | 38 ± 2.8         |

Note: Data are reported as n (%) or as mean ± standard deviation unless stated otherwise.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

aData are reported as median (interquartile range).

bData available for n = 35 participants (Sham n = 18; Active n = 17).
Device compliance

In the feasibility population, compliance with the preoperative stimulation schedule was 4.7 ± 0.7 out of 5 days in the Sham group and 4.7 ± 1.1 in the Active group. Full compliance (5 days) was observed in 15/19 (78.9%) and 18/20 (90.0%), respectively. Compliance with the postoperative stimulation schedule was 4.1 ± 1.1 out of 5 days in the Sham group and 4.4 ± 1.5 in the Active group. Full compliance (5 days) was observed in 8/19 (42.1%) and 16/20 (76.2%), respectively. A decrease in compliance was observed on the first and final postoperative days, which was most prominent in the Sham group (Figure 2).

Device usability

In the feasibility population, the median SUS output was 80/100 (IQR 75–87.5) in the Sham group and 82.5/100 (IQR 74.4–97.5) in the Active group, indicating acceptable usability for both types of

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**Table 2: Procedure and pathology characteristics**

| Procedure                        | Sham device (n = 19) | Active device (n = 20) |
|----------------------------------|---------------------|------------------------|
| Right hemicolectomy              | 8 (42.1%)           | 8 (40.0%)              |
| Extended right hemicolectomy     | 1 (5.3%)            | 2 (10.0%)              |
| Transverse colectomy             | 0 (0.0%)            | 0 (0.0%)               |
| Left hemicolectomy               | 5 (26.3%)           | 3 (15.0%)              |
| Sigmoid colectomy                | 0 (0.0%)            | 0 (0.0%)               |
| Anterior resection               | 5 (26.3%)           | 7 (35.0%)              |
| Procedure approach               |                     |                        |
| Laparoscopic                     | 16 (84.2%)          | 20 (100.0%)            |
| Robotic                          | 3 (15.8%)           | 0 (0.0%)               |
| Conversion to open               | 2 (10.5%)           | 1 (5.0%)               |
| Unplanned stoma                  | 2 (10.5%)           | 1 (5.0%)               |
| Duration of surgery (min)        | 184 ± 64            | 198 ± 59               |
| Tumour T stage                   |                     |                        |
| T0 (premalignant)                | 0 (0.0%)            | 1 (5.0%)               |
| T1                                | 3 (15.8%)           | 3 (15.0%)              |
| T2                                | 3 (15.8%)           | 4 (20.0%)              |
| T3                                | 7 (36.8%)           | 8 (40.0%)              |
| T4                                | 4 (21.1%)           | 4 (20.0%)              |
| Not available                     | 2 (10.5%)           | 0 (0.0%)               |
| Tumour N stage                   |                     |                        |
| N0                                | 15 (78.9%)          | 11 (55.0%)             |
| N1                                | 1 (5.3%)            | 7 (35.0%)              |
| N2                                | 1 (5.3%)            | 2 (10.0%)              |
| Not available                     | 2 (10.5%)           | 0 (0.0%)               |
| Tumour M stage                   |                     |                        |
| M0                                | 16 (84.2%)          | 20 (100.0%)            |
| M1                                | 2 (10.5%)           | 0 (0.0%)               |
| Not available                     | 1 (5.3%)            | 0 (0.0%)               |

Notes: Data are reported as n (%) or as mean ± standard deviation. Disease stages are according to final postoperative histology.

**Table 3: Safety outcomes**

| Clavien–Dindo complication grade | Sham device (n = 19) | Active device (n = 20) |
|----------------------------------|---------------------|------------------------|
| No complication                  | 10 (52.6%)          | 9 (47.4%)              |
| Grade 1                          | 2 (10.5%)           | 7 (20.0%)              |
| Grade 2                          | 5 (26.3%)           | 3 (14.3%)              |
| Grade 3                          | 1 (5.3%)            | 1 (5.0%)               |
| Grade 4                          | 0 (0.0%)            | 0 (0.0%)               |
| Grade 5                          | 1 (5.3%)            | 0 (0.0%)               |

Postoperative complications

- Acute kidney injury 2 (10.5%) 0 (0.0%)
- Myocardial infarction 0 (0.0%) 0 (0.0%)
- Cerebrovascular event 0 (0.0%) 0 (0.0%)
- Anastomotic leak 1 (5.3%) 1 (5.0%)
- Intra-abdominal collection 0 (0.0%) 0 (0.0%)
- Venous access infection 0 (0.0%) 0 (0.0%)
- Pneumonia 3 (15.8%) 1 (5.0%)
- Venous thromboembolic event 0 (0.0%) 1 (5.0%)
- Surgical site infection 3 (15.8%) 0 (0.0%)
- Urinary tract infection 1 (5.3%) 1 (5.0%)
- Others a 4 (21.1%) 3 (15.0%)

Length of hospital stay (days)

- 7.4 ± 6.8 7.1 ± 5.3

Unplanned critical care admission 1 (5.3%) 1 (5.0%)

Hospital readmission 1 (5.3%) 0 (0.0%)

Mortality (within 30 days of surgery) 1 (5.3%) 0 (0.0%)

Treatment-related adverse events

- Headache 0 (0.0%) 0 (0.0%)
- Stimulation pain 1 (5.3%) 1 (5.0%)
- Tooth pain 0 (0.0%) 0 (0.0%)
- Neck strain 0 (0.0%) 0 (0.0%)
- Hoarseness 0 (0.0%) 0 (0.0%)
- Voice change 0 (0.0%) 0 (0.0%)

Note: Data are reported as n (%) or as mean ± standard deviation.

aOthers comprised: colonic perforation (n = 1; Sham); intra-abdominal haematoma (n = 1; Sham); high-output stoma (n = 1; Active); malaena (n = 1; Active); mechanical fall (n = 1; Sham); subcutaneous wound haematoma (n = 1; Active); wound dehiscence (n = 1; Sham).
device. Across both groups, 36/37 (97.3%) participants agreed or strongly agreed that the device was easy to use and 31/37 (83.8%) disagreed or strongly disagreed that it was cumbersome. When using the device, 34/37 (91.9%) participants felt confident and 2/37 (5.4%) felt that they needed assistance. When asked about training, 34/37 (91.9%) participants felt that most people would learn to use the device quickly. Differences between Sham and Active groups were minimal and are shown in Figure S1.

Bowel recovery outcomes

In the feasibility population, the most prominent differences in bowel recovery were time to first flatus (2.35 ± 1.32 vs 1.65 ± 0.88 days) and time to tolerance of solid diet (2.18 ± 2.21 vs 1.75 ± 0.91 days) in Sham and Active groups, respectively. The time to first stool was approximately the same across both groups (4.18 ± 1.85 vs 4.20 ± 1.36 days). When expressed positively, the time to achieve the GI–3 outcome was 2.94 ± 1.98 days. When expressed negatively, the time to achieve the GI–2 outcome was 4.53 ± 2.03 vs. 4.25 ± 1.33 days. Overall, a nasogastric tube was required in 5/37 (13.5%) participants, including 2/17 (11.8%) in the Sham and 3/20 (15.0%) in the Active group. Total parental nutrition was required by a single participant in each group. Postoperative morphine consumption between days 0 and 3 (expressed as oral morphine equivalent values) was 139 ± 175 mg and 122 ± 140 mg, respectively. A full outline of bowel recovery outcomes is shown in Table 4.

DISCUSSION

This early development study supports the feasibility of self-administered nVNS after major colorectal surgery. Treatment-related adverse events were infrequent, nonserious and similar across Sham and Active groups, indicating a satisfactory safety profile in this population of patients undergoing major colorectal surgery. Compliance with the stimulation schedule was good and the usability of the device was found to be readily acceptable. Whilst it is not possible to comment reliably on the clinical efficacy of the treatment from this study, the findings warrant further investigation in an adequately powered trial.

In preclinical models of ileus, electrical stimulation of the vagus nerve reduces intestinal inflammation and accelerates the recovery of bowel function via a cholinergic anti-inflammatory pathway in the gut [7]. Neuroanatomical evidence confirms that vagal efferents located in the bowel wall interact with macrophages (probably via enteric neurones) to reduce the expression of inflammatory mediators and decrease smooth muscle dysfunction [8,17]. This has been translated to patients undergoing laparotomy, where invasive stimulation of the vagus nerve has been shown to reduce interleukin (IL)-6 and IL-8 expressed in whole blood [9]. Invasive stimulation is challenging, however, as it requires dissection of the vagus nerve from the subdiaphragmatic oesophagus with a possible risk of injury and prolonged operating time. Noninvasive approaches mitigate this risk and are supported with similar evidence for proof-of-concept. For instance, in studies of healthy volunteers, nVNS increases cardiac vagal tone and reduces markers of systemic inflammation [13,18]. In preclinical studies, it increases intestinal transit and prevents both systematic and intestinal inflammation [19,20]. Interestingly, some evidence suggests that activation of the cholinergic anti-inflammatory pathway (using prucalopride) is more efficacious when done before surgery [21]. This is being explored further in a wider body of research [22] and is why patients performed pre- and postoperative stimulation in the present study.

This study provides constructive data to inform the ongoing translation of nVNS in the setting of major colorectal surgery. Firstly, overall compliance to the intervention was good but a small decrease was noted on the first and last postoperative days. It is speculated that the initial decrease may reflect difficulty in self-administering the device immediately after surgery, whilst the latter may reflect a lack of motivation once bowel function has returned. Secondly, the usability of the device was considered acceptable and approached the level considered to be excellent. This is promising in the current population since a number of challenges to self-administration exist in the perioperative period, including drowsiness, reduced mobility and pain. Whilst the current population comprised patients being treated for bowel cancer, it is proposed that these usability findings are generalizable across similar
settings of colorectal and abdominal surgery. Finally, the incidence of postoperative complications was balanced between groups and complications were mostly minor, which supports a satisfactory safety profile of nVNS in this surgical population. Importantly, this excluded patients with major cardiac or cerebrovascular disease, in whom nVNS may not be appropriate.

### TABLE 4 Bowel function outcomes

|                         | Sham device | Active device |
|-------------------------|-------------|--------------|
| **Time to first flatus (days)** | 17a | 20 | 1.65 ± 0.88 |
| All surgery             | 2.35 ± 1.32 | 2.63 ± 1.51 | 1.64 ± 0.81 |
| Right-sided surgery     | 9  | 11 | 2.11 ± 1.17 | 1.67 ± 1.00 |
| Left-sided surgery      | 8  | 11 | 4.18 ± 1.85 | 4.2 ± 1.36 |
| **Time to first stool (days)** | 17a | 20 | 4.2 ± 1.36 |
| All surgery             | 8  | 11 | 4.00 ± 1.93 | 4.09 ± 1.45 |
| Right-sided surgery     | 9  | 11 | 4.33 ± 1.87 | 4.33 ± 1.32 |
| Left-sided surgery      | 8  | 11 | 4.18 ± 1.85 | 4.25 ± 1.33 |
| **Time to tolerance of solid diet (days)** | 17a | 20 | 1.75 ± 0.91 |
| All surgery             | 8  | 11 | 3.25 ± 2.81 | 1.27 ± 0.47 |
| Right-sided surgery     | 9  | 11 | 1.22 ± 0.83 | 2.33 ± 1.00 |
| Left-sided surgery      | 8  | 11 | 4.53 ± 2.03 | 4.25 ± 1.33 |
| **Time to GI−2 composite outcome (days)** | 17a | 20 | 4.25 ± 1.33 |
| All surgery             | 8  | 11 | 4.63 ± 2.33 | 4.09 ± 1.45 |
| Right-sided surgery     | 9  | 11 | 4.44 ± 1.88 | 4.44 ± 1.24 |
| Left-sided surgery      | 8  | 11 | 2.33 ± 1.12 | 2.67 ± 1.00 |
| **Time to GI−3 composite outcome (days)** | 17a | 20 | 2.25 ± 0.85 |
| All surgery             | 8  | 11 | 3.63 ± 2.56 | 1.91 ± 0.54 |
| Right-sided surgery     | 9  | 11 | 2.33 ± 1.12 | 2.67 ± 1.00 |
| Left-sided surgery      | 8  | 11 | 4.53 ± 2.03 | 4.25 ± 1.33 |
| **Need for nasogastric tube** | 17a | 20 | 3 (15.0%) |
| All surgery             | 2 (11.8%) | 2 (11.8%) | 3 (15.0%) |
| Right-sided surgery     | 8  | 11 | 2 (25.0%) | 3 (27.3%) |
| Left-sided surgery      | 9  | 11 | 0 (0.0%) | 0 (0.0%) |
| **Need for parenteral nutrition** | 17a | 20 | 1 (5.0%) |
| All surgery             | 1 (5.9%) | 1 (5.9%) | 1 (5.0%) |
| Right-sided surgery     | 8  | 11 | 1 (12.5%) | 0 (0.0%) |
| Left-sided surgery      | 9  | 11 | 0 (0.0%) | 1 (11.1%) |
| **Oral morphine equivalent consumption (POD 0-3) (mg)** | 18b | 20 | 122 ± 140 |
| All surgery             | 139 ± 175 | 129 ± 174 | 122 ± 140 |
| Right-sided surgery     | 10 | 9 | 147 ± 185 | 9 | 153 ± 168 |

Notes: Data are reported as n (%) or as mean ± standard deviation. GI-2 and GI-3 are composite measures of bowel function as per the Method. Abbreviation: POD, postoperative day.

aTwo patients returned to theatre prior to the return of bowel function and are excluded from the analysis.
bOne patient returned to theatre prior to POD 3 and is excluded from the analysis.

Strengths of this study include its randomized and blinded design. This permitted an unbiased assessment of safety, compliance and acceptability, whilst balancing possible underlying confounders between groups. The use of a self-administered sham is novel and may represent a suitable comparator treatment in future definitive research. Questions remain, however, as to the robustness of sham controls in neuromodulation research due to possible placebo effects noted in previous reports [23]. Limitations are also recognized. Firstly, as an early development study, the sample size was purposefully small and was insufficient to draw conclusions related to clinical efficacy. Secondly, fluctuations in treatment compliance over time were most prominent in the Sham group, which may indicate a limitation in participant blinding. Since no formal assessment of blinding was performed, it was not possible to explore this further. Finally, to quantify clinical variability a wide selection of bowel-related outcomes were explored and the resulting observations were mixed. Whilst this is acceptable in an early development study, future studies of efficacy will demand a single agreed outcome or outcome set in order to reach decisive conclusions.

In summary, this early development study supports the safety, compliance and usability of self-administered nVNS after major colorectal surgery. Ongoing work will explore the feasibility of a definitive clinical trial, including considerations of recruitment, blinding, training activities and follow up. Importantly, it will also explore patient perspectives on the treatment schedule and will seek to identify residual barriers to compliance [22]. To support the selection of outcomes in a definitive trial and other similar research, a core outcome set for bowel recovery is under development by an international collaboration of patients and healthcare providers [24]. This will provide an agreed set of outcomes relevant to ileus after major abdominal surgery and will rationalize the variation in outcome reporting identified previously [25]. The role of patients and other stakeholder groups will be essential during this work to ensure that any positive findings are readily implementable in practice.

**CONFLICT OF INTERESTS**

No competing interests. This was an investigator-initiated, industry-supported study. Its design and analysis were performed independently of the industry partner.

**AUTHOR CONTRIBUTIONS**

SJC and DGJ conceptualized the study and its design. MN provided patient and public insight into the design and delivery of the study. SJC and JAH performed study activities and collected data. TC and NC provided statistical support. NC is the statistical guarantor and DGJ is the overall study guarantor.

**DATA AVAILABILITY STATEMENT**

Proposals for further analyses may be forwarded to the corresponding author. These shall be reviewed by the study team, including a
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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