Safety and Efficacy of Intermittent Colonic Exoperistals is Device to Treat Chronic Constipation: A Prospective Multicentric Clinical Trial

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Safety and Efficacy of Intermittent Colonic Exoperistalsis Device to Treat Chronic Constipation: A Prospective Multicentric Clinical Trial

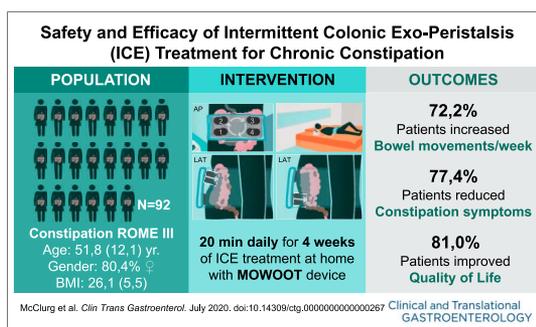Doreen McClurg, PhD[1], Lorna Booth, MSc[1] and Immaculada Herrero-Fresneda, PhD[2]

INTRODUCTION: Chronic constipation is associated with various comorbidities and reduced quality of life. Current solutions, either pharmacological or invasive, show limited efficacy. Manual colon-specific massage is a well-established intervention to treat chronic constipation, but it should be applied daily. MOWOOT automatically provides intermittent colonic exo-peristalsis (ICE) treatment like that in manual massage.

METHODS: This study assessed the safety and effectiveness of the ICE device to treat chronic constipation due to neurogenic bowel dysfunction or idiopathic causes with high component of pelvic floor disorders. The ICE device was used daily for 20 minutes over 4 weeks. Each participant was followed for 9 consecutive weeks. The same outcome measures (primary: complete bowel movements per week; secondary: Knowles Eccersley Scott Symptom Score and Patient Assessment of Constipation Quality of Life among others) were assessed at baseline (V1), last intervention weeks (V2), and post-treatment (V3). Responders were defined for selected outcomes as better results at V2 respect to V1.

RESULTS: N = 92 adult patients constituted the intention-to-treat population, with N = 65 as the per protocol population. Adherence (quantity of treatment received) was ≥95% in the intention-to-treat population. Adverse events related with the treatment were low (8.7%). Using the device significantly increased the number of complete bowel movements per week (V2 − V1 = 1.8 [2.7], $P < 0.0001$), reduced the symptoms of chronic constipation (Knowles Eccersley Scott Symptom Score V2 − V1 = −3.9 [5.0], $P < 0.0001$), improved quality of life (Patient Assessment of Constipation Quality of Life V2 − V1 = −0.7 [0.8], $P < 0.0001$), and facilitated a reduction in laxatives. Colon transit and fecal consistency were not modified. There was a high number of responders (>70%).

DISCUSSION: Considering safety, adherence, and efficacy being demonstrated, the results favor the use of MOWOOT to treat chronic constipation (Visual abstract, Supplementary Digital Content 1, http://links.lww.com/CTG/A440).

Safety and Efficacy of Intermittent Colonic Exo-Peristalsis (ICE) Treatment for Chronic Constipation

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INTRODUCTION

Constipation is a common condition (24% of the general population (1)) that is often managed by self-medication or medical consultation, but outcomes are not always satisfactory. The prevalence is up to 80% in patients with neurological conditions (2–4), such as spinal cord injury, multiple sclerosis, or Parkinson disease, and up to 60% in the elderly, especially if living in residential or care home settings (5).

Chronic constipation is associated with various comorbidities, such as fecal incontinence, fecal impaction, hemorrhoids, rectal prolapse, etc, (6–8) and, although rare, there are several potentially life-threatening complications (9,10). Furthermore, constipation is associated with increased psychological distress and reduced patient's health-related quality of life (8,11).

The guidelines on management of chronic constipation in adults are based on a step-by-step approach (12–14). After a first recommendation of lifestyle changes (increased fluid and fiber intake and physical activity), the next step is directly based on pharmaceutical solutions such as laxatives. However, most laxative agents show limited efficacy for the chronic use, especially in the elderly or neurogenic bowel dysfunction (NBD) populations with comorbid conditions and concomitant medications and the potential for adverse events (AEs) (15,16). Further steps include "minimal" invasive solutions (enemas and transanal irrigation) and finally highly invasive surgical procedures (colonic pacemakers implants or stoma) (9,17).

Manual colon-specific massage is a well-established intervention to treat chronic constipation (18–20). It is recommended as an adjunct treatment in some guidelines and can be administered by healthcare clinicians, but to achieve results, it should be applied daily, which is then expensive. For patients in home settings, this results in a serious drawback because they do not have daily access to a clinician or care taker to perform this massage, and self-administration is difficult, especially for the movement restricted, chronically ill and elderly population.

The MOWOOT device has been developed to address these obvious shortcomings of manual abdominal massage and provide an automated, intermittent colonic exo-peristalsis (ICE) treatment (Figure 1). The hypothesis of this trial was that the automatic and reproducible ICE treatment administered daily could ameliorate constipation in chronically affected people. Thus, the aim of the study was to assess the safety and effectiveness of automated ICE in home-use settings for patients suffering from chronic constipation due to NBD or idiopathic causes.

METHODS

Further information about methods is detailed in the protocol and SAP document in ClinicalTrials.gov (NCT04262752).

Study device and intermittent colonic exo-peristaltic treatment

MOWOOT (usMIMA S.L., Barcelona, Spain) is a CE-certified class IIa medical device that has been designed in collaboration with Institute Guttmann (Barcelona, Spain) to automatically administer a consistently reproducible ICE treatment without the input of a clinician or care taker.

The device is composed of 2 main pieces: the desktop box containing the control buttons to select the treatment time, frequency, and pressure and the massager belt that fits around the patient's abdomen using Velcro fastenings and provides the rhythmic ICE treatment (see Video on when and how use MOWOOT, Supplementary Digital Content 4, http://links.lww.com/CTG/A439).

The ICE treatment was designed according to physiological colon parameters (21–25) of pressure (0'5–0'7 bar) and frequency (8–13'25 cycles per minute) and can be administered once to 3 times a day for 5–20 minutes. To assure uniform treatment in all patients during the study, here, ICE treatment was fixed at 0'65 bar and 8 cycles per minute. The intervention consisted in 20 minutes of daily treatment with the ICE device for 4 weeks.

Study design

The study is a prospective, open-label, international multicenter trial. It complies with the Declaration of Helsinki (2013), ISO14155: 2011 standard, and the GCP & ICH guidelines according to the MEDDEV guidance. It was approved by the corresponding institutional ethics committees.

Designed to be conducted at home, each participant was followed on scheduled visits and telephone calls for 9 consecutive weeks. A healthy diet was maintained throughout the study. The same outcome measures were assessed before (2 weeks baseline, V1), immediately after the treatment (4 weeks intervention, V2), and again at the end of the study (1-week washout + 2 weeks post-treatment, V3) (Table 1).

Participants and sites

Adults with >1 year of chronic constipation, according to ROME-III criteria (26), due to either NBD or idiopathic causes, were recruited from tertiary centers by Glasgow Caledonian University (Glasgow, United Kingdom), Hospital de Terrassa (Barcelona, Spain) and Mútua de Terrassa (Barcelona, Spain). All patients were explored for constipation root cause and diagnosed as either idiopathic or NBD years before enrolling this study. NBD patients suffered from multiple sclerosis or Parkinson disease 5–15 years before commencing the trial and ranged in disability from using a walking stick to being confined to a wheelchair. Written informed consent was obtained from all participants. Inclusion and exclusion criteria are detailed in ClinicalTrials.gov (NCT04262752) and Supplementary Digital Content 1, http://links.lww.com/CTG/A436. Or the other way around, at your criteria.

Variables: primary and secondary end points

The primary outcome was the number of complete bowel movements per week as recorded in the bowel diaries. "Complete" means the subjects feel that they have emptied their bowels completely.

The secondary outcome measures aimed to assess the safety, efficacy, quality of life, and acceptability of the ICE treatment. Concomitant medication and adverse events were coded using the WHODRUGS and MEDDRA dictionaries, respectively. Minutes and complete massages received were automatically registered by the device software. Participants had to perform 80% of the massage intervention to be deemed adherent.
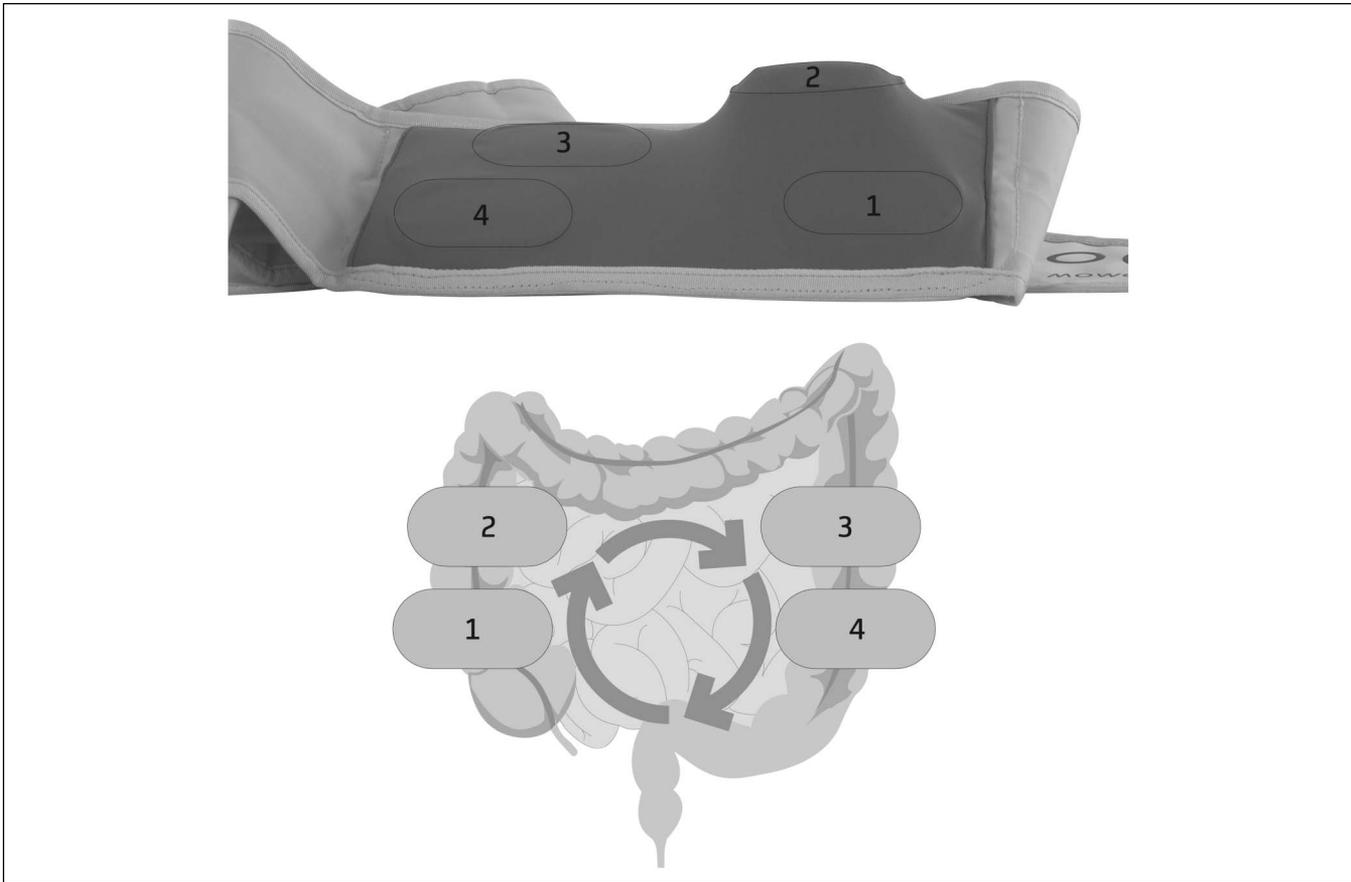
Figure 1. Intermittent colonic exo-peristalsis (ICE) device. The ICE device externally generates rhythmic, wave-like pressurizations on the abdomen following the colon's path, resembling the natural peristaltic contractions of a healthy colon. The actuators, positioned on the ascending and descending segments of the colon, inflate sequentially from 1 to 4 in clockwise direction. This cycle is continuously repeated for 20 minutes when the ICE device automatically stops the treatment.

Questionnaires and procedures

Bowel diary recorded desire to defecate, number of complete defecations, number of unsuccessful evacuation attempts, painful evacuation, abdominal pain, time taken to evacuate, straining effort, feeling of incomplete evacuation, bloating, influence of constipation on daily activities, need of digital assistance, laxatives, enemas and suppositories (LaxES) dosage and days of use, and concomitant medication.

Knowles Eccersley Scott Symptom Score (KESS (27)) is an 11-item questionnaire to diagnose constipation. The assessed items are duration of constipation, laxative use, frequency of bowel movements, unsuccessful evacuatory attempts, feeling of incomplete evacuation, abdominal pain, bloating, enemas/digitation, time taken, difficulty evacuation, and stool consistency. Total score ranges from 0 (no symptoms) to 39 (high symptom severity). A cutoff score of ≥11 indicates constipation.

Bristol stool scale (28) is a worldwide used visual analog scale (VAS) that semiquantitatively assesses fecal consistency from 1 (hard, pellet feces) to 7 (liquid diarrhea). Here, categories 1 and 2 indicate constipation, 3 and 4 are considered normal, and 5 to 7 indicate soft to liquid feces.

Colonic transit (CT) was evaluated in all participants under their usual LaxES treatment by a single abdominal x-ray at 120 hours after taking 20 radiopaque markers. People retaining >4 markers in the colon are classified under delayed CT (29).

The Patient Assessment of Constipation Quality of Life (PAC-QoL (30)) is a validated self-reported questionnaire that measures quality of life of subjects with constipation. Each of the 28 items is scored from 0 to 4. The lower the score the better quality of life.

Participants were also asked to rate their individual satisfaction with bowel function by answering the question "How do you feel about your defecatory function?" on a VAS from 0 ("No problems to defecate") to 10 ("A lot of problems to defecate").

Demographic and medical history information was collected during the recruitment visit V0. The idiopathic subjects underwent anorectal manometry (31,32) and a physical examination to assess possible functional defecation dysfunction (FDD). For ethical reasons, NBD subjects were excluded from these tests and were assumed to have some degree of FDD.

Subjects followed their usual LaxES treatment during the study period but were able to adjust intake according to any change in their symptoms unless medically advised not to. All concomitant medications taken during the study were recorded in the bowel diary.

In summary, the bowel diaries were filled out daily by the participants throughout the 9 weeks of the study. The questionnaires KESS, PAC-QoL, BRISTOL, and VAS were completed 3 times coinciding with the visits V1, V2, and V3. CT was assessed at V1 and V2 (Table 1).

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Table 1. Study design

Period	Recruitment	Basal control		Intervention (ICE interventional treatment)				Wash-out	Post-treatment	
Week		w1	w2	w3	w4	w5	w6	w7	w8	w9
Day		1–7 d	8–14 d	15–21 d	22–28 d	29–35 d	36–42 d	43–49 d	50–56 d	57–63 d
Visits and questionnaires	V0 informed consent	V1 (14 d) Bristol KESS PAC-QoL VAS		V2 (42 d) Bristol KESS PAC-QoL VAS					V3 (63 d) Bristol KESS PAC-QoL VAS	
Follow-up phone calls			Phone call d10	Phone call d17	Phone call d24	Phone call d31	Phone call d38		Phone call d52	Phone call d59
Bowel diary (BD)		BD1 w1	BD1 w2	BD2 w1	BD2 w2	BD2 w3	BD2 w4	BD w-o	BD3 w1	BD3 w2
CT's and manometry	Manometry	CT1 (pills d10, RX d14)		CT2 (pills d38, RX d42)						
ICE treatment		At V1: deliver ICE device (check NHU)		20 min daily at V2: collect ICE device (check NHU)						

There is no day 0. NHU is number of hours of use (automatically registered by the software of each device). Manometries were only done to idiopathic no-NBD patients, ideally at V0 but could be done at any time along the 9 weeks of the study. Questionnaires were filled at visit times.

CT, colonic transit; ICE, intermittent colonic exo-peristalsis; KESS, Knowles Eccersley Scott Symptom Score; PAC-QoL, Patient Assessment of Constipation Quality of Life; VAS, visual analogue scale.

Statistical analysis

The statistical analysis was performed according to the previously designed "Statistical Analysis Plan" using SAS version 9.4 and reported in accordance with the ICH E9 "Statistical Principles in Clinical Trials."

The sample size was established in n = 96 (see Supplemental Digital Content 2, http://links.lww.com/CTG/A437, detailing sample size). Analysis was performed by the intention-to-treat (ITT) population for all variables and the per protocol (PP) population for the primary outcome. All participants who underwent at least 1 intervention with the ICE device were included in the safety analysis (SAF).

The primary outcome was also analyzed with 2 imputation methods: last observation carried forward (LOCF) and mean methods. The categorical variables are summarized as percentages, whereas continuous variables are described as mean (SD). Statistical comparisons were made using 2-sided tests at the α = 0.05 significance level. For V2 − V1 analysis, the paired t test was used for numeric variables and the McNemar test was used for binary variables. In all cases, P values are presented. The ITT sample was also analyzed according to the presence or absence of NBD and to body mass index (BMI).

For the additional responder analysis, participants were dichotomized into yes/no for the primary and selected secondary outcomes according to the responder's definition "show better results after intervention respect to baseline" (V2 − V1 >0 for complete bowel movements per week and V2 − V1 <0 for KESS and PAC-QoL).

Multivariate analysis was adjusted by (i) effects of % LaxES dose per week and number of days with LaxES and/or digitation per week and (ii) covariate NBD.

RESULTS

One hundred patients were included into the study (Figure 2). Ninety-two received at least 1 treatment with the ICE device (ITT and SAF), and 65 completed the study as PP. Reasons for noncompletion included protocol deviations and dropouts unable to complete the intervention because of nonrelated worsening of multiple sclerosis (n = 4) and nonrelated adverse events (n = 4).

The mean BMI was 26.1 kg/m^2; average age was 51.8 years, and 80.4% were women (Table 2).

At baseline, 89% (82/92) of patients reported 4 to 6 of 6 of the symptoms included in the Rome III criteria. NBD was present in 59% (54/92; 53 with multiple sclerosis and 1 with Parkinson disease), with a mean history of 5–10 years of constipation symptoms. Idiopathic constipation was present in 41% (38/92) of participants and averaged more than 20 years with symptoms. Pelvic floor disorders/functional defecation disorders affected 95% (36/38) of idiopathic patients, with 52.8% of them presenting sphincter dyssynergia (Table 2). Delayed transit was present in 51% (47/92) of all participants (Table 2).

Primary outcome measure "complete bowel movements per week"

There was a significant increase of 1.8 in the number of complete bowel movements per week: V1 4.7 (3.4) to V2 6.5 (4.5), $P < 0.0001$ (Table 3). This result was consistent in both the PP and ITT populations with all the imputation methods used. In the multivariate analysis adjusted for effects of laxatives, enemas, suppositories, and digitations, there was also a significant mean difference of 1.84 ($P < 0.0001$) (Table 4). There was a similar number of responders (72.2% patients increasing their complete bowel movements) in idiopathic and NBD participants (Table 5). Except for the underweight participants, an increase in complete bowel movements per week was shown in all BMI groups ($P < 0.05$, $19 \leq$ BMI < 35) (Table 6).

Secondary outcomes

KESS score decreased by a mean of 3.9 ($P < 0.0001$) (Table 3 see Supplemental Digitary Content 3, http://links.lww.com/CTG/A438, detailing KESS score). In the multivariate analysis, there was also a significant mean decrease of 3.20 ($P < 0.001$) (Table 4).

The PAC-QoL decreased by a mean of 0.7 ($P < 0.001$) (Table 3). In the multivariate analysis, there was also a significant mean decrease of 0.61 ($P < 0.001$) (Table 4). Satisfaction as measured by the VAS also improved significantly −2.4 (2.6) $P < 0.001$.

The mean number of responders was from 77.4% (KESS) to 81% (PAC-QoL) (Table 5).
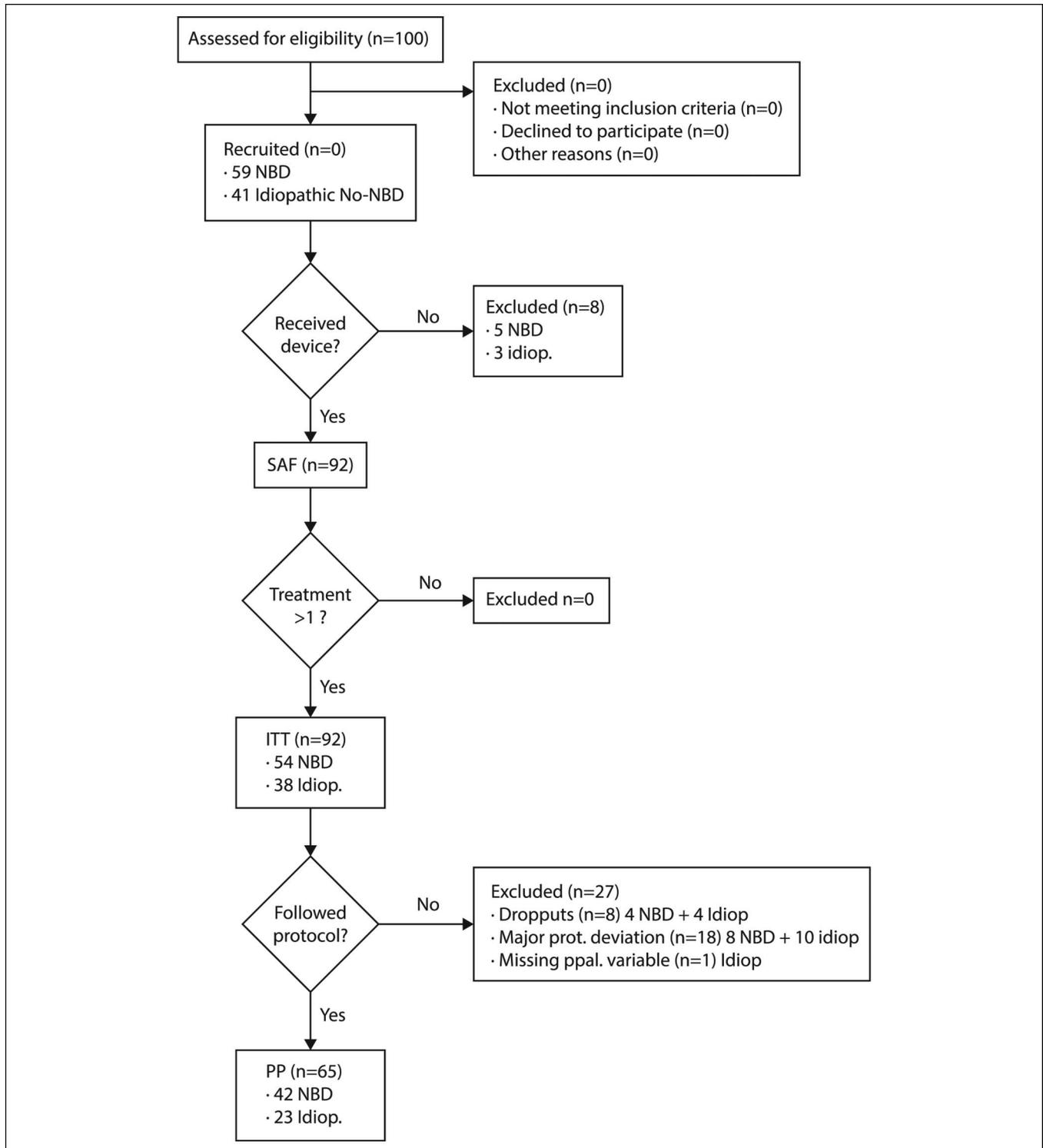
Figure 2. Flow chart. All subjects who received a device were included in the "safety" population (SAF) for safety analysis. All subjects who received at least 1 ICE treatment were included in the "intention-to-treat" population (ITT). The patients who followed the protocol as described were included in the "per protocol" population (PP). All outcomes were analyzed for the ITT population. The primary outcome was also analyzed for the PP population. In addition, the ITT population was analyzed comparing people with neurogenic bowel dysfunction (NBD) vs people with idiopathic constipation from unknown origin (idiopathic no-NBD).

In all BMI groups, the ICE treatment improved both the symptoms of chronic constipation ($P < 0.05$ in $19 \leq$ BMI<35) and the quality of life ($P < 0.05$ in BMI <35) (Table 6).

During the intervention, there was no change in the stool type, already normal at baseline, although there was a trend to softer stool (3.1 [1.8] to 3.3 [1.6]; $P = 0.3285$). The dose and number of

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Table 2. Demographic data and relevant history for constipation in the ITT population sample (n = 92) at enrolment

Demographic data	
Females, n (%)	74 (80.4)
Males, n (%)	18 (19.6)
Age, yr, mean (SD); min-max	51.8 (12.1); 19-74
Age, yr, median (Q1; Q3)	53.0 (46.0; 59.5)
BMI, kg/m^2, mean (SD); min-max	26.1 (5.5); 17-44
BMI, kg/m^2, median (Q1; Q3)	25.5 (21.7; 28.5)
ITT sample by BMI, n (%)	
Underweight (BMI <19)	4 (4.3)
Normal (19 ≤ BMI < 25)	40 (43.5)
Overweight (25 ≤ BMI < 30)	31 (33.7)
Obese I (30 ≤ BMI < 35)	11 (12)
Obese II (35 ≤ BMI < 40)	3 (3.3)
Obese III (40 ≤ BMI)	3 (3.3)
Relevant history for constipation, n (%)	
Neurologic disorders causing NBD	54 (58.7)
Neurologic disorders not causing NBD	10 (10.9)
NBD duration of constipation 5–10 yr	22 (41.5)
Non-NBD duration of constipation >20 yr	24 (63.2)
Psichiatric disorders	36 (39.1)
Metabolic/endocrinologic disorders	19 (20.7)
Laxatives (at enrollment)	63 (68.5)
Active medication	58 (63)
Medication inducing constipation (MIC)	42 (45.7)
Previous treatments for constipation	48 (52.2)
Pelvic floor disorders	>36 (39.1)
Pelvic floor surgery	30 (32.6)
Sensation of anal blockade or obstruction	73 (79.3)
Digital manoevres to evacuate	44 (47.8)
Obstetric trauma (over 74 women)	22 (29.7)
Delayed CT	47 (51.6)
Previous treatments for constipation, n (%)	
Laxatives	37 (40.2)
Anal irrigation	5 (5.4)
Biofeedback	3 (3.3)
Sacral neuromodulation	3 (3.3)
Suppositories/enemas	3 (3.3)
Abdominal massage	1 (1.1)
Ventral mesh rectocery	1 (1.1)
Pelvic floor disorders in no-NBD (N = 38), n (%)	
Pelvic surgery	21 (55.3)
Sensation of anal blockade or obstruction	30 (78.9)
Digital manoevres to evacuate	22 (57.9)

Table 2. (*continued*)

Demographic data	
Obstetric trauma (over 36 women)	11 (30.6)
Vaginal vault prolapse (over 36 women)	2 (5.5)
Rectocele	9 (24.3)
Cystocele	1 (2.7)
Sphincter dyssynergia	19 (52.8)

Most subjects were women and middle aged. The most common neurologic disorders not causing NBD were migraine and fibromyalgia. The mainpsychiatric disorders described were depression and anxiety. Principal metabolic or endocrinological disorders were Diabetes Mellitus and hypothyroidism. Apart from laxatives, the main active medication taken by patients during the study were antidepressants and antihypertensive drugs. The MIC mainly comprises opioids, benzodiazepine derivates, selective serotonin inhibitors, calcium + vitamin D, and some nonsteroidal anti-inflammatory drugs. All the 38 (100%) idiopathic no-NBD patients tried previous treatments for constipation, mainly laxatives. The physical examination and manometry performed only to no-NBD subjects revealed that 36 out of 38 (94.7%) presented with one or more pelvic floor problem, with 52.8% patients with sphincter dyssynergia.
BMI, body mass index; CT, colonic transit; ITT, intention to treat; NBD, neurogenic bowel dysfunction.

days per week with laxatives or suppositories were reduced (% dose Lax: −11.0 (75.3) P = 0.0075; days Lax: −0.4 (1.7) P = 0.0278; %dose Sup: −14.7 (74.5) P = 0.0297; days Sup: −0.2 (0.8) P = 0.0071). The number of days that enemas or digitation were used also reduced slightly, but not significantly.

At baseline, 51% of patients were classified under "delayed CT." After the intervention it decreased, although not significantly, to 46.3%.

All secondary outcomes showed a trend to return to control basal values after the wash out and post-treatment period (V3), except for LaxES, which continued to slope down (Table 3).

Adherence of the 92 patients, i.e., the mean percentage of the actual vs predefined treatment durations (minutes) and the mean percentage of the actual vs predefined completed treatments (number of complete massages), was 96% (SD 14) and 95% (SD 14), respectively, as recorded by the ICE device. Many of the patients were keen to keep the device and continue to use it after the trial was complete.

Safety results

There were no serious adverse events (n = 0) related with the ICE device (Table 7). Only 1 serious adverse event occurred (1.1%, foot cellulitis, recovered), which was not related with the intervention. The total number of registered AEs was n = 62, affecting n = 35 participants (38.0%). Only n = 8 (8.7%) of these AEs might be related with the use of the ICE device. All patients recovered from their unrelated AE's.

DISCUSSION

This is the first large study on the use of a mechanical device to perform abdominal massage for the relief of symptoms of chronic constipation and overcomes the inherent lack of standardization when either care takers or patients themselves undertake the massage, whilst conferring autonomy to the patient.

Table 3. Primary and secondary outcomes

	V1	V2	V3	V2 − V1	$P_{V2 − V1}$	$P_{NBD\ vs\ no-NBD}$
No. of complete bowel movements per week						
PP	5.0 (3.6)	6.7 (4.6)	5.1 (3.9)	1.6 (2.7)	<0.0001	
ITT (no imputation)	4.7 (3.4)	6.5 (4.5)	5.0 (4.5)	1.8 (2.7)	<0.0001	
ITT (LOCF)	4.7 (3.5)	6.5 (4.4)	5.0 (5.1)	1.8 (2.6)	<0.0001	
ITT (mean method)	4.7 (3.5)	6.5 (4.5)	5.0 (5.1)	1.8 (2.7)	<0.0001	
KESS score						
All	20.6 (5.9)	16.9 (7.2)	18.4 (6.6)	−3.9 (5.0)	<0.0001	
NBD	18.5 (5.3)	13.5 (5.8)	15.9 (6.1)	−5.2 (4.8)	<0.0001	0.0043
No-NBD	23.6 (5.4)	22.1 (6.1)	22.0 (5.6)	−2.1 (4.8)	0.0178	
PAC-QoL						
All	2.3 (0.7)	1.6 (0.9)	2.0 (0.9)	−0.7 (0.8)	<0.0001	
NBD	2.1 (0.7)	1.2 (0.8)	1.8 (0.9)	−1.0 (0.8)	<0.0001	<0.0001
No-NBD	2.5 (0.8)	2.3 (0.7)	2.4 (0.7)	−0.2 (0.5)	0.0158	

The primary outcome was analyzed for the PP population (n = 65) and for the ITT population (n = 92) with 2 imputation methods: LOCF and mean method. Results displayed as mean (SD). P: paired t test for bivariant analysis V2 − V1, and unpaired t test in KESS and PAC-QoL for comparing NBD (n = 54) vs no-NBD (n = 38). According to KESS, the score 11 acts as cut-off for considering a person as "no constipated" (score ≤11) or "constipated" (score >11). The lower score of PAC-QoL the better quality of life. Above 2 is considered as "unsatisfaction" rate and below 2 as "satisfaction."
ITT, intention to treat; KESS, Knowles Eccersley Scott Symptom Score; LOCF, last observation carried forward; NBD, neurogenic bowel dysfunction; PAC-QoL, Patient Assessment of Constipation Quality of Life.

Manual abdominal massage has been shown to be beneficial for the treatment of chronic constipation in clinical trials at distinct settings (18–20,33–36). Because the ICE medical device reproduces the abdominal manual massage, its mechanism of action should be the same. It is hypothesized that this may include one or more of the following:

1. Mechanical mobilization and propulsion of feces (37,38),
2. stimulation of colonic secretion and hydration by enhancing blood flow (39),
3. restoring parasympathetic tone and stimulating somato-autonomic reflexes (18,40,41),
4. stimulation of colonic motility by increasing serotonin levels (42), and
5. improving microbiota composition (43) and reducing abdominal bloating (44,45).

The number of complete defecations per week increased significantly during the treatment period despite a reduction in the use of laxatives and suppositories while stool consistency became softer. In addition, after the intervention constipation symptoms—such as

Table 4. Multivariant analysis adjusted by laxatives, enemas, suppositories (LaxES), and digitations

	V2 − V1 mean	95% CI	$P_{V2 − V1}$	$P_{NBD\ vs\ no-NBD}$
No. of complete bowel movements per week				
All	1.84	1.15 to 2.54	<0.0001	—
NBD	2.04	1.30 to 2.79	<0.0001	0.4317
No-NBD	1.57	0.66 to 2.48	0.0007	
KESS score				
All	−3.20	−4.32 to −2.07	<0.0001	—
NBD	−5.18	−6.48 to −3.88	<0.0001	0.0022
No-NBD	−1.95	−3.55 to −0.36	0.0165	
PAC-QoL				
All	−0.61	−0.79 to −0.43		—
NBD	−0.96	−1.14 to −0.78	<0.0001	<0.0001
No-NBD	−0.17	−0.40 to 0.05	0.1281	

Mean of differences between V2 and V1 adjusted by effect of % recommended dose of LaxES per week and number of days with LaxES and/or digitation per week. Results confirmed the same differences than those in the bivariant analysis.
CI, confidence interval; KESS, Knowles Eccersley Scott Symptom Score; NBD, neurogenic bowel dysfunction; PAC-QoL, Patient Assessment of Constipation Quality of Life.

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Table 5. Responder analysis

	All	NBD	No-NBD	OR	*P*
No. of complete bowel movements per week	72.2%	70.2%	75.0%	1.25	0.6653
KESS	77.4%	86.0%	64.7%	3.34	0.0274
PAC-QoL	81.0%	90.0%	67.6%	4.59	0.0121

An additional responder analysis was done for the primary and selected secondary outcomes. Responders were defined as those participants showing better results after intervention respect to baseline, this is, V2 − V1 >0 for complete bowel movements per week; and V2 − V1 <0 for KESS and PAC-QoL. Results are displayed as % of participants responding to the treatment for each assessed outcome. OR and *P* for NBD vs no-NBD.
KESS, Knowles Eccersley Scott Symptom Score; NBD, neurogenic bowel dysfunction; OR, odds ratio; PAC-QoL, Patient Assessment of Constipation Quality of Life.

feeling of incomplete evacuation, bloating, and abdominal pain, pain in evacuation, and time taken—ameliorated (see Table, Supplementary Digital Content 3, http://links.lww.com/CTG/A438, with KESS detail). Moreover, participants reported a significant increase in quality of life and satisfaction after the ICE treatment. The users reported the ICE experience as still and relaxing. Accordingly, the adherence to treatment was notably high (>95%) in contrast with another innovative but invasive solution also intended to induce peristalsis (46).

Altogether, the participants showed significant improvements and benefited from MOWOOT treatment. Overweight and obese patients included. A slight tendency to even higher response rates was observed for the neurogenic patients. A possible explanation might be found in the loss of muscle tone in the abdominal wall of the NBD patients because of the high level of disability of some. The benefits of abdominal massage in spinal cord injury people, who likely do have more definable impairments in abdominal wall contractile function, has been already described (34). Another possible reason might be the long-standing, more severe constipation of the enrolled idiopathic patients (baseline KESS score 23.6; 95% FDD). Evacuatory disorders alone would be a reason for a propulsive therapy such as MOWOOT to fail just like it could be a reason for previous failure of oral laxatives in such patients.

Because FDD could be responsible for delayed CT (47–49) and the ICE treatment does not treat pelvic floor problems, it is not surprising that the percentage of those with delayed CT did not change significantly overall or within the NBD or idiopathic groups. Moreover, nearly all the non-NBD patients in our sample were affected by FDD, and those who suffer from NBD most likely have some degree of dyssynergia. Thus, all of them may have had a delayed marker test from the FDD.

People with multiple sclerosis have a higher incidence of constipation compared with the general population, but the causative factors are not fully understood (50). It is believed to be a combination including intrinsic gut pathology potentially causing reduced transit, pelvic floor dyssynergia, and multifactorial behavioral scenarios, e.g., medication, diet, reduced exercise, etc. The treatment options, however, are limited and often using, for example, laxatives increases the likelihood of fecal incontinence, and patients usually dislike taking additional medication. Transanal irrigation has also shown some efficacy but is not always continued (51). An option such as using the ICE treatment is an important addition in their

overall management strategy that can be used as a stand-alone treatment or in combination.

The ICE treatment should be performed at least once a day as long as the symptoms of constipation persist. In contrast to laxatives, MOWOOT treatment is more effective in the long term, the more habitually it is performed. It is possible to interrupt the treatment for a few days if needed. However, patients must resume treatment immediately regularly to avoid recurrence, as shown by the post-treatment data.

Our study has some limitations. One is the lack of manometry in the NBD patients (not done for ethical reasons), and another is the single x-ray method used that does not allow to measure the CT time but only to assess normal vs delayed CT. Thus, we cannot further discuss the influence of FDD on transit time in our sample. Finally, as a medical device trial, patients and investigators could not be blind to treatment, but those

Table 6. Outcomes by body mass index (BMI)

	V2 − V1	P_{V2-V1}
Complete bowel movements per week		
All	1.6 (2.7)	<0.0001
Underweight (BMI <19)	−0.3 (1.6)	0.7538
Normal (19 ≤ BMI < 25)	1.5 (2.6)	0.0017
Overweight (25 ≤ BMI < 30)	1.8 (2.7)	0.0018
Obese I (30 ≤ BMI < 35)	2.7 (3.4)	0.0255
Obese II (35 ≤ BMI < 40)	3.5 (2.3)	0.1181
Obese III (40 ≤ BMI)	3.0 (1.4)	0.2048
KESS score		
All	−3.9 (5.0)	<0.0001
Underweight (BMI < 19)	−5.7 (5.7)	0.2265
Normal (19 ≤ BMI < 25)	−3.3 (4.7)	<0.0001
Overweight (25 ≤ BMI < 30)	−2.8 (3.8)	0.0006
Obese I (30 ≤ BMI < 35)	−6.9 (7.6)	0.0185
Obese II (35 ≤ BMI < 40)	−5.7 (3.1)	0.0848
Obese III (40 ≤ BMI)	−10.5 (3.5)	0.1488
PAC-QoL		
All	−0.7 (0.8)	<0.0001
Underweight (BMI < 19)	−1.7 (0.6)	0.0368
Normal (19 ≤ BMI < 25)	−0.6 (0.8)	<0.0001
Overweight (25 ≤ BMI < 30)	−0.4 (0.6)	0.0031
Obese I (30 ≤ BMI < 35)	−0.9 (0.8)	0.0019
Obese II (35 ≤ BMI < 40)	−1.0 (0.6)	0.0947
Obese III (40 ≤ BMI)	−1.2 (1.0)	0.3385

A statistical additional analysis was carried out on a potentially limiting high BMI. The data were segmented into 6 groups by obesity severity based on the World Health Organization classification (see also Table 2). Results displayed as mean (SD). *P*: paired Wilcoxon test. Except for the primary outcome in the underweight patients, all the outcomes improved in all BMI segments. In the extreme groups (underweight: n = 4, obese II and III: n = 3 each) statistical significance could not be achieved.
KESS, Knowles Eccersley Scott Symptom Score; NBD, neurogenic bowel dysfunction; PAC-QoL, Patient Assessment of Constipation Quality of Life.

Table 7. Adverse events (AEs) possibly related with the intermittent colonic exo-peristalsis device

	Patients, n (%)	Events, n	Duration (d)	Severity
Abdominal distension (gastrointestinal disease)	2 (2.2)	2	3.0 (0.0)	Moderate
Abdominal pain (gastrointestinal disease)	1 (1.1)	1	11.0 (0.0)	Moderate
Diarrhoea (gastrointestinal disease)	1 (1.1)	1	2.0 (0.0)	Mild
Back pain (musculoskeletal and connective tissue disease)	2 (2.2)	2	6.5 (4.9)	Moderate
Urinary tract infection (infections and infestation)	1 (1.1)	1	8.0 (0.0)	Mild
Erythema (skin and subcutaneous tissue disease)	1 (1.1)	1	1.0 (0.0)	Mild

Each AE is described according to preferred term (system organ class). The results are displayed as number and percentage of patients reporting each AE, and number of events reported for each AE (i.e., 2 patients reported 1 abdominal distension event each). All participants spontaneously recovered from their AE's. Only 4 did not complete the study due to an unrelated AE.

undertaking the analysis were. The common recommendation for a clinical design is a randomized controlled trial. However, a self-controlled trial was favored here, as in other trials with chronically constipated people (46) reflecting the heterogeneity of both the pathology and the conventional treatment approach (52–55) and can produce statistically valid and relevant data while reducing the number of participants and time (56–60) (see Supplementary Digital Content 2, http://links.lww.com/CTG/A437, detailing sample size).

Further studies are required to determine the cost-effectiveness of using the ICE device. At present, the initial out-lay may be prohibitive and long-term effectiveness needs to be established to offset the initial expenditure. Using a care taker to undertake the massage is also expensive, whereas self-massage can be ineffective and tiring to the patient; however, laxative use can be costly both to the national health system and the patient. The consequences of some cases of chronic constipation can be serious; indeed, the cost to the NHS in England of unplanned emergency hospital admissions was £71 million in 2017/18 with the average General Practitioner seeing 6.3 patients a week with constipation (61). Unfortunately, in extreme cases, death can occur. The results of this study are therefore important because it provides a simple yet effective additional treatment option as part of a management pathway for the treatment of chronic constipation.

Considering that either the safety, adherence, and the efficacy of the ICE treatment have been demonstrated, the results favors the use of MOWOOT to treat chronic constipation. We have demonstrated that using the device daily for 4 weeks significantly increased the evacuation frequency, reduced the symptoms of chronic constipation, improved quality of life, and, in some instances, facilitated a reduction in the use of laxatives.

We suggest that the device could also be used in other populations in which chronic constipation prevalence is high, i.e., those with reduced mobility, in a care home setting or on long-term medication, e.g., opioids, and its use should therefore be considered as a no-drug, noninvasive self-help management option.

CONFLICTS OF INTEREST

Guarantor of the article: Immaculada Herrero-Fresneda, PhD.
Specific author contributions: D.M.: as lead principal investigator, designed and conducted the study; reviewed the statistical analysis plan, interpreted data, and wrote the manuscript. L.B.: as nurse investigator, conducted the study and collected the data. I.H.F.: as coordinator investigator, designed the study and the statistical analysis plan, interpreted the data, and wrote the manuscript.

Study Highlights

WHAT IS KNOWN

✓ Chronic constipation is a common condition with numerous comorbidities and reduced patient's health-related quality of life.

✓ Current treatment for chronic constipation including pharmacological and invasive therapies have limited efficacy.

✓ Abdominal massage, a well-established intervention to treat constipation, needs to be received daily for 10–20 minutes with force enough to be effective.

WHAT IS NEW HERE

✓ MOWOOT is a medical device that automatically reproduces an intermittent colonic exo-peristaltic (ICE) treatment similar to manual abdominal massage.

✓ The ICE treatment is shown here to be safe and efficacious against chronic constipation.

TRANSLATIONAL IMPACT

✓ The ICE medical device enables patients to daily apply a colon-specific abdominal massage autonomously at home with 100% reproducibility.

✓ The ICE treatment may reduce the use of laxatives on an individual basis. If used at early stages of constipation, it could avoid colon surgical interventions in the long term.

COLON

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