

Efficacy and safety of vibrating capsule for functional constipation (VICONs): A randomised, double-blind, placebo-controlled, multicenter trial

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Summary

Background Functional constipation (FC) is an intractable disease that carries large financial burden as well as emotional and physical stress. We aimed to assess the efficacy and safety of the newly developed smartphone-controlled vibrating capsule (VC) in patients with FC.

Methods From December 2018 to February 2020, we did a multicenter, blinded, placebo-controlled randomised trial in six top general hospitals in China focusing on patients aged 18 to 80 with FC. Patients were randomly assigned in a 1:1 ratio to receive VCs or placebo treatment for six weeks (two capsules per week) after a two-week baseline period. The primary outcome was the responder rate, defined as the proportion of patients with an increase of at least one complete spontaneous bowel movement (CSBM) per week during treatment compared to baseline in the full analysis set. This trial is registered with ClinicalTrials.gov, number NCT04671264, and is completed.

Findings 107 patients aged from 18 to 74 were randomly assigned to receive VC ($n = 53$) or placebo treatment ($n = 54$). The responder rate in the VC group was significantly higher than that in the placebo group (64.2% vs. 35.8%; difference, 27.7% [95% CI, 10.4–45.1]; $P = 0.005$). More patients in the VC group reported weekly CSBMs ≥ 1 for at least four weeks during treatment (difference, 22.7% [95% CI, 8–46]; $P = 0.022$) and follow-up period (difference, 17.3% [95% CI, 0–35]; $P = 0.048$). The mean Patient Assessment of Constipation-Symptoms score and Patient Assessment of Constipation-Quality of Life score differed significantly from the baseline in both groups (all $P < 0.0001$). The most common adverse event associated with VC was abdominal discomfort (3.7%).

Interpretation VCs can promote defecation, as well as ameliorating symptoms and improving the quality of life in patients with FC with sustained efficacy. VC appears to be a potential alternative physical treatment for FC with the exact mechanism and parameters warranting further investigation.

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Keywords: Vibrating capsule; Functional constipation; Randomised controlled trial; Complete spontaneous bowel movement

Abbreviations: FC, Functional constipation; VC, Vibrating capsule; CSBM, Complete spontaneous bowel movement

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Research in context

Evidence before this study

Vibrating capsule (VC) is based on the concept of physiotherapeutics, and the effect of VC in patients with functional constipation (FC) has not been thoroughly investigated. We searched PubMed for articles published up to February 1, 2022, using the search terms (“vibrating capsule” OR “vibrant capsule” and “constipation”) with no language restriction, and identified four relevant articles, with one published by our team carried out in animals, and three clinical trials. Confirmative data supporting the effect of VC in patients with FC were not provided.

Added value of this study

This randomised trial confirmed the efficacy of VC, an innovative non-pharmacological treatment modality for FC for the first time. More patients in the VC group reported ≥ 1 complete spontaneous bowel movement per week over baseline during the treatment period (64% vs. 36%), with a between-group difference of 28% (95% CI, 10–45%, $P = 0.005$). Results showed that VCs can promote defecation, ameliorate symptoms, and improve the quality of life in patients with FC with sustained efficacy.

Implications of all the available evidence

With continuous innovations in treatment modalities, the availability of abdominal physical stimulation is increasingly being recognized. To our knowledge, this is the first multicenter randomised clinical trial to validate the superiority of novel smartphone-controlled VCs in the treatment of FC. VC might be a valuable and promising non-pharmacotherapy option for patients with FC and the inspiring results of VCs might help launch a new era of capsule endoscopy as a therapeutic modality.

Introduction

As a type of functional bowel disorder, functional constipation (FC) is diagnosed according to the symptom-based Rome criteria, with symptoms of difficult, infrequent, or incomplete defecation and altered stool consistency without an organic etiology.¹ A large-size meta-analysis reported a pooled prevalence of chronic idiopathic constipation (CIC) as 14% (95% CI, 12–17%) in the general population,² which was even more common and severe in women, elderly individuals,³ and those with lower socioeconomic status,² and is expected to rise over the next few years.⁴ An eastern population-based survey showed that the prevalence of FC, a subtype of CIC, was approximately 6.1%⁵ and was even higher in the west, as 7.9–8.6%.⁶ Repeated

consultations, unnecessary investigations, and a long disease course greatly affect the quality of life and psychological pressure of patients⁷ and constitute a huge financial burden,⁸ bringing significant challenges in disease management. The mainstays of treatment include diet and lifestyle interventions and pharmacological, surgery, and biofeedback therapy.⁹ Due to drug dependence, drug tolerance and side effects, including exacerbated constipation, and melanosis coli,¹⁰ non-pharmacological treatments have gradually received attention but are variable in quality.¹¹

Vibrating capsules (VCs) are based on the concept of physiotherapeutics and were first proposed by Ron et al.¹² as a safe and effective approach to promote mean weekly spontaneous bowel movements (SBMs) in patients with CIC. The assumption is that mechanical induced normal peristaltic waves in the large intestine will improve motility and alleviate constipation. However, the efficacy of VC in accelerating colonic transit was not validated in another study.¹³ Given the defects and equivocal results in previous studies, we developed an innovative, smartphone-controlled VC system. The safety and efficacy in promoting defecation have been elucidated in animal studies¹⁴ and our pilot study.¹⁵ Thus, the objective of this study was to assess the efficacy and safety of these novel VCs for FC treatment.

Methods

Study design and participants

We conducted a multicenter, blinded, placebo-controlled randomised trial in six top general hospitals in China. The study protocol appears in Supplement 1. Patients with FC were prospectively enrolled from December 14, 2018, to February 24, 2020. The study was approved by the institutional review board at all participating centers. No subsequent amendments of the protocol were made in the process of study implementation. The trial was performed in accordance with the principles of the Declaration of Helsinki and reported in accordance with CONSORT guidelines. An independent Data and safety monitoring committee (DSMC) appointed by the ethics committee and the Shanghai and National Medical Products Administration provided trial regular oversight.

The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial and this report to the protocol.

Patients from 18 to 80 years of age with FC (revised Rome IV criteria) were recruited from the outpatient clinic for eligibility evaluation, with self-reported complete spontaneous bowel movements (CSBMs) per week as less than three for the last three months and symptom onset at least six months prior to enrollment and presenting with at least one of the following symptoms during more than 25% of defecations: straining, lumpy

or hard stools based on Bristol Stool Form Scale (BSFS), sensation of incomplete evacuation, and sensation of anorectal obstruction/blockage and manual maneuvers to facilitate defecation.

Patients were excluded if they were pregnant or lactating or had “alarm” symptoms in recent years, including abnormal weight loss (more than 10% in the last three months), bloody stool (except hemorrhoids), infection, allergies to polymeric materials, and a permanent pacemaker (e.g., implantable cardioverter-defibrillator) or any electronic/magnetic/mechanically controlled devices; had difficulty swallowing the capsules; had organic lesions (including Zenker’s diverticulum, suspected bowel obstruction, bowel perforation, diabetes mellitus, gastric outlet obstruction prior to bowel obstruction, and Crohn’s disease); or refused to participate. Patients could be enrolled one month after polypectomy (except for ESD) with a diameter of polyps less than one centimeter; otherwise, the interval was prolonged to three months. Colonoscopy was required in patients without colonoscopy within a year. Patients did not swallow the capsules until three weeks after the colonoscopy for restoration of baseline defecation. Patients were asked to refrain from making any major lifestyle changes (e.g., starting a new diet or changing their exercise pattern) during the study. Written informed consent was obtained from each patient before eligibility evaluation.

Randomisation and masking

Randomisation occurred in a 1:1 fashion stratified by enrolling hospitals using randomisation block sizes of four with a random number table generated by the investigator using a central randomisation system. Allocation sequence with sham capsules or VCs were prepared and stored in sequentially numbered, opaque, sealed envelopes. Patients, clinical research coordinators (CRCs), and outcome assessors remained unaware of the treatment assignments until the database was unlocked. Allocation was not revealed until the end of the trial or the occurrence of serious adverse events (SAEs) related to VC.

Procedures

The entire process included a two-week run-in period¹⁶ and a six-week treatment period, followed by a follow-up period of four weeks or until the use of laxatives. The run-in period allowed for wash out of laxatives and other disallowed medications, eligibility evaluation, and gathering of baseline from diary cards filled out by patients. Eligible patients were randomly assigned to the VC group or identical sham capsule group by CRCs.

The VC system (Vibravot, Ankon Medical Technology Co., Ltd) consisted of a vibrating capsule, an external configuration device (ECD), and a mobile

application named Weitong. The capsule was 26.7 mm in length, 11.8 mm in diameter, and 4.5 g in weight.¹⁴ VC details are available in Supplement 1. The vibrating sequence began after a predetermined delay of 8 h to allow the capsules to enter the colon, and the vibration lasted for six hours. Vibration was set at twelve cycles per minute in a low-medium-high stimulation loop with a frequency of three to nine Hz. In case of adverse events (AEs), patients could suspend or restart the vibration through phone or ECD after consultation with the investigators. The appearance, regimen of administration and wireless communication of the sham capsules were identical to VCs with no vibration occurring.

During treatment, patients were required to swallow one capsule every three to four days for a total of twelve capsules. Bisacodyl enteric-coated tablets no more than 15 mg (Pharmaceutical University Pharmaceutical Co., Ltd, Nanjing, China) or enema (intolerance of bisacodyl tablets) were allowed as rescue medicine to relieve severe constipation (defined as no defecation for at least 72 h or onset of intolerable symptoms) after consultation with investigators and were forbidden within 24 h before or after administration of capsules. Patients with capsules in the body should be kept away from a strong magnetic field, and no more than two capsules should be allowed in the body at the same time. Otherwise, rescue medicine should be applied. Patients were required to complete the daily diary cards (Supplement 1 Appendix 4) and were required to visit every two weeks (a window of three days) for distribution and retrieval of capsules, rescue medicine and diary cards and evaluation of efficacy and safety during the six-week study period.

Once capsule retention occurs (the capsule remains in the body for more than 14 days), endoscopy may be performed for capsule removal. All AEs reported by the patients or discovered from electronic medical records were assessed for severity and relationship with study treatment by the investigators, with appropriate measures taken in time and documented in detail. SAEs had to be reported to the principal investigator and DSMC within 24 h.

Outcomes

The primary outcome was the responder rate, defined as the proportion of patients with an increase of CSBMs/week ≥ 1 ¹⁷ during the six-week treatment period compared to baseline. A CSBM was defined as an SBM (occurring in the absence of rescue medication within 24 h of the BM), with the report of a sense of complete evacuation.

The prespecified key secondary outcomes included the change in the mean weekly CSBMs and SBMs from baseline every two weeks and at week six; the proportion of patients with an increase of CSBMs/week ≥ 1 from baseline every two weeks and for at least four weeks of

the treatment period; the proportion of patients with a mean weekly CSBMs and SBMs ≥ 3 at week six; the proportion of patients with a decrease of mean Patient Assessment of Constipation-Quality of Life (PAC-QoL)¹⁷ and Patient Assessment of Constipation-Symptoms (PAC-SYM)¹⁸ score ≥ 1 from baseline at week six; the change in the mean PAC-QoL and PAC-SYM score from baseline over every two weeks; stool consistency scored by BSFS over six weeks, and frequency of rescue medicine use during the treatment.

The exploratory outcomes included subgroup analysis and sustained efficacy of the primary outcome, change from baseline in the mean PAC-SYM total score, three subscale scores, and mean PAC-QoL total score. Safety evaluations were conducted at each study visit, including physical examinations, vital sign measurements, and standard laboratory tests.

Statistical analysis

A sample size of 106 patients was determined, assuming a difference of 38% between the VC and sham capsule groups in the CSBM responder rate in the pilot study, 90% power, 5% superior margin with a single-sided type I error of 0.025, and 20% dropout rate.

Efficacy analyses were performed in the full analysis set (FAS, all randomly assigned patients with baseline characteristics who swallowed at least one VC according to the principle of intention-to-treat) and per protocol set (PPS, patients who completed the treatment plan with no severe protocol violations). Safety analyses were accessed in the safety set (SS, all randomised patients).

The descriptive statistics of measurement data were analyzed by the means with standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for nonnormally distributed data. We presented categorical variables as the frequency.

The primary outcome was prespecified to be a superiority analysis using the Cochran-Mantel-Haenszel test with pooled investigator sites as a stratification variable via mean and nonresponder imputation. Prespecified sensitivity analyses for the primary outcome included complete- and worst-case analyses. Heterogeneity of the treatment effect across centers was evaluated by including an interaction term in the regression mode. No interim analyses were done. Post hoc subgroup analysis for sustained efficacy of VC during the follow-up were conducted for the primary outcome.

For continuous data in secondary outcomes as the change in the mean weekly CSBMs, two independent sample t-test or Wilcoxon rank-sum test was used to compare between groups after normality and variance homogeneity tests and the between-group difference was estimated based on Hodges-Lehmann estimator of location shift. For the categorical data including the proportion of patients with an increase of CSBMs/week ≥ 1 , Pearson's chi-squared test was used to compare between

the two groups with 95% CI calculated based on the Wald approach. If necessary, Fisher's exact test was used.

In the presentation of the primary outcome, a between-group difference with a 95% CI not including the null was considered statistically significant. The *P* values and 95% CI for other parameters were two-sided, and differences with *P* < 0.05 were considered statistically significant. Analyses were performed using SAS (version 9.2) and R (version 3.6.1). This trial is registered with ClinicalTrials.gov, number NCT04671264, and is completed.

Role of the funding source

The VICONs trial was supported by the grant "One hundred leading scientists for 21st century" of Health Department of Shanghai Municipal Government (to ZL, No.2017BR005). The funder critically reviewed and adjusted the study design, and also inspected the results, but had no role in data collection, data analysis, interpretation, writing of the report or the submission process. All authors had full access to all data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Overall, 155 patients aged from 18 to 74 were screened from November 14, 2018 to February 24, 2020, and 107 patients were randomly assigned to receive VCs (*n* = 53) or sham capsules (*n* = 54) (Figure 1, Tables S1.1 and S1.2). The final follow-up was completed in all patients on May 9, 2020. Forty-eight patients were excluded with consent withdrawal (*n* = 30) as the most common reason. Demographics and baseline characteristics of the patients were balanced across groups (Tables 1 and S2).

During the treatment, 53 (100%), 52 (98%), and 50 (94%) patients in the VC group and 52 (98%), 50 (94%), and 49 (93%) patients in the placebo group completed the two-week, four-week, and six-week visits, respectively. Forty-nine (93%) and 48 (91%) patients swallowed nine or more capsules in these two groups (Table S1.3). One patient in the placebo group withdrew before the distribution of capsules, and the FAS population included 106 patients. Eighty-seven patients (82%) completed the assigned treatment protocol, and all six visits comprised the PPS population.

Primary outcome

The responder rates in the VC group and placebo group were 64% (34/53) and 36% (19/53), respectively, in the FAS population with a between-group difference of

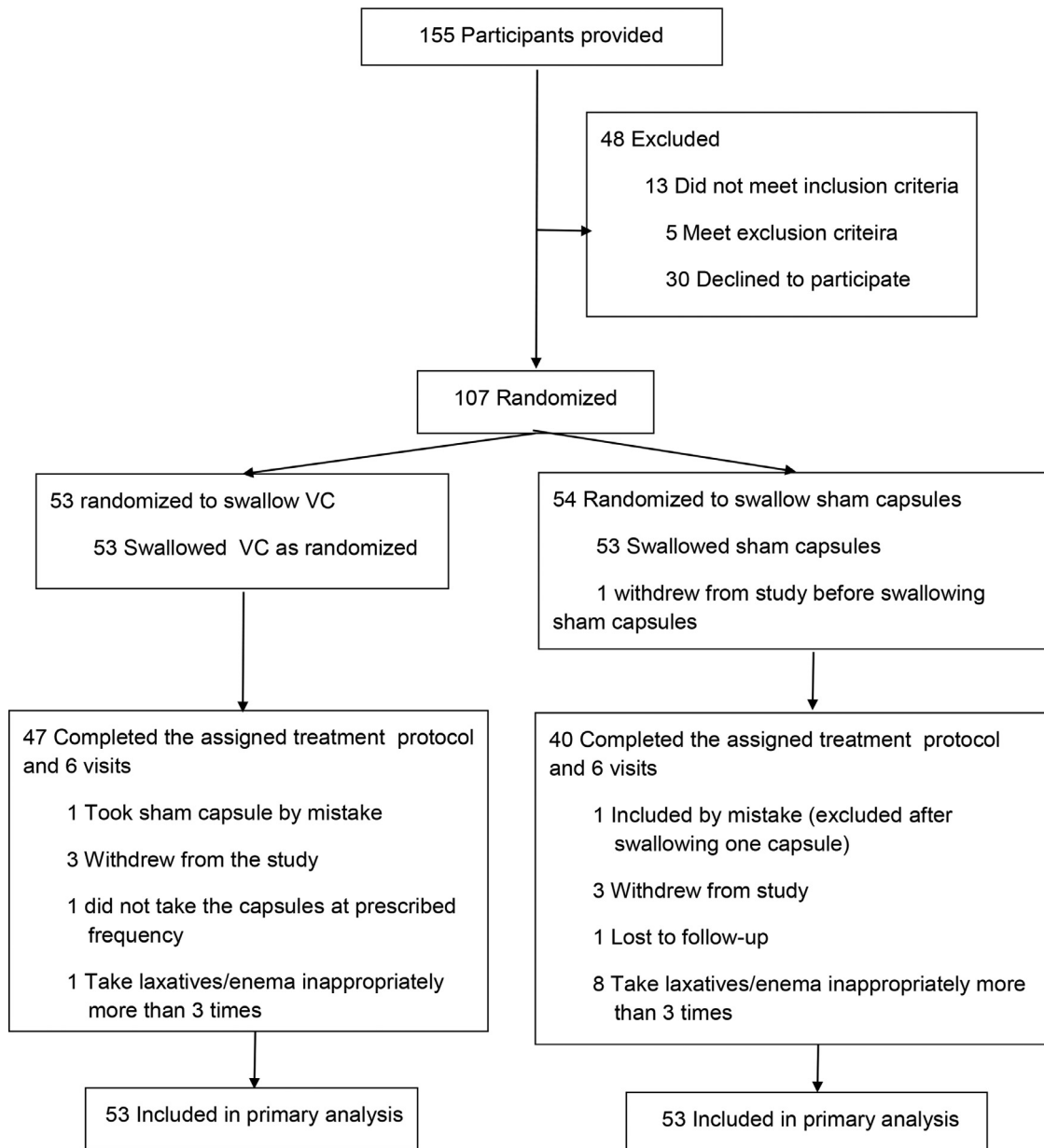


Figure 1. Patient organization chart in a randomized clinical trial of vibrating capsules vs. sham capsules in patients with functional constipation.

28% (95% CI, 10–45%, $P = 0.0051$) and a number needed to treat of 3.61 (95% CI, 2.22–9.62), suggesting the efficacy of VC in the treatment of FC (Table 2). Similarly, there were significant differences in primary outcome in prespecified sensitivity analyses in the PPS population and complete- and worst-case analyses. The poolability test of the primary outcome across centers was verified (P values for the interaction effects >0.15) (Tables S3.1–S3.4).

Secondary outcomes

Table 2 presents the key secondary outcomes. The change in the medium weekly CSBMs from baseline was significantly greater in the VC group than in the placebo group during the first two weeks (difference, 0.50 [95% CI, 0.00–1.18]; $P = 0.020$) and the entire treatment period (difference, 0.52 [95% CI, 0.02–1.03]; $P = 0.026$) (Figure 2A,B). Additionally, more patients in the VC group reported an increase of CSBMs ≥ 1

	Placebo group (n = 53)	VC group (n = 53)
Sex		
Male	5 (9%)	5 (9%)
Female	48 (91%)	48 (91%)
Age	43.2 (13.4)	42.8 (14.3)
Age < 65 yr	49 (93%)	50 (94%)
BMI (kg/m ²)	22.5 (2.4)	22.5 (2.2)
CSBMs/wk	0.0 (0.0–1.5)	0.0 (0.0–0.5)
SBMs/wk	2.0 (0.5–2.5)	1.5 (1.5–2.5)
PAC-QoL score	1.32 (0.85)	1.29 (0.74)
PAC-SYM score	1.02 (0.76)	1.23 (0.67)
Bristol Stool Form Scale		
BSFS = 1,2	99 (36%)	120 (48%)
BSFS = 3,4	125 (45%)	84 (33%)
BSFS = 5–7	53 (19%)	48 (19%)
Survey on previous treatment		
Dietary therapy	31 (59%)	32 (60%)
Drug therapy	29 (55%)	25 (47%)
Ineffective or insufficient treatment	34 (64%)	39 (54%)

Table 1: Demographics and baseline characteristics.
Abbreviations: VC, vibrating capsule; BMI, body mass index; CSBM, complete spontaneous bowel movements; IQR, interquartile range; SBM, spontaneous bowel movements; PAC-QoL, Patient Assessment of Constipation-Quality of Life; PAC-SYM, Patient Assessment of Constipation-Symptoms; BSFS, Bristol Stool Form Scale.

during the first two weeks (difference, 26% [95% CI, 7–44]; $P = 0.0080$) (Figure 2E), at week six (difference, 27% [95% CI, 8–46]; $P = 0.0062$), for at least four weeks during the treatment ($P = 0.022$) and during the follow-up (difference, 17% [95% CI, 0–35]; $P = 0.048$) (Table S4.1.1–S4.1.5). No significant improvement was seen in the proportion of patients with CSBMs/week ≥ 3 at week six (Table S4.1.2) or secondary outcomes related to SBMs (Figure 2C,D,F) (Tables S4.2.1–S4.2.4).

The administration of VCs did not affect stool consistency ($P = 0.12$) (Table S4.4.1). The diachronic change in rescue medicine use during treatment from baseline was significantly decreased in both groups. However, there was no great between-group difference during the treatment period ($P = 0.70$) (Table S4.5).

The efficacy of VC in relieving constipation was also evidenced by significant decreases in the mean PAC-SYM questionnaire score from baseline over weeks one to two (difference, -0.25 [95% CI, -0.50 – 0.00]; $P = 0.028$), three to four (difference, -0.42 [95% CI, -0.58 , -0.17]; $P = 0.0006$), and five to six (difference, -0.25 [95% CI, -0.50 , -0.08]; $P = 0.012$). The PAC-SYM subscale score was statistically reduced from baseline for the Stool Form Score (difference, -0.40 [95% CI, -0.80 , -0.20]; $P = 0.011$). The mean PAC-SYM and PAC-QoL total scores differed significantly from the baseline in both groups (all $P < 0.0001$), with no significant changes observed in mean PAC-QoL total scores between groups (Tables S4.3.1–S4.3.11).

Safety outcomes

The safety evaluation was based on the SS population, 23 (43%) patients in the VC group and 23 (43%) in the placebo group reported AEs with all abnormalities in laboratory test and physical examination listed in Table S5. After assessment by the investigators, treatment-related AEs were reported in seven (14%) and six (11%) patients in these two groups. One SAE in the VC group was pregnancy. No treatment related SAEs occurred and no significant difference in the proportion of patients with specific AEs existed between the two groups (all $P > 0.05$) (Table 3). Two patients in the VC group withdrew from the study because of pregnancy (SAE unrelated to the treatment) and fever.

The mean discharge time of VCs was similar to that in the placebo group (52.78 vs. 54.93 h, $P = 0.77$), with the longest being 235.2 h, and no capsule retention occurred (Table S4.4.2).

Discussion

In this multicenter randomised clinical trial among patients with FC, smartphone-controlled VC safely and significantly promoted defecation, alleviated constipation severity, improved quality of life, and reduced pharmacological treatments and was well tolerated. By mechanical stimulation of the gastrointestinal walls, VCs promoted bowel movement immediately without impacting stool consistency and displayed potential sustained efficacy. VC might be a valuable and promising non-pharmacotherapy option for patients with FC.

	Placebo group N = 53	VC group N = 53	Difference (95% CI)	P value [†]
Primary outcome				
Patients with an increase of CSBMs per week ≥ 1 during 6 weeks	19 (36%)	34 (64%)	28% (10%, 45%)	0.0051
Secondary and exploratory outcomes				
CSBMs				
Change from baseline in CSBMs per week				
Weeks 1–6	0.78 (0.00 to 1.50)	1.36 (0.40 to 2.17)	0.52 (0.02, 1.03)	0.026
Weeks 1–2	0.29 (0.00 to 1.28)	1.21 (0.00 to 2.59)	0.50 (0.00, 1.18)	0.020
Weeks 3–4	1.00 (0.00 to 1.62)	1.50 (0.00 to 2.15)	0.37 (0.00, 1.00)	0.18
Weeks 5–6	0.78 (0.00 to 1.91)	1.57 (0.30 to 2.84)	0.50 (0.00, 1.16)	0.089
Patients with an increase of CSBMs per week ≥ 1				
Weeks 1–2	17 (33%)	31 (59%)	26% (7%, 44%)	0.0080
Weeks 3–4	26 (52%)	34 (65%)	13% (–6%, 32%)	0.17
Weeks 5–6	21 (43%)	31 (62%)	19% (–0%, 38%)	0.057
Week 6	22 (45%)	36 (72%)	27% (8%, 46%)	0.0062
Patients with an increase of CSBMs per week ≥ 1 for at least 4 weeks	21 (42%)	33 (65%)	23% (4%, 42%)	0.022
Patients with CSBMs per week ≥ 3 at week 6	14 (29%)	20 (40%)	11% (–7%, 30%)	0.23
Patients with an increase of CSBMs per week ≥ 1 during follow-up	10 (20%)	19 (37%)	17% (0%, 35%)	0.048
SBMs				
Change from baseline in SBMs per weeks				
Weeks 1–6	1.02 (0.51 to 2.44)	1.34 (0.67 to 2.29)	0.13 (–0.44, 0.61)	0.61
Weeks 1–2	0.69 (0.07 to 2.37)	1.19 (0.10 to 2.47)	0.11 (–0.51, 0.76)	0.67
Weeks 3–4	1.5 (0.44 to 2.32)	1.22 (0.35 to 2.06)	–0.13 (–0.75, 0.50)	0.64
Weeks 5–6	1.29 (0.44 to 2.84)	1.66 (0.79 to 2.60)	0.29 (–0.39, 0.91)	0.39
Patients with SBMs per week ≥ 3 at week 6	27 (55%)	33 (66%)	11% (–8%, 30%)	0.27
PAC-QoL				
Change from baseline in the mean PAC-QoL total score				
Weeks 1–2	–0.25 (–0.75 to –0.08)	–0.37 (–0.79 to –0.04)	–0.04 (–0.26, 0.15)	0.74
Weeks 3–4	–0.29 (–0.82 to –0.08)	–0.61 (–1.07 to –0.21)	–0.18 (–0.42, 0.04)	0.12
Weeks 5–6	–0.30 (–1.11 to –0.09)	–0.61 (–0.95 to –0.27)	–0.18 (–0.40, 0.09)	0.15
Patients with a decrease of PAC-QoL ≥ 1 at week 6	13 (27.1%)	12 (24.5%)	–2.6% (–20.0%, 14.8%)	0.77
PAC-SYM				
Change from baseline in the mean PAC-SYM total score				
Weeks 1–2	–0.13 (–0.75 to 0.17)	–0.50 (–0.83 to –0.17)	–0.25 (–0.50, –0.00)	0.028
Weeks 3–4	–0.21 (–0.67 to 0.00)	–0.67 (–1.08 to –0.33)	–0.42 (–0.58, –0.17)	0.0006
Weeks 5–6	–0.38 (–0.71 to –0.04)	–0.67 (–1.00 to –0.33)	–0.25 (–0.50, –0.08)	0.012
Patients with a decrease of PAC-SYM ≥ 1 at week 6	7 (15%)	13 (27%)	12% (–4%, 28%)	0.15
Change from Baseline in the mean PAC-SYM sub-scale scores at Week 6				
Abdominal symptoms	0.00 (–0.50 to 0.00)	–0.25 (–0.75 to 0.00)	0.00 (–0.25, 0.00)	0.21
Rectal symptoms	0.00 (–0.33 to 0.00)	0.00 (–0.67 to 0.00)	0.00 (0.00, 0.00)	0.92
Stool form	–0.70 (–1.30 to –0.10)	–1.20 (–1.80 to –0.80)	–0.40 (–0.80, –0.20)	0.011
Bristol Stool Form Scale				
BSFS = 1,2	365 (31%)	354 (29%)		0.12
BSFS = 3,4	515 (43%)	589 (48%)		
BSFS = 5–7	308 (26%)	281 (23%)		
Change in the rescue medicine use from baseline	0.00 (–0.49 to 0.00)	0.00 (–0.03 to 0.00)	0.00 (0.00, 0.00)	0.70

Table 2: Efficacy and safety outcomes.

Abbreviations: VC, vibrating capsule; CSBM, complete spontaneous bowel movements; SBM, spontaneous bowel movements; PAC-QoL, Patient Assessment of Constipation-Quality of Life; PAC-SYM, Patient Assessment of Constipation-Symptoms; BSFS, Bristol Stool Form Scale.

[†] The P value for the primary outcome is a one-sided P value for superiority, calculated in the FAS population; the P values for the other parameters are two-sided P values calculated in the FAS population.

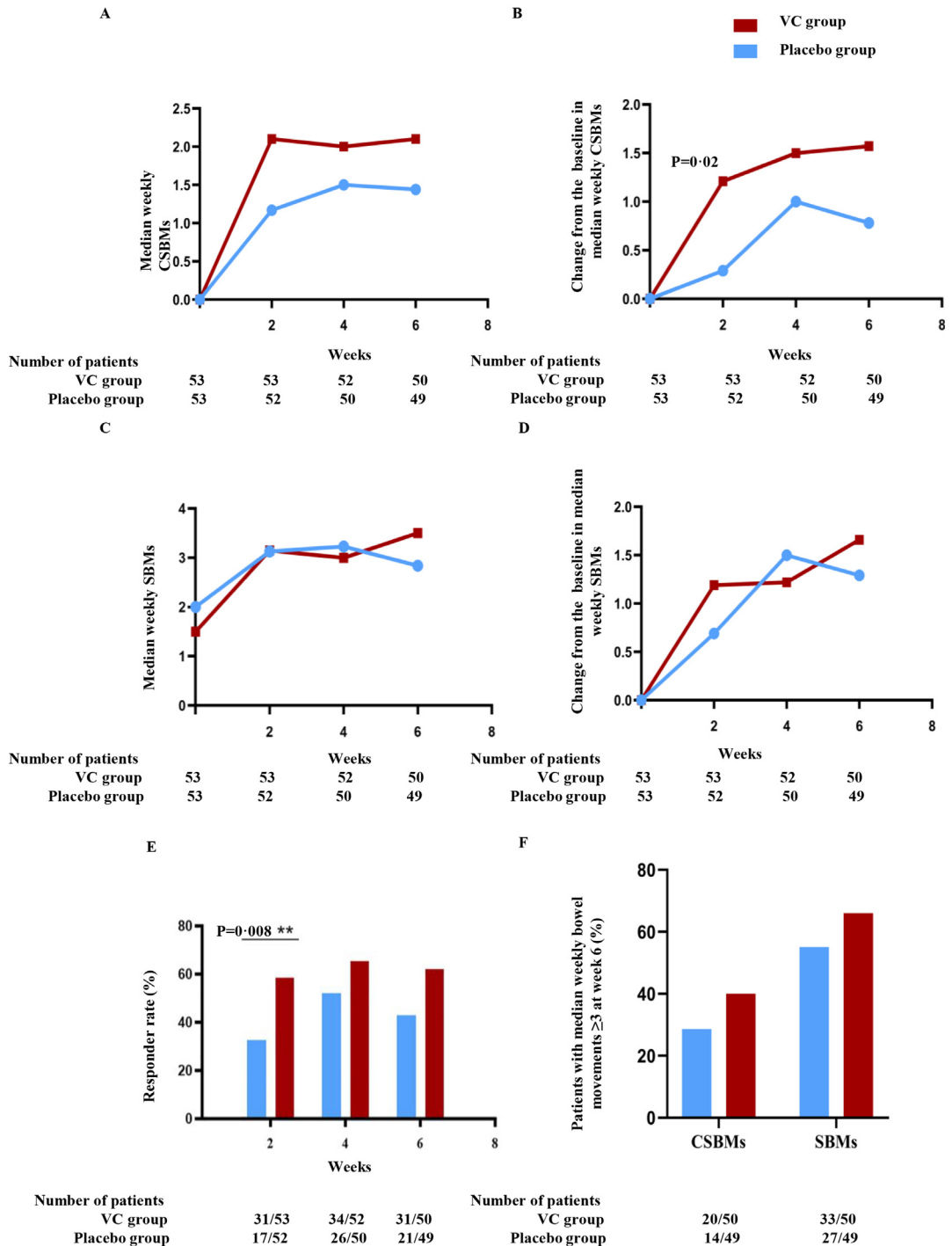


Figure 2. The diachronic change in the complete spontaneous bowel movements (CSBMs) and spontaneous bowel movements (SBMs) per week during treatment.

A. The median weekly CSBMs; B. the change in the median weekly CSBMs from baseline. The change in the median weekly CSBMs from baseline was significantly improved in the vibrating capsule group than in the placebo group during the first two weeks ($P = 0.020$); C. the median weekly SBMs; D. the change in the median weekly SBMs from baseline; E. the responder rate. More patients receiving vibrating capsules reported increase of CSBMs ≥ 1 during the first two weeks ($P = 0.0080$); F. the proportion of patients with median weekly CSBMs or SBMs ≥ 3 at week 6.

** denotes $P < 0.05$.

	VC group (N = 53)	Placebo group (N = 54)	P value
Adverse events summary			
Adverse events	23(43.4%)	23(42.6%)	1.00
Serious adverse events	1(2%)	0	0.50
Withdrew from trial due to adverse events	2(4%)	0	0.24
Fatal adverse events	0	0	1.00
Treatment related adverse events			
Abdominal discomfort*	2 (4%)	2 (4%)	1.00
Fecal occult blood	3 (6%)	2 (4%)	0.69
Back pain	0	1 (2%)	1.00
Diarrhea	0	3 (6%)	0.24
Pharyngitis	1 (2%)	0	0.50
Fever	1 (2%)	0	0.50

Table 3: Adverse events (safety population).

*Abdominal discomfort included pain and distention.

Currently, decreasing the severity of symptoms, prolonging the therapeutic effect, and improving the quality of life are the main goals of treatment for FC. With continuous innovations in treatment modalities, the availability of abdominal physical stimulation, including abdominal massage,¹⁸ whole-body vibration,¹⁹ micro-physiotherapy,²⁰ interferential electrical stimulation,²¹ and acupuncture²² is increasingly being recognized and shows different degrees of effectiveness. The exact mechanism by which physical stimulation promote constipation is still unclear and speculated to be related to parasympathetic and local reflexes,¹⁹ which increase gastrointestinal motility and relax sphincters.²³ VCs may enhance the effect with the innovative transition of external mechanical stimulation into direct stimulation of the gastrointestinal walls. To the best of our knowledge, the VICONs trial was the first to validate the superiority of novel smartphone-controlled VCs in the treatment of FC.

Significant improvement in CSBMs was observed early during treatment (during the first two weeks), with sustained efficacy maintained for the remainder of the treatment period and the follow-up period. However, this result seemed different from that in previous research exploring the mechanistic effects of VC in CIC. Research by Rao et al.²⁴ showed that there were significantly more% CSBMs in the VC group than in the sham group during and within three hours of vibration, but not the responder rate defined as patients with ≥ 1 CSBMs per week over baseline. Different capsules and vibration modes may contribute to the superiority of VCs in our study. The VC applied in this study was slightly larger, with a higher vibration frequency (12 cycles per minute in a low-medium-high stimulation loop with a frequency of three to nine Hz vs. three times per minute at 0.05 Hz) and longer working hours (six hours vs. two hours).

At present, biofeedback therapy is considered to be the most promising nonpharmacotherapy, with an effective rate reported to be more than 40%.²⁵ According to three previous studies, VCs can promote CSBMs in up to 50% of patients and may accelerate colonic transit.^{13,24} Combined with the responder rate of 64% in this study, we hold the idea that VC is effective in promoting defecation.

Compared with placebo, VC relieved constipation severity reflected by the diachronic change in the mean PAC-SYM total score from baseline, which was consistent with the results of pharmacotherapy such as prucalopride.¹⁶ However, there was no significant improvement in the PAC-QoL score between the two groups. The homogeneous result of intergroup difference in the mean PAC-QoL total score and significant reduction of intragroup difference in both questionnaires reflected a strong placebo effect in both treatments. The placebo effect has been systematically described in clinical trials of CIC, with a range from 4 to 44%,²⁶ which is consistent with results in other functional gastrointestinal diseases.⁷ Psychological comorbidity was caused by repeated consultations, unnecessary investigations and impaired health-related quality of life in patients with FC. Thus, more personalized treatment focusing on both symptoms and underlying psychology are advocated for the future.

The efficacy of VCs was achieved with low rates of AEs and discontinuations due to treatment-related AEs, indicating a benign safety profile and favorable tolerability. The stool consistency in both groups remained unchanged, consistent with the results in our prior animal¹⁴ and pilot studies,¹⁵ partly supporting the underlying mechanism of VC as direct stimulation of intestinal walls and enhanced movement of stool.²⁴

The strengths of the study include the test of superiority, multicenter randomised placebo-controlled design, rigorous study process, and exploration of sustained

efficacy. Despite the strengths above, there exist several potential limitations. First, the majority of the enrolled patients were female, although consistent with the epidemiology of constipation²⁷ and normal in the general population studies of constipation, this may impact the generalization of the efficacy in men. Second, a strong placebo effect and the change of lifestyle in the study may interfere with the efficacy analysis. Third, the treatment period was shorter than that in the recommendation (12 weeks) with no long-term follow-up data and subgroup analysis in patients based on the Colonic Transit Test.²⁸ Studies exploring the cost-effectiveness ratio, the relationship between the curative effect and course of treatment, combined efficacy with other therapies and efficacy analysis in special populations, including children, patients with diabetes, and patients with different subtypes, are warranted in the future.

Capsule endoscopy has changed traditional gastrointestinal examinations into a noninvasive way. At present, it is combined with artificial intelligence, mechanical actuation and bowel modeling technology and is developing toward miniaturization and multifunction with recent advances in therapeutics.²⁹ Given the risks including capsule retention,³⁰ capsule-related contraindications should be carefully checked before swallowing.

In conclusion, this study confirmed the efficacy and safety of VCs in promoting defecation, relieving symptoms, and improving quality of life with a high safety profile and tolerability. The novel VC appears to be a potential alternative physical treatment for FC with the exact mechanism warranting further investigation.

Contributors

JHZ and YYQ drafted the manuscript. WNC, ZW, XQL, YHF and ZL participated in the enrollment of patients in the study. YYQ and JHZ performed the statistical analysis. JP and HC participated in the acquisition of data. YL, BMW, JNL, BL, XLZ and DWZ lead the site-specific recruitments and carried out the study interventions. ZL and ZSL conceived the project and led the study. ZL obtained funding of the study. All authors had access to the study data directly and reviewed and approved the final manuscript.

Data sharing statement

If requested, deidentified data collected for the VICONs trial, the study protocol, and informed consent form can be made available. Please contact Zhuan Liao (liaozhuan@smmu.edu.cn), who will review all requests. Requests should fulfill the following access criteria: research can only be conducted in collaboration with and after approval of the VICONs trial investigators, and with a signed data access and sharing agreement. The members of the VICONs trial investigators must approve all research done with the shared data.

Declaration of interests

Zhuan Liao declares that this study was funded by “One hundred leading scientists for 21st century” of Health Department of Shanghai Municipal Government. The vibrating capsule system (including capsule and configurator) were provided by ANKON Medical Technologies (Shanghai) Co. All other authors have nothing to declare.

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Supplementary materials

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