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Effects of the vibrating capsule on colonic circadian rhythm and bowel symptoms in chronic idiopathic constipation

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Abstract

Background: Constipated patients remain dissatisfied with current treatments suggesting a need for alternative therapies.

Aim: Evaluate the mechanistic effects of oral vibrating capsule in chronic idiopathic constipation (CIC) by examining the temporal relationships between the onset of vibrations, complete spontaneous bowel movements (CSBM), and circadian rhythm.

Methods: In post hoc analyses of two double-blind studies, CIC patients (Rome III) were randomized to receive 5 active or sham capsules/week for 8 weeks. The capsules were programmed for single vibration (study 1) or two vibration sessions with two modes, 8 hours apart (study 2). Daily electronic diaries assessed stool habit and percentage of CSBMs associated with vibrations. Responders were patients with ≥ 1 CSBM per week over baseline.

Results: 250 patients were enrolled (active = 133, sham = 117). During and within 3 hours of vibration, there were significantly more % CSBMs in the active vs. sham group (50% vs. 42%; P = .0018). In study 2, there were two CSBM peaks associated with vibration sessions. Significantly more % CSBMs occurred in active mode 1 (21.5%) vs. sham (11.5%); (P = .0357). Responder rates did not differ in study 1 (active vs. sham: 26.9% vs. 35.9%, P = .19) or study 2 (mode 1 vs. sham: 50% vs. 31.8%, P = .24; mode 2 vs. sham: 38.1% vs. 31.8%, P = .75). Device was well-tolerated barring mild vibration sensation.

Conclusions: Vibrating capsule may increase CSBMs possibly by enhancing the physiologic effects of waking and meals, and augmenting circadian rhythm, although responder rate was not different from sham. Two vibration sessions were associated with more CSBMs.

KEYWORDS

circadian rhythm, constipation, motility, Vibrating capsule

Trial registration: ClinicalTrials.gov Identifier: NCT03031301, ClinicalTrials.gov Identifier: NCT03879239

2 | INTRODUCTION

Chronic constipation is a common gastrointestinal disorder, that is estimated to affect up to 27% of the population, most of whom are women (~75%[1]). Severe constipation (eg, two bowel movements a month) is reported almost exclusively in women. It is more prevalent among people of color than among white persons, and its prevalence increases with age.[1] Chronic constipation significantly affects quality of life and is perceived by patients as a severe illness.[1-3] This burden is further compounded by significant direct and indirect costs, and for instance, chronic constipation is the sixth leading reason for an ambulatory clinic visit.[3,4]

Surveys show that many constipated patients are dissatisfied with current treatments; a US study showed that 47% of constipated patients are not completely satisfied with their current constipation treatment,[3] causing many patients to express an interest in new therapies.[5]

A promising avenue for constipation therapy is direct mechanical stimulation of the intestine, or dispersion of stool within a hollow lumen facilitating movement. Previous studies using various types of external vibration devices, such as a vibrating platform or an external vibrating belt,[6,7] have suggested that vibration devices may help constipation. Wu and colleagues tested low-intensity whole-body vibration induced by a noninvasive oscillation platform and found that it may be an effective therapy for reducing symptom severity in patients with chronic functional constipation compared to a control group of no treatment.[6] The vibrating capsule, builds on these electro-mechanical devices, and unlike external vibration, the vibrating capsule may stimulate the intestinal wall by local contact and enhance movement of stool, but this hypothesis merits further testing.

The vibrating capsule is a novel, miniaturized capsule device[8] developed as an alternative non-pharmacological treatment modality for gut dysmotility. The capsule is activated by an electromagnetic signal and it carries an activation code produced by the base unit. The code includes the timing and duration of vibration for each capsule.

Our hypothesis was that colonic vibrations could induce satisfactory bowel movements coinciding with colonic circadian rhythm, resulting in relief of constipation. This was based on a previous study in healthy volunteers, where we observed a significant increase in the mean number of bowel movements/week after treatment with the vibrating capsule and without significant adverse effects (AE).[8] However, its effects in patients with chronic constipation and its mechanism of action are unclear.

In post hoc analyses of two randomized, double-blind, sham-controlled studies, we assessed the effects of the vibrating capsule on the frequency, timing, and circadian rhythm of bowel movements in patients with chronic idiopathic constipation (CIC), by examining the temporal relationship between activation of vibration and the occurrence of complete spontaneous bowel movements (CSBM). Additionally, we assessed whether there was a dose response, that is, whether two vibration sessions per day resulted in more bowel movements.

Key Points

- Vibrating capsule is a novel non-pharmacological treatment option for constipation. We assessed its effects on frequency, timing and circadian rhythm of bowel movements and bowel symptoms in chronic constipation.
- Post-hoc analyses of two double blind sham controlled studies showed that during and within 3 hours of the onset of vibrations, a significantly greater percentage of complete spontaneous bowel movements (CSBM) occurred in the active capsule group compared to the sham group, and 2 vibration sessions induced more CSBMs, although responder rates did not differ between groups.
- Vibrating capsule may improve constipation by augmenting the physiological effects of waking and meals on bowel movements and circadian rhythm.

3 | MATERIALS AND METHODS

3.1 | Study design and population

Both studies were prospective, adaptive, multicenter, randomized, double-blind, and sham-controlled. The studies were conducted in multiple medical centers in the USA between February 2017 and March 2018. Subjects with CIC (Rome III criteria[9]) who self-reported constipation symptoms and were refractory to osmotic and stimulant laxatives for at least one month were recruited for both studies. All subjects were adults ≥ 22 years old who had between 1 and 3 spontaneous bowel movements (SBM) per week. To be eligible, subjects had to have a normal colonoscopy within 10 years, or be < 50 years old and without a family history of colorectal cancer or any alarm symptoms.[10] Patients with any history of complicated/obstructive diverticular disease, documented/suspected intestinal obstruction, significant gastrointestinal disorder (including ulcerative colitis, Crohn's disease, gastrointestinal malignancy) or gastroparesis, patients with a history of an eating disorder, a history of Zenker's diverticulum, dysphagia, Barrett's esophagus, esophageal stricture or achalasia, were all excluded from the study. Subjects with pelvic floor dysfunction/defecatory disorder, based on subject history such as use of digital maneuvers to evacuate or feeling of anal blockage or diagnosis of mega-rectum, congenital anorectal malformation and clinically significant rectocele were also excluded. Use of medications that may affect intestinal motility such as prokinetics, anti-Parkinsonian medications, opioids, calcium channel blockers, or chronic use of non-steroidal anti-inflammatory drugs were grounds for exclusion, except antidepressants, thyroid or hormonal replacement therapy, and then only when on stable doses for at least 3 months prior to enrollment. Each subject provided a signed informed consent form prior to any study-related procedure. The studies were approved by each center's institutional review board.

In both studies, subjects underwent 2 weeks of baseline evaluation/run-in and 8 weeks of randomized treatment. The study design

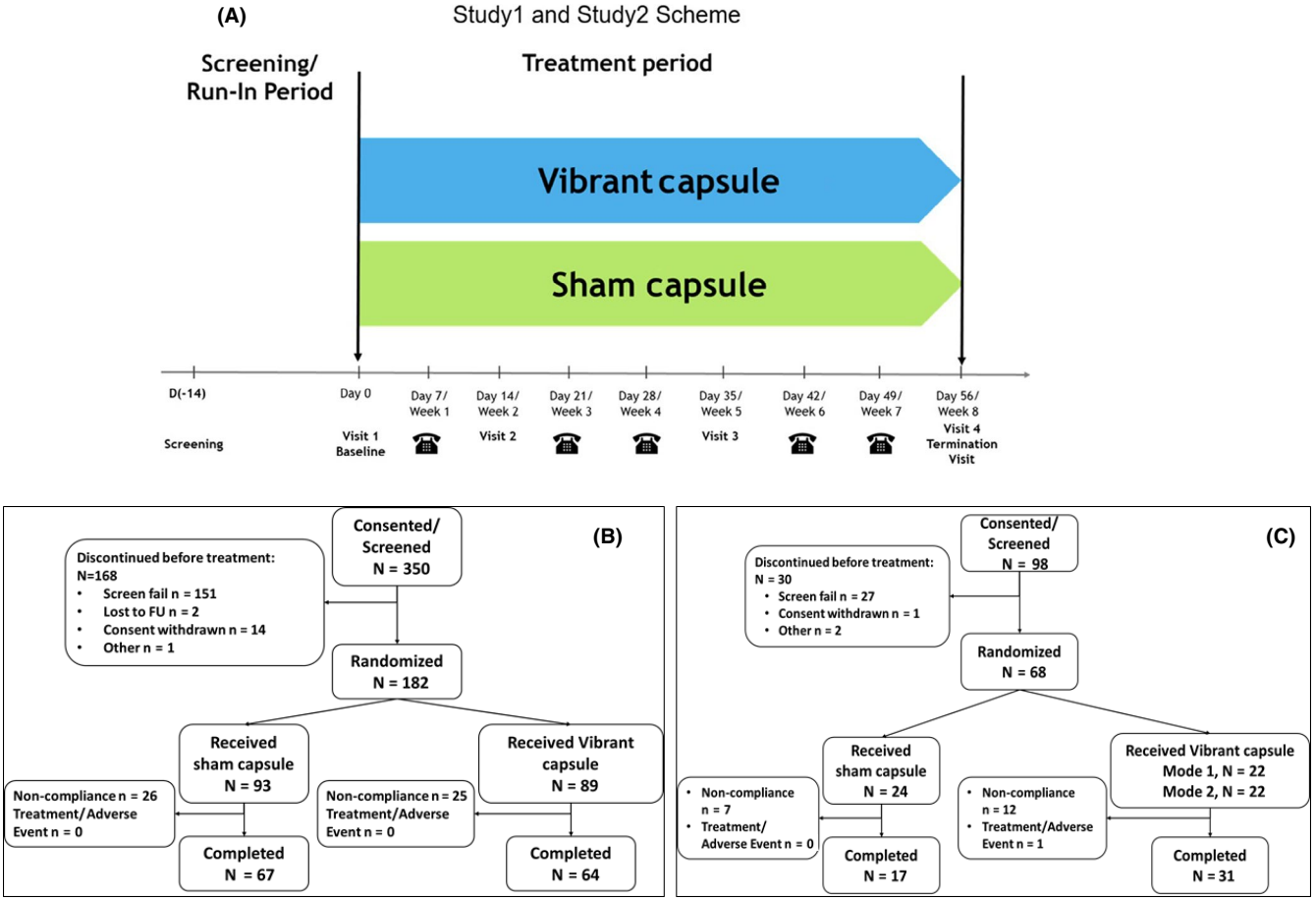

FIGURE 1 Studies 1 and 2—scheme and consort flow diagrams

is shown in Figure 1A. The full protocols are available on the journal's website.

3.2 | Intervention

In both studies, there was a 2-week run-in period that allowed for wash out of laxatives and other disallowed medications, and to gather baseline and eligibility information (see eDiary below). Following this period, at the baseline visit, subjects were randomized to receive either the vibrating capsule (Vibrant®, Vibrant Ltd, Hakochav Yokneam, Israel) or an identical sham capsule. Prior to swallowing the capsule, the patient was instructed on how to activate the capsule by inserting it into a base unit. This step sets and records the timing and duration of vibration for the capsule and creates an accurate record of compliance. The capsule includes a flat motor, electronic card and batteries, all encapsulated in a 2-piece shell, 24.2 ± 0.1 mm in length and 11.3 ± 0.1 mm in diameter.[8] It vibrates at a frequency of 0.05 Hz (3 times/minute).

In study 1, the capsule was programmed to induce a single, intermittent, vibration session for approximately 2 hours that began 8 hours after swallowing the capsule. Patients were instructed to activate and take the capsule between 9 PM and 10 PM, before bedtime, so that the vibration would start around 6 AM. Capsules were taken once a day, 5 times/week, and each vibration session lasted 2 hours.

In study 2, the capsule was programmed to induce two vibration sessions, each two-hours long. The first session was designed to start in the morning, as in study 1 (around 6 AM), and the second session started 17 hours after ingestion, approximately at noontime. In addition, in study 2, there were two treatment groups, each with a different activation mode: mode 1 included 3 vibrations/min with 100% repetition for the entire session, and mode 2 included 3 vibrations/min and 50% repetition for the entire session. Subjects received 1 capsule/day, 5 times/week. After 4 weeks, the weekly capsule administration regimen was changed from 5 times/week to 2 times/week. This was done in order to evaluate the effect of an average of between 2 and 5 capsules a week with multiple vibration sessions.

The sham capsule was identical to the active capsule and was activated by using a base unit. However, after ingestion it was programmed not to vibrate. The regimen of administration of the sham capsule was identical to the active capsule for both studies. Study staff were unaware of subject active/sham group allocation. Rescue medication was allowed only after 3 consecutive days without a bowel movement, and its use was documented in the eDiary. Patients were allowed either bisacodyl suppository or Fleets enema or bisacodyl 5 mg tablet per PI discretion.

TABLE 1 Demographics and Baseline Characteristics. It has been modified to include the data requested by both reviewers

	Study 1		Study 2		
	Active (n = 89)	Sham (n = 93)	Active Mode 1 (n = 22)	Active Mode 2 (n = 22)	Sham (n = 24)
Age (years)—mean ± SD	45.36 ± 13.08	42.67 ± 11.15	44.39 ± 12.71 *	41.85 ± 10.70	41.3 ± 13.58
Gender					
Male	18 (20.2%)	22 (23.7%)	3 (14.29%) *	4 (18.18%)	3 (12.50%)
Female	71 (79.8%)	71 (76.3%)	18 (85.71%) *	18 (81.82%)	21 (87.50%)
Body Mass Index—mean ± SD	29.75 ± 6.81	28.71 ± 5.85	29.71 ± 5.32	32.57 ± 11.02	29.98 ± 9.31
Ethnicity					
Caucasian	37 (41.57%)	29 (31.18%)	6 (28.57%) *	5 (22.73%)	9 (37.50%)
Hispanic or Latino	17 (19.10%)	22 (23.66%)	4 (19.05%) *	8 (36.36%)	6 (25.00%)
Black or African-American	32 (35.96%)	33 (35.48%)	10 (47.62%) *	7 (31.82%)	9 (37.50%)
Native or Indian American	1 (1.12%)	4 (4.30%)	1 (4.76%) *	1(4.55%)	
Asian/ Pacific Islander	1 (1.12%)	3 (3.23%)		1(4.55%)	
Other	1 (1.12%)	2 (2.15%)			
Clinical Characteristics					
Duration of constipation (years)—mean ± SD	11.67 ± 12.46	13.09 ± 12.19	14.86 ± 10.79	8.45 ± 6.70	11.15 ± 12.33
Positive according to the Rome III criteria	89 (100%)	93 (100%)	22 (100%)	22 (100%)	24 (100%)
Weekly bowel movements—mean ± SD	1.93 ± 0.59	1.92 ± 0.64	1.76 ± 0.55	1.75 ± 0.38	1.99 ± 0.80
Weekly spontaneous bowel movements – mean ± SD	1.79 ± 0.59	1.78 ± 0.57	1.48 ± 0.66	1.49 ± 0.63	1.75 ± 0.73
Weekly complete spontaneous bowel movements—mean ± SD	0.45 ± 0.70	0.40 ± 0.59	0.44 ± 0.71	0.46 ± 0.74	0.55 ± 0.63
Bristol stool form- mean ± SD	2.36 ± 1.29	2.24 ± 1.13	2.18 ± 1.27	2.50 ± 1.53	2.47 ± 1.28
Straining—mean ± SD	4.33 ± 2.30	4.77 ± 2.30	4.36 ± 2.22	4.26 ± 2.33	3.92 ± 2.07
Rescue medication use (%)	15.7%	16.3%	9.1%	9.1%	20.8%

*n = 21

3.3 | Measurements

Each subject filled out an eDiary starting with the first day of the run-in period and for the entire duration of 8-weeks. The eDiary was provided to the subjects as a downloadable application for use on their personal mobile phones. The eDiary consisted of questions about bowel movements, their timing during the day and associated clinical symptoms, use of rescue medication, and use of other medications or supplements. This information was transferred to the electronic case report from (eCRF) daily. AEs were documented throughout the study. A baseline CSBM value was defined as the last valid value prior to treatment. CSBM success (responder rate) was defined as an increase of at least one CSBM/ week during at least 6 of the 8 weeks of treatment when compared to the baseline.

3.4 | Statistical methods

For study 1, a sample size of 214 subjects was planned to provide 80% power at an overall 5% (2.5% for each one of the two primary endpoints) level of significance (two-sided) to detect a difference of 20% in success rate (see definition below), assuming a success rate of 25% in the sham arm.

The sample size was increased to at least 238 subjects (119 in each arm) to account for a potential 10% of dropouts. Eligible subjects were randomized to one of the two treatment groups based on a pre-defined randomization scheme with random size blocks stratified by center. For study 2, no formal sample size was calculated. A sample size of 22 subjects in each study arm was deemed sufficient to achieve the trial goals. Eligible subjects were randomized to one of the three treatment groups based on a randomization scheme with fixed blocks stratified by center. Statistical analyses were performed using SAS® (SAS Institute, Cary NC, USA). Nominal *P*-values of two-sided statistical tests are presented. Baseline demographic and other baseline characteristics, as well as safety analyses, were performed on all enrolled subjects. If diary information (days or weeks) were not reported, they were counted as having zero CSBM. Chi-square test was used to compare the timing between CSBM and vibration, and the number and percentage of CSBMs and to compare the response rate between the studies

arms. The purpose of the post hoc analyses was to understand the timing of CSBMs across a 24-hour day, and specifically to define the % of CSBMs occurring during or close to vibration cycles, in order to reveal the immediate effect of vibration. By comparing the distribution of CSBMs over time and in relation to the vibrations, we hoped to better understand the mechanism of action of the capsule.

4 | RESULTS

4.1 | Demographics

Study 1 enrolled a total of 182 subjects, of whom 89 were randomized to receive the active capsule and 93 the sham capsule. No subject terminated participation due to an AE (Figure 1B). Study 2 enrolled a total of 68 subjects, of whom 22 were randomized to mode 1 active arm, 22 to mode 2 active arm, and 24 to sham arm (Figure 1C). The demographic features and other baseline characteristics were similar between the active and sham arms in both studies. In all groups, the mean age was between 41 and 45 years; the majority of subjects were females, and the ethnic distribution of the population was approximately equal between the two studies and active vs. sham capsules. The mean body mass index for all groups was in the range defined as obese (range of mean BMI: 28.71 ± 5.85-32.57 ± 11.02 kg/m^2), and the mean duration of constipation was between 8 and 14 years. In total, 15 patients reported use of antidepressant drugs, 8 on active treatment, and 6 in the sham group (Table 1).The use of rescue medication was not significantly different between the groups; study 1, active vs. sham, 18.0% vs. 13.0%; study 2, active mode 1 vs. mode 2 vs. sham, 18.2% vs. 0.0% vs. 12.5%, respectively.

4.2 | Effects of the vibrating capsule on CSBM and circadian rhythm

In study 1, a higher proportion of CSBMs was reported, either during the vibration session or in up to 3 hours after the vibration time. Within this time window, there was a statistically significant and enhanced effect of the active capsule compared to the sham. About 50% of the CSBMs reported by subjects in the active arm occurred during or near the vibration time, compared to 42% with the sham capsule (P = .0018) (Figure 2A, Table 2). In study 2, the timing of the onset of CSBM showed a distinct pattern that correlated with the timing of the vibration sessions. We observed two peaks for the CSBMs, each occurring in close proximity to the vibration session (Figure 2B), one in the morning, upon awakening and the other around noon, close to mealtime. During these time intervals, following vibrations, the active capsule group showed a significantly larger effect on the onset of CSBMs compared to the sham group (Figure 2). Overall, 21.5% of the CSBMs reported by subjects in active mode 1 of study 2 occurred during or near vibration time, and this was significantly higher when compared to the 11.5% seen in the sham group (P = .0357) (Figure 2B).

The CSBM responder rates did not differ between the active and sham groups either in study 1 (active vs. sham: 27.9% vs. 35.9%, P = .1973) or in study 2 (mode 1 vs. sham: 50% vs. 31.8%, P = .2429; mode 2 vs. sham: 36.4% vs. 31.8% P = .7505).

4.3 | Pooled analysis

The entire population of patients treated with the active capsule was pooled from both studies and compared to the pooled population of sham-treated subjects. These post hoc analyses focused

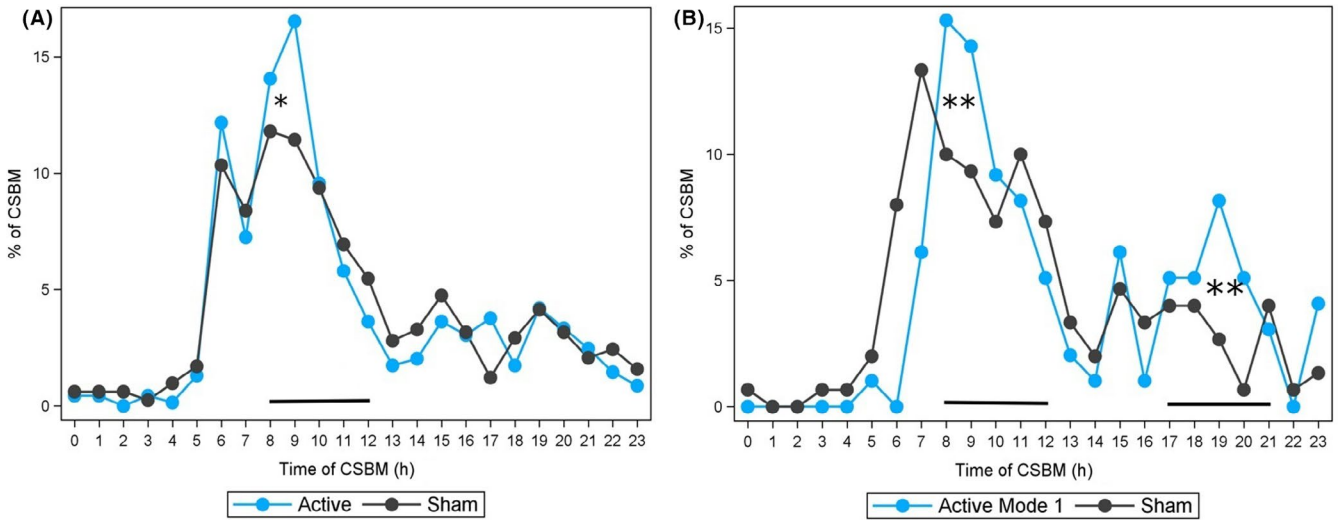

FIGURE 2 Correlations between the timing of vibration and the percentage of complete spontaneous bowel movements (CSBMs). Time 0 on the X-axis is the time of ingestion of the capsules; black lines in both graphs denote the period of active vibration, one session in (A) study 1 and 2 sessions in (B) study 2

TABLE 2 This shows the number and % of CSBMs that occurred during or close to the vibration time (window) per subject as well as the change in the number of CSBMs/week in each group

	Study 1		Study 2	
	Active	Sham	Active (mode 1)	Sham
CSBM reported within or close to stimulation time window per subject (mean) CSBM reported within or close to stimulation time window (%)	3.88 50%	3.75 42%	0.91 21.5%	0.71 11.5%
P-value	0.0018		0.0357	
	Study 1		Study 2	
	Active	Sham	Active (Pooled)	Sham
Change from Baseline in mean weekly CSBM	1.14 ± 1.73	1.455 ± 1.91	1.22 ± 1.57	1.41 ± 1.71
P-value (*t* test)	0.2434		0.6386	

on the 48 hours following the administration of the last capsule in the study. Again, 2 peaks of distribution of CSBMs were observed, one occurring approximately 10-12 hours after capsule ingestion, often upon awakening, and in close correlation to the timing of vibration, and another, at approximately 19-20 hours after capsule ingestion, close to the mealtime. We also observed a third peak of activity, approximately 36 hours after ingestion of the last capsule, and this coincided with the waking response on the morning of the second day. Although the response was lower than in the first morning, we observed a higher frequency of CSBM in the combined vibrating capsule groups compared to the combined sham capsule groups. This additional peak suggests a residual effect of the active capsule after the last administration (Figure 3).

4.4 | Adverse effects

The vibrating capsule was generally well-tolerated. No serious adverse events (SAE) were reported in study 2. In study 1, there was one SAE consisting of an anxiety attack in a patient randomized to the sham group and one SAE consisting of pelvis fracture in the active capsule group. Both of these were unrelated to study treatment. The overall incidence of AE was low, and most AE were mild and transient (Table 3). Specifically, the incidence of diarrhea was similar between the active and sham groups in both studies.

5 | DISCUSSION

Here, we assessed whether the vibrating capsule enhances the percentage of complete spontaneous bowel movements and its temporal

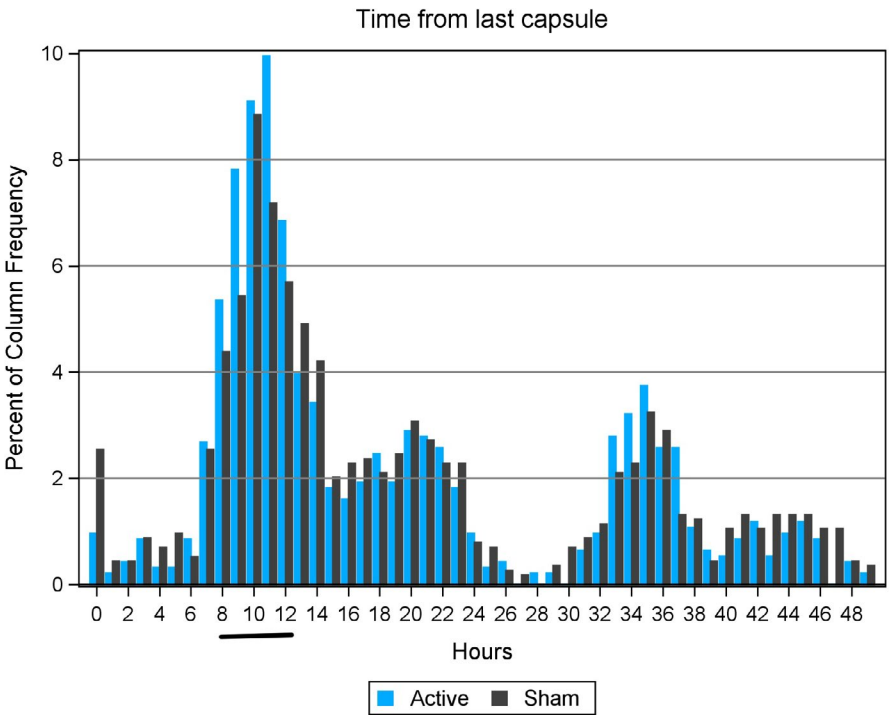

FIGURE 3 Frequency of complete spontaneous bowel movements (CSBMs) following the last administration of capsules. Time 0 on the X-axis is the time of ingestion of the capsules; black horizontal line in the graph denotes the period of active vibration of the last capsule

TABLE 3 Device-related adverse events

	Study 1						Study 2									
	Active			Sham			Active Mode 1			Active Mode 2			Sham			
Related AE	No. of Reports	No. of Subj.	%	Reports No. of	No. Subj. of	%	Reports No. of	No. Subj. of	%	Reports No. of	No. Subj. of	%	Reports No. of	No. Subj. of	%	
All	21	8	9.0%	2	1	1.1%	3	1	4.6%	2	2	9.1%	3	3	12.5%	
Vibration sensation	20	8	9%	1	1	1.1%	2	1	4.6%	2	2	9.1%	3	3	12.5%	
Gas	-	-	-	-	-	-	1	1	4.6%	-	-	-	-	-	-	
Passing 3 capsules at once	1	1	1.1%	-	-	-	-	-	-	-	-	-	-	-	-	
Uncomfortable BM	-	-	-	1	1	1.1%	-	-	-	-	-	-	-	-	-	
Diarrhea	-	-	-	1	1	1.1%	-	-	-	1	1	4.6%	1	1	4.2%	

relationship to stool evacuation in individuals with chronic constipation. In these post hoc analyses, we found significantly greater percentage of CSBMs during the active vibration period when compared to the sham capsule period. This observation suggests that the active capsule may augment the intrinsic biologic changes of colonic motility that occur after waking[11] and after meals.[12] However, based on the responder definition selected for these studies, overall, there was no significant difference in the responder rates for bowel symptoms, between the active and sham groups.

Here we also examined any potential effects of stimulating twice a day vs. once a day. In study 1, patients were administered 5 capsules/week and each capsule was programmed for a single vibration session whereas in study 2, patients were administered 5 capsules/week, and each capsule was programmed for 2 vibration sessions. The responder rates in the sham, and active arms of study 1 were similar. In study 2, the responder rates in both active arms tended to be higher than in the sham arm, but there was no difference between the two arms, possibly due to a type II error from the small sample size. However, in study 2, the timing of the onset of CSBMs showed a distinct pattern that was associated with the timing of vibration sessions in that two peaks were observed in close proximity to the vibrating sessions, one in the morning and the other in the late afternoon possibly around mealtime. The percentage of CSBMs in the vibrant capsule group (mode 1) was significantly higher when compared to the sham capsule group. These observations suggest that 2 vibration sessions a day may have a better effect on the weekly frequency of CSBMs than a single session, but this merits confirmation from a larger sample of patients. Also, in a previous smaller study of 12 patients, using 5 capsules/ week, although 25% of patients in the active group had more rapid colonic transit, there was no statistically significant difference between the active and sham groups.[13] Overall, these observations suggest that multiple vibration sessions, timing of capsule ingestion and frequency of vibrations may each affect the efficacy of this treatment modality.

Healthy subjects tend to have bowel movements during the day, mainly after waking or after a meal, but rarely during the night. In a study of colonic pressure activity over 24 hours in 25 ambulatory healthy subjects, we have previously demonstrated a biologic circadian rhythm consisting of a marked decrease in colonic pressure activity at night and a significant increase in pressure activity following waking and after meals.[11] In a follow-up study, we showed that patients with chronic slow transit constipation had significantly decreased colonic pressure activity following waking or meals when compared to control subjects.[12] Shemerovskii [14] studied the circadian dynamics of defecation in 341 individuals and showed that healthy individuals had a bowel movement every day in the morning between 6 AM and noon. Those with irregular bowel habits had bowel movements three to four times a week, with most bowel movements occurring in the evening hours between 8 PM and midnight. Thus, the human colon is naturally programmed to empty in the morning, upon awakening and this biorhythm may be significantly altered in patients with chronic severe constipation.[11,12,15] However, in this study, patients had mild

to moderate constipation and the circadian rhythm appears to be preserved in these subjects.

Furthermore, these observations support the paradigm that the digestive tract has an internal clock that responds to the body's circadian clock but also has some level of independent function and an intrinsic ability to respond to environmental cues including changes in feeding schedule.[16] Indeed, clock genes, particularly Per2, are rhythmically expressed within the epithelial cells and myenteric plexus of the colon and display circadian rhythm properties[17,18]

Although there are several useful therapies for chronic idiopathic constipation including laxatives, [1,19] and newer compounds such as secretagogues, sometimes they may cause unpredictable bowel movements and/or side effects including diarrhea.[20,21] We found that the vibrating capsule was well-tolerated in both studies and had an overall favorable safety profile with minor and transient adverse events, and no significant concerns for safety. Importantly, it does not seem to cause significant diarrhea or nausea.

Our studies have limitations including the exploratory nature of study design, the post hoc analyses, the use of multiple vibration paradigms, and nested within study 2, two different modes of capsule activation, as well as the small sample sizes. Further, while the subjects were well-matched with sham controls, the choice of the sham control may have prevented a true understanding of the magnitude of the vibrating capsule's effect. Also, there was a withdrawal rate of approximately 25%-30% in both studies, possibly owing to patient compliance or perceived lack of efficacy, but not due to any significant adverse events. Finally, gastrointestinal transit time was not assessed in this study and may have provided important mechanistic insights regarding CSBM, circadian rhythm and lack of response from diffuse gastrointestinal motility dysfunction. Also, the relationship between vibrations and circadian rhythm may require evaluation by a study in which vibrations are administered at different times of the day. Further, these observations build on other techniques such as transabdominal interferential electrical stimulation that have been shown to improve slow transit constipation.[22-24]

In conclusion, these post hoc analyses suggest that the vibrating capsule may enhance the normal physiologic effects of waking and meals on bowel movements, although its overall effect on bowel symptoms in constipated patients was not different from that of the sham capsule. The use of two vibration sessions a day may additionally increase the proportion of CSBMs but this requires further studies. These observations together with the favorable safety profile suggest that this promising technology may help patients with chronic constipation, but it requires confirmation in better designed, larger, sham, or placebo-controlled studies.

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DISCLOSURES

Writing Assistance: Medical writing support for this manuscript was provided by Shiri Diskin, PhD (Bioforum, Israel) and paid for by Vibrant Ltd.

CONFLICTS OF INTEREST

SR, AL, and EMMQ: Serve on the advisory board of Vibrant capsule technology and have received honoraria and research grant support for performing clinical studies.

AUTHOR CONTRIBUTIONS

SR involved in study concept and design; acquisition of data; analysis and interpretation of data, manuscript writing, and critical revision of the manuscript for important intellectual content; AL, WC, EMMQ, and KF involved in acquisition of data; analysis and interpretation of data, manuscript writing, and critical revision of the manuscript.

All authors have reviewed this final version (4/21/2020) and have approved it for submission.

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