

Use of a Squatting Assist Device in Patients With Constipation

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Title of the study:	Use of a Squatting Assist Device in patients with Constipation (Version 3 3/7/2024)
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Abstract

Background: Defecation is attributed to increased intra rectal pressure coordinated with relaxation of the anal sphincter and pelvic floor muscles. Relaxation of the puborectalis straightens the anorectal angle, which facilitates defecation. In several developing countries, people defecate in the squatting position, which facilitates defecation. In an uncontrolled study, a squatting assist device (Squatty Potty®) improved bowel symptoms in constipated patients. It is however unclear if the device is beneficial for all patients or for selected patients (e.g., those with pelvic floor dysfunction). **Aims:** To conduct a single-center, prospective, randomized controlled clinical trial to investigate the effect of the squatting assist device (Squatty Potty®) on symptoms and rectal evacuation in constipated patients. We hypothesize that the regular squatting assist device (7 inches) but not a sham device (2 inches tall) will improve symptoms of constipation. **Methods:** 85 female patients who satisfy Rome III criteria for functional constipation will be randomized to a regular or sham Squatty Potty® for 4 weeks. Bowel symptoms will be compared before and during treatment. Rectal evacuation will be assessed with defecography without and with the device. The primary outcome will be the change in weekly complete spontaneous bowel movements (bowel movement not accompanied by use of a laxative enema, suppository or manual maneuvers for disimpaction in the preceding 24 hrs. and a sense of complete evacuation) with use of the footstool compared to a 14-day baseline period. We anticipate that this study will clarify the utility of squatting assist devices for managing constipation.

A. Background and Significance

Normal defecation is initiated by rectal distention with stool, which produces the urge to defecate. Thereafter, rectal contraction associated with relaxation of the internal and external anal sphincters results in defecation (Figure 1).¹

It has been suggested that the squatting posture facilitates defecation compared to a Western style commode perhaps because this position allows greater straightening of the anorectal angle.² In one study of six healthy volunteers, the anorectal angle at rest was significantly greater in the squatting position; however the basal abdominal pressure was not significantly different.³ In another study of 30 healthy volunteers, the anorectal angle (132° versus 92°) and perineal descent were greater (8.4 cm vs. 6.6 cm) in the squatting than seated positions. It has been suggested that the seated position may predispose to functional rectal outlet obstruction.⁴ The squatting position also improved the ease of defecation, which was reported as “easy” or “very easy” by 82% of subjects reported that in the squatting position, 51% while seated on a 31-32 cm high toilet, and 39% while seated on a 41-42 cm high toilet.⁵

Among patients, the anorectal angle was wider at rest ($117.9 \pm 3.6^{\circ}$ versus $93.8 \pm 6.7^{\circ}$, Mean $\pm$ SD) and during straining ($118.2 \pm 4.9^{\circ}$ versus $95.2 \pm 7.8^{\circ}$) in the squatting than the seated position in 24 patients with spastic pelvic floor syndrome and symptoms of obstructive defecation.⁶ In the only study on use of the squatting assist device, 151 out of 153 subjects who used the device reported a significant improvement in the constipation score after a period of 4 weeks (mean scores $\pm$ SD before and after use of device were 9.08 ± 1.05 and 5.61 ± 2.47 with lower score indicating improved symptoms).⁷ However, this study was not published in a peer-reviewed journal and is only available on the website of the manufacturer of the Squatty Potty device.

While these studies suggest that there are advantages to defecating in the squatting position, several questions remain. These studies were small, uncontrolled, and did not

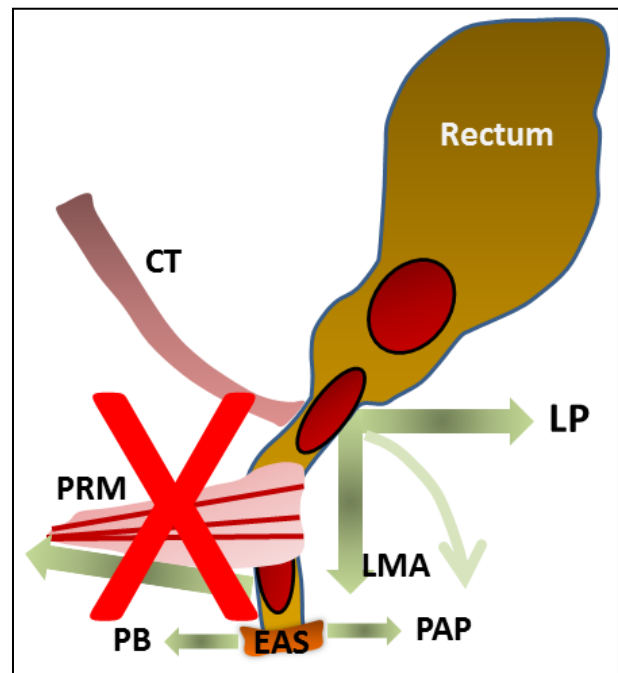


Figure 1. A hypothesis for the anatomical basis of defecation. CT- connective tissue, LP- levator plate, LMA- longitudinal muscle of anus, PRM- puborectalis muscle, PB- perineal body, EAS- external anal sphincter, PAP- posterior anal plate. The anterior wall of rectum is anchored passively by its connective tissue (CT) attachment to the vagina and utero-sacral ligaments. The PRM relaxes, indicated by a large “X”. The LP and conjoint LMA then contract to open out the ARA (curved green arrow). The fecal bolus (ovoids) is deformed and descends into the anus. The EAS relaxes. Contraction of the anterior portion of pubococcygeus muscle (forward arrow) pulls the perineal body (PB) forward to open the lower part of the anal canal. Backward contraction of the post-anal plate (PAP) assists this action by splinting the posterior anal wall

evaluate the effects of the squatting position on symptoms. Moreover, it is unclear if a squatting position benefits all patients or only a subset of patients with chronic constipation. These questions are important because Western style toilets are universal in the United States. Constipation is very common, with an estimated prevalence of 20% in the adult population and 50% of people over 65 years of age.^{8,9}

B. Specific Aims

The specific aims of this study are as follows:

1. To assess the effects of a squatting assist device (Squatty Potty®) on bowel symptoms in patients with chronic constipation.

Hypothesis. The regular (i.e., 7") but not the sham (2") squatting assist device will improve bowel symptoms in patients with chronic constipation.

2. To investigate the effects of Squatty Potty® on rectoanal motion and rectal evacuation assessed with manometry alone during combined manometry-defecography in constipated patients.

Hypothesis. In constipated patients, the regular (i.e., 7") but not the sham (2") Squatty Potty® will:

a) Increase anal relaxation and the rectoanal gradient during rectal evacuation assessed with manometry

b) Increase the rectoanal angle at rest and during evacuation, anal diameter during evacuation, anal relaxation and rectal emptying during rectal evacuation assessed with manometry-defecography

3. To assess if the effects of Squatty Potty® on rectal evacuation predicts its effects on bowel symptoms

Hypothesis. The acute effects of the squatting assist device on rectal evacuation parameters evaluated with manometry and separately with manometry-defecography will predict its effects on bowel symptoms in constipated patients.

4. To obtain patient feedback on Squatty Potty® and to evaluate the factors that explains patient satisfaction.

Hypotheses. a) A majority of patients will find it easy to use the squatting assist device.

b) Patients with a greater BMI and a lesser improvement in bowel symptoms will be less satisfied with the device.

C. Research Design and Methods.

1. Overall experimental design.

This randomized trial in 85 patients includes screening, run-in, and treatment periods (Figure 2). Up to 250 patients will be consented to ensure that 85 patients enter the treatment phase (Phase 3 below) of the study. **While the investigators and patients will be aware of the height of the squatting assist device, patients will not be informed that the 7" device is the active treatment and the 2" device is the sham treatment.** Patients will be asked to refrain from making any major lifestyle changes (e.g., starting a new diet or changing their exercise pattern) during the study. Questionnaires will be administered either in paper or electronic format.

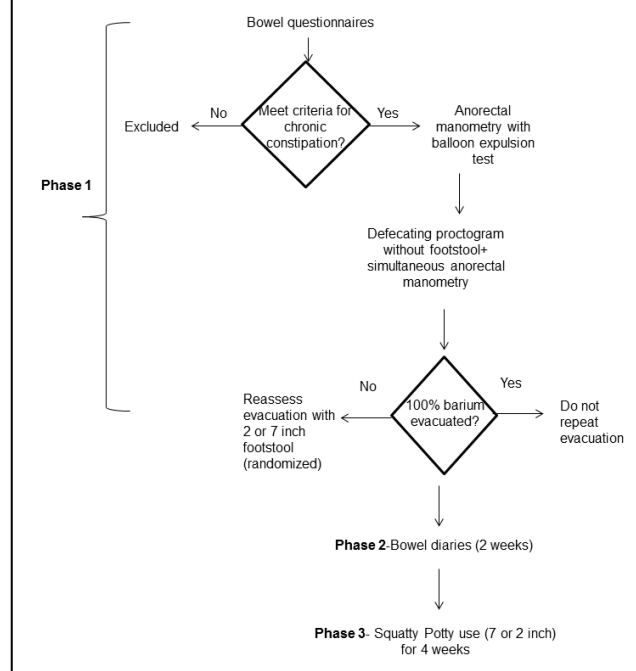
Period 1 (Screening Period).

During the screening visit, patients will complete questionnaires that assess bowel habits and other GI symptoms and the Hospital Anxiety and Depression questionnaire. In an attempt at (i) avoiding situations where we recognize subjects are not eligible to participate when they present at the screening visit and (ii) to reduce the time taken for visits, we propose, when feasible, to ask participants to complete the questionnaires before they come for their screening visit. If subjects are not subsequently consented/enrolled into the study, their responses will be destroyed.

Those patients who are currently on medications to treat constipation or other ineligible medications (e.g. anticholinergics and opioids) will be asked to discontinue them at least three days (72 hours) prior to their screening visit and remain off them until completion of the study (at least 6 weeks). Patients on a stable, continuous regimen of fiber therapy for at least 30 days prior to enrolment will be allowed to continue the same, provided that they do not change their dose during the study.

Patients who meet eligibility criteria (see Section 2.0) will undergo physical examination during which a urine pregnancy test, a blood draw for genetic and epigenetic analyses, and asked to provide a stool sample for evaluating the microbiome. If the urine pregnancy test is negative, an anorectal manometry (ARM) with balloon expulsion test (BET) and a defecating proctogram (DP) with simultaneous ARM (without BET) will be performed (Figure 2).

Figure 2. Study design



Period 2 (Run-in period).

During this period, patients will fill out daily bowel diaries for 14 days to assess baseline bowel movements (BMs). Bowel diaries will assess the a) spontaneity b) consistency (on the Bristol stool form scale), c) ease of passage of stools, d) the need to strain, e) sense of complete evacuation and f) need to use a suppository or enema with each bowel movement. The bowel diaries will be averaged weekly. Participants who miss more than 2 days of entry in the bowel diary in a seven day period will first be contacted to ascertain if they had any bowel movements on the missed days. If they did but did not document them, then they will be asked to fill out bowel diaries for another week. If they did not have bowel movements on those days that will be documented in the diary. Participants who cannot complete their diaries within 14 days will be provided additional time to do so.

If during this period (and also period 3), patients do not have a bowel movement for 48 hours, they may use "rescue medications" to help with constipation. First, they can use a bisacodyl suppository or tablet (10 mg) and if still no bowel movement, a Fleets enema 24

hours later. If still no bowel movement, then they should contact the study team for additional doses of bisacodyl or enema. Oral laxatives will not be permitted during the study because they may affect bowel habits for a longer duration. Patients will need to record their use of bisacodyl or enema in the bowel diary. Rescue medications are not permitted within two days (48 hours) prior to starting the use of Squatty Potty®. Patients reporting watery stools (Type 7 on the Bristol Stool Form Scale [BSFS]), for any SBM, or loose (mushy) stools (Type 6 on the BSFS) for more than two SBMs in their bowel diaries will be excluded.¹⁰

Patients who have an average of less than three complete spontaneous bowel movements (CSBMs) per week during the 14-day run-in period will be eligible for treatment with the footstool (See table 1 for definitions of SBM and CSBM).

Patients will be asked to mail or email completed diaries weekly. Electronic diaries will be filled out online daily and will be reviewed by study staff. Patients who fill out less than 5 days of the diary in the preceding week will be asked to fill out the diary for an additional 1 week.

Period 3 (Treatment with Squatty Potty®).

Patients whose bowel diaries satisfy eligibility criteria will be randomized in a 1:1 ratio to either a 7 inch or 2 inch high Squatty Potty® for 4 weeks. This period will be considered to have started on the date the patient uses the footstool for the first time and will end 4 weeks from that date. The randomization, to be prepared by Dr. Zinsmeister, will be balanced on age (<65 vs. ≥ 65 y), BMI (<30 vs. ≥ 30 kg/m²), and assignment to 2" versus 7" during the defecating proctogram – see below.

Patients will be instructed to use Squatty Potty® for each and every bowel movement during this period. Completed diaries will be mailed or emailed at the end of each week to be reviewed by study staff. We will send the patient's name, address and which height footstool the patient is randomized to the manufacturer who will then mail that size footstool to the patient.

Table 1 Definition of parameters and outcome measures used in the study

Parameter	Definition
SBM (Spontaneous bowel movement)	A bowel movement that occurred without requiring the use of a laxative or enema in the preceding 24 hours or of manual disimpaction
CSBM (Complete spontaneous bowel movement)	An SBM associated with a feeling of complete emptying of the bowel
Complete bowel diary	Daily diary entry for at least 5 out of the last 7 days
Incomplete bowel diary	Diary with two or more days of missing entries
Responder to Squatty Potty	Answers "yes" to the question "Compared to before you started the study, have you experienced adequate relief of constipation?" at any time during the treatment period
"Responder"- clinically significant improvement in abdominal bloating or pain	Improvement in the average weekly abdominal bloating or discomfort score of at least 0.5

“Responder”- clinically significant improvement in severity of constipation	Improvement in the average weekly abdominal bloating or discomfort score of at least 1.0
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2. Human subjects.

a) Inclusion criteria.

- i. Adult females aged 18-80 years. Previous studies investigating association between squatting and defecation included patients upto 82 years of age (Table 2) providing the basis for the upper limit of age for this study.
- ii. Able and willing to provide written informed consent before participating in the study
- iii. Able to communicate adequately with the investigator and to comply with the requirements for the entire study
- iv. Meet Rome III criteria for functional constipation as assessed by questionnaires in period 1, i.e., report at least 2 of the following symptoms for last 3 months or more with symptom onset at least 6 months prior to diagnosis: a) <3 SBMs/week b) hard or lumpy stools $\geq$ 25% of time c) straining $\geq$ 25% of time d) sense of incomplete evacuation $\geq$ 25% of time e) feeling of anorectal blockage $\geq$ 25% of time or f) manual manoeuvres to facilitate defecation $\geq$ 25% of time. Patients who meet Rome III criteria for irritable bowel syndrome will also be eligible provided they also meet above criteria.

Table 2 Age range of studies investigating squatting and constipation		
Author	Study	Age range
Sikirov ⁵	Comparison of straining during defecation in three positions	17-66 years
Rad ⁴	Comparison of squatting and Western style defecation on anorectal measurements	11-75 years
Taylor ⁷	Comparing symptoms of constipation before and after using Squatty Potty®	9-82 years
Sakakibara ³	Impact of body position on defecation	36-44 years

b) Exclusion criteria

- i. Clinical evidence of significant cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematological, neurological, psychiatric or other disease that may interfere with the objectives of the study and/or pose safety concerns.
- ii. History of total, hemi- or subtotal colectomy at any time or other abdominal operations within 60 days prior to entry into the study. Segmental resection of the colon (e.g. sigmoid resection) for diverticulitis will be permitted.
- iii. Current or past history of colon or rectal cancer, scleroderma, inflammatory bowel disease, congenital anorectal abnormalities, rectal prolapse, solitary rectal ulcer syndrome, history of rectal resection or pelvic irradiation
- iv. Active cancer
- v. Pregnant or nursing women, prisoners and institutionalized individuals
- vi. Weight > 300 lbs. as the weight limit for Squatty Potty® is 350 lbs.
- vii. Current or prior use of Squatty Potty®
- viii. Medications

- a. Current use of opioid analgesics. Patients on opioids will be allowed to participate if they have discontinued them for at least 3 days (72 hrs.) before date of screening and are willing to stay off them for the duration of the study.
- b. Current use of anticholinergics (e.g. nortriptyline, amitriptyline, hyoscyamine). Patients who use low dose tricyclic antidepressants (nortriptyline upto 50 mg/day or amitriptyline upto 25 mg/day) will be eligible provided they do not increase the dose during the study period. Patients on higher doses or on other anticholinergics are eligible to participate if they can discontinue their medication at least 3 days (72 hrs) before the date of screening and are willing to stay off them till the study is complete.
- c. Current use of laxatives (MiraLax, Ex-lax, senna, herbal supplements), linaclotide, lubiprostone, and prucalopride to treat constipation- patients using these medications will be eligible to participate if they can discontinue the medication at least 3 days (72 hrs.) before the date of screening and are willing to stay off them till the study is complete.

Table 3. Assessment of Symptoms

The following questionnaires will be administered either by mail, email or phone during the study.

Periods of study	Period1 (Initial visit)	Period 2 (Baseline)	Period 3 (Treatment)
Duration	1-2 days	2 weeks	4 weeks
Bowel questionnaire	X		At end
PACSYM questionnaire		At end	At end
PACQOL questionnaire ¹¹		At end	At end
Hospital anxiety and depression questionnaire	X		
Daily bowel diaries		Daily	Daily
Severity of abdominal bloating and discomfort using 5 point ordinal severity scale (1= none, 2= mild, 3= moderate, 4= severe, 5= very severe)		Daily	Daily
Severity of constipation using the 5-point ordinal severity scale (1= none, 2= mild, 3= moderate, 4= severe, 5= very severe)		At end	Weekly
Adequate relief of constipation ("Compared to before you started the study, have you experienced adequate relief of constipation? "), yes-no response			Weekly
Global relief of constipation using a 7-point balanced scale (1=completely relieved, 2=			Weekly

considerably relieved, 3= somewhat relieved, 4= unchanged, 5= somewhat worse, 6= considerably worse, 7= as bad as I can imagine)			
Satisfaction with Squatty Potty® (1=not at all satisfied, 2=a little satisfied, 3=moderately satisfied, 4=quite satisfied, 5=very satisfied) ¹²			At end

Except for items marked “daily” or “weekly” all questionnaires will be administered once during a given period

3. Experimental procedures

The experimental procedures and the measured outcomes from them are summarized in Table 4

Table 4. Experimental procedures and parameters measured

Test	Parameter measured
Anorectal manometry parameters	Anal pressure and intra-rectal pressure at rest, during squeeze and evacuation Change in anal pressure during evacuation (compared to rest) Recto-anal gradient Rectal sensation Balloon expulsion time
Defecating proctogram	Rectal evacuation (percentage of barium evacuated within 60 seconds) Anorectal angle Distance between anorectal junction and the pubosacral line Diameter of anal opening Length of anal canal Rectal length Mid-rectal diameter Posterior anorectal angle (PARA) at rest, during squeeze and maximum straining
Blood	Genome-wide analysis of single nucleotide polymorphisms
Stool	Stool microbiome
Nutritional Assessment	Habitual dietary intake 72 hours food record to assess actual intake prior to the microbiome stool specimen collection.

- a) **History and physical examination.** During the initial screening visit, eligible patients will undergo, at the discretion of the investigators, a physical examination (if an adequate exam has not been performed in last 3 months).

- b) **Anorectal manometry.** This will be performed with established techniques at baseline in all participants. After rectal cleansing with 1-2 sodium phosphate (Fleets, C.B. Fleet, Lynchburg, VA) enemas, anorectal manometry and rectal balloon expulsion will be assessed. Using high-resolution manometry (Given Imaging), anal pressures will be measured at rest, during squeeze, simulated evacuation, and a Valsalva maneuver first in left lateral and then in the seated position without the footstool. Rectal sensation will be assessed by distending the rectal balloon with air in a graded manner. Balloon expulsion time will be assessed in seated position after filling the rectal balloon with 50 ml of water. In order to study the effect of the footstool on anorectal pressures and defecation dynamics, anorectal manometry (without balloon expulsion test) will be performed again simultaneously with the defecating proctogram in seated position. This time, pressures will be measured first without and then either the 2 inch or 7 inch tall footstool. Participants will be assigned to one of the two footstools randomly. To minimize displacement in the seated position, the anorectal catheter will be stabilized by a plastic clip affixed to the medial thigh by adhesive tape.
- c) **Defecating proctography with simultaneous ARM.** This will be performed with established techniques in the Department of Radiology. The patient will be given one cup of thin barium (10 ml or 0.33 ounces) to drink one hour before the exam in order to opacify the small bowel. At the time of the study, in order to define anatomic landmarks on fluoroscopic images, metallic markers will be affixed (using adhesive tape) to the skin overlying the tip of the coccyx, the pubic ramus and the anal verge. The manometry catheter will then be placed with the participant in the left lateral position. To minimize displacement of the anorectal catheter in this position, it will be stabilized by a plastic clip affixed to the medial thigh by adhesive tape. Approximately 180ml (6 ounces) of barium paste will then be inserted into the patient's rectum. The participant will then be seated on a portable, radiotransparent commode positioned within fluoroscopy tower. Dynamic maneuvers (rest, squeeze and evacuation) will be performed while fluoroscopic screening is performed. Rectal evacuation will be assessed by comparing rectal area measured on fluoroscopic images, after vs before the evacuation attempt.
- Patients who evacuate less than 100% of barium after 60 seconds will be randomized to a 2" or 7" footstool (randomization to be assigned by Dr Zinsmeister) and again asked to strain for upto 60 seconds. Rectal evacuation will be assessed as discussed previously.
- Manometry data and fluoroscopic images will be integrated with the ManoScan V module (Given Imaging). We estimate that the upper limit of radiation exposure time will be 120 seconds. In order to reduce the participant's exposure to radiation, the use of spot films will be minimized and radiological reporting performed from the screening images. While the proctography protocol is similar to clinical practice, the integrated procedure (manometry-defecography) is a research procedure developed in IRB 13-7488. During all 3 of the dynamic maneuvers (rest, squeeze and evacuation), parameters that will be analyzed from the fluoroscopic images are anorectal angle, distance between anorectal junction and the pubosacral line, anal canal diameter and anal canal length. Parameters that will be analyzed from ARM are rectal, upper and lower anal canal pressures, and the recto-anal pressure gradient.
- d) **Blood draws.** Towards our long-term objective of understanding genetic and epigenetic mechanisms contributing to chronic constipation, a blood sample (30 ml in

EDTA) will be collected to uncover associations between single nucleotide polymorphisms (SNPs) and epigenetic markers. DNA extraction will be conducted at the BAP Lab. Genome-wide analysis will be conducted using Illumina 610 QUAD microarray or comparable approaches. Genotype-phenotype correlations will be examined using these patients and other patients in ongoing studies.

- e) **Stool Collection for fecal microbiome.** Standardized instructions and stool kits will be provided to patients for collecting a single stool sample, which will be frozen and stored in a -80°C freezer. Microbial DNA will be extracted from stool and tissue samples using standardized methods as described by us in a recent article.¹⁴ Phylotype profiles of the microbiome from colesévelam and placebo treated FI populations will be generated using deep rDNA hypervariable tag sequencing of the hypervariable V3-V5 region of the SSU rRNA gene, which has been validated for use with human microbiomes and is one of the methods of choice for the HMP. With the longer reads from the MiSeq (250x250 paired end reads), our sequencing will include both the V3-V5 RGTs making for a more optimal phylogenetic analysis.¹⁴ Phylotype profiles of the mucosa-associated microbiome will be generated using rDNA sequencing of the hypervariable V3-V5 region, which has been validated for standard use by the human microbiome project. The 500 base pair reads will ensure a better optimal phylogenetic identification. Barcoding samples prior to sequencing will yield approximately 20,000 reads/sample, ensuring detection of both dominant (core microbiome) and poorly represented taxa (variable microbiome). Identifying the existent taxa, diversity, and ecological relationships within each sample requires that we process large volumes of 16S DNA sequence data. In order to accomplish this task we will follow protocols that we have quantitatively shown to be optimal. Reads will be aligned using our own custom multiple alignment tool (TORNADO v2.0) that has been optimized the production of taxonomic calls and alignments for downstream analysis such as OTU clustering and phylogeny from paired end reads. Sequences will be culled according to initial quality files using QIIME, pre clustered in order to reduce the number of unique reads due to sequencing errors using mother, and aligned using the new version of the TORNADO pipeline for paired end reads. TORNADO v2.0 will then be used to obtain the taxa calls that will be used in later correlation analysis. Second, quantitative PCR assays targeting functional genes *mcrA* and *mrtA* (methanogens) *dsrA* (sulfate-reducing bacteria) and *hydA* (hydrogen-producing bacteria) will be performed on both stool and following published protocols. Similarly, different sulfate-reducing genera will be quantified with validated 16S primers. The abundance of functional genes will be correlated to physiological parameters. Subsequent QPCR assays on microbial groups that are significantly distinct in sequencing analyses may also be performed.
- f) **Nutritional Assessment.** This is an important covariate in the analysis of the fecal microbiome. Habitual dietary intake will be assessed at baseline using an electronic graphical food frequency questionnaire (FFQ) (VioCare Technologies, Inc. 145 Witherspoon Street, Princeton, NJ 08542). This questionnaire is based on the Women's Health Initiative FFQ and has been adapted by VioCare in an electronic computer-administered format to evaluate dietary intake over a three month period. It employs the Minnesota NDS nutritional analysis database for nutrient analyses. The FFQ has been validated and compares well with nutrient intake validated against food records and four 24-hr dietary recalls^{18,19} (ii) Participants will keep food records of their actual dietary intake for 72 hours prior to collecting the stool specimen for microbiome

analysis. The food records will be analyzed for energy, protein, fat, carbohydrate and fiber content by the CRTU nutrition staff using the ESHA Food Processor software (Version 11.0) developed by ESHA Research, Salem, Oregon 97309-1028.¹⁴

As of 3/7/2024 no longer part of the study procedures as unable to obtain a supplier of the Mega-Brush.

g) Outcome measures

These will be compared between those assigned to the 7 inch and those assigned to the 2 inch Squatty Potty.

Primary outcome

The primary outcome measure is the change in mean weekly complete spontaneous bowel movement (CSBM) frequency from baseline period to the 4 week treatment period See table 1 for definition of CSBM). The calculation of CSBM frequencies in the pre-treatment and treatment period are summarized in Table 5.

Table 5 Calculations from bowel diaries

Weekly CSBM frequency = (Number of CSBMs recorded in 7 days /Number of days with bowel entries) X 7
Weekly SBM frequency = (Number of SBMs recorded in 7 days /Number of days with bowel entries) X 7
Mean weekly CSBM frequency at baseline = Sum of weekly CSBM frequencies (i.e. week 1+ week 2) ÷ 2
Mean weekly CSBM frequency during use of Squatty Potty = Sum of weekly CSBM frequencies (i.e. week 1+ week 2+ week 3 + week 4) ÷ 4
Mean weekly SBM frequency at baseline = Sum of weekly SBM frequencies (i.e. week 1+ week 2) ÷ 2
Mean weekly SBM frequency during use of Squatty Potty = Sum of weekly SBM frequencies (i.e. week 1+ week 2+ week 3 + week 4) ÷ 4
Average daily stool consistency = Sum of BSF scores for all bowel movements that day ÷ Number of bowel movements
Weekly stool consistency = (Sum of BSF scores for each day with a recorded bowel movement/Number of days with a recorded bowel movement) X 7

Secondary outcomes

Outcomes will be assessed as change from the baseline period to the week 4 of treatment period except where indicated.

- a) Response to use of Squatty Potty. Responders will be defined as those who answer “yes” to the question “Compared to before you started the study, have you experienced adequate relief of constipation?” at any time during the treatment period. We will compare demographics, anorectal and defecography parameters (Table 5) between responders and non-responders separately for the 2 and 7 inch footstools
- b) Change in mean weekly SBM frequency

- c) Change in other diary measures of defecation such as mean BSFS and frequency of straining.
- d) Change in abdominal symptoms (e.g. discomfort and bloating). An improvement in the abdominal discomfort and bloating score of 0.5 and constipation severity score of 1.0 was reported to be perceived as beneficial by constipated patients receiving linaclotide,¹⁰ and will be used to define responders for these end points.
- e) Change in global assessment (e.g. i.e., constipation severity, adequate and global relief of constipation and satisfaction with treatment) - week 4 vs. baseline, week 2, 3 and 4 vs. week 1 during treatment period.
- f) Change in Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire scores
- g) Anal manometry parameters. The parameters that will be assessed are summarized in Table 4.
- h) Defecating proctogram parameters. The parameters that will be assessed are summarized in Table 4. The changes (after – before footstool) will be evaluated and compared between 2” and 7” footstools using the baseline value as a covariate.¹⁵
- i) Compare the height from the floor to the top of the toilet seat without Squatty Potty (Figure 4) between responders and non-responders to the footstool (as defined in Table 1). Participants will be asked to measure this for their respective commodes.

Figure 4. Toilet height measurement



h) Data and statistical analysis.

Sample size estimate

There is no study comparing the use of the squatting assist device to placebo. In the only uncontrolled, unpublished study on use of the squatting assist device, 153 subjects who used the device reported a significant improvement in the constipation score after a period of 4 weeks (mean scores $\pm$ SD before and after use of device were 9.08 ± 1.05 and 5.61 ± 2.47 with lower score indicating improved symptoms). Further, 98% of all subjects in this study had an improvement in their constipation score after using the squatting assist device for 4 weeks.⁷ We estimate that about 30% patients who are randomized to the sham device (2 inch) will report “adequate relief of constipation”. Using a conservative estimate that about 60% patients using the taller (7 inch) squatting device will achieve self-reported adequate relief of constipation, we estimate that we will need 80 subjects (40 in each group) to detect this difference with a power of 80% at an alpha level of 0.05. Assuming that 5% of patients will have incomplete diaries¹⁶, we plan to recruit 85 patients in all for this study (41 per group).

i. Statistical analysis

The primary efficacy end point will be the change in mean weekly CSBM rate (during treatment period) from the 14-day baseline period. Table 5 summarizes how we will calculate CSBM rate from bowel diaries. CSBM and SBM frequencies will also analyzed using a responder definition, with a responder defined as a) a patient who, for 3 of the 4 treatment weeks, had a weekly CSBM or SBM rate ≥ 3 and an increase ≥ 1 relative to baseline or b) patients who were CSBM responders and had either an improvement in their Bristol stool form scale or straining score of ≥ 1 for 3 of 4 weeks without worsening of either. The two “responder” groups will be compared separately to corresponding “non-responders”. An improvement in the abdominal

discomfort and bloating score of 0.5 and constipation severity score of 1.0 will be used to assess responders for these end points. Change from baseline end points will be analyzed using an analysis of covariance using the treatment period value as the response and the baseline value as a covariate. Other covariates to be considered include percentage of barium evacuated during defecating proctography without and with 2" or 7" footstool and the change between these approaches, anal resting pressure, and balloon expulsion time (on a linear scale or categorized as normal or abnormal). The change from baseline values will be reported as the least-squares means from the analysis of covariance (ANCOVA) model based on the patient's overall average score during Period 3 (except for SBMs and CSBMs, where overall weekly rates will be calculated). Binary responses or end points will be analyzed using a Cochran-Mantel-Haenszel (CMH) test. These endpoints will use Hochberg or Sidak adjustment for multiple comparisons.¹⁷ Time-to-event data will be analyzed using log-rank tests. Data for missing bowel diary values will be imputed using data from completed studies as discussed above. The relationship between symptoms and objective parameters will be evaluated with Spearman's rank correlation coefficient. All p-values will be based on 2-sided tests.

Subject Safety

Only subjects who are eligible based on pre-defined criteria, an interview and a physical examination, and screening tests will be enrolled. The consent form details issues related to privacy, withdrawal from studies, and use of blood for genetic analyses among other items. Additional details as follows:

1. **Anorectal assessments** are extremely safe; discomfort, if any during rectal distention is mild and tolerable and the risk of rectal perforation in an uninflamed rectum is negligible. Studies will be conducted by trained technicians or fellows.
2. **Squatting** has been shown to be safe and none of the studies reported any adverse effects with it.
3. **Defecating proctography** is a safe test that will be conducted in the clinical practice by a Staff radiologist. Because it entails radiation exposure, pregnant and nursing women will be excluded from the study.

Since we are not using any drugs, DSMP is not necessary. Patients who are positive for depression by the Hospital Anxiety and Depression questionnaire will be offered referral to Psychiatry. If the patient endorses suicidal thoughts then we will first and foremost offer support. If the patient is on Mayo campus and in department, we will then have a co-worker page 911 and ask for Security. The study coordinator will contact the principal investigator immediately to alert them that of the situation. The study staff will stay with the patient until Security arrives at the location. If the patient is not on Mayo campus, then the study staff will keep the patient on the line and have a co-worker page 911.

Study procedures are conducted by trained and experienced personnel. Monitoring for any problems with use of Squatty Potty® will be reviewed by the PI. All communications pertaining to the study will be stored or documented.

4. **Data Integrity.** Only subjects who are eligible based on pre-defined criteria, an interview and a physical examination will be enrolled. Transcription of data is accurate and complete. Calculations will be standardized and accurate. The study technician will monitor data after every study.

5. **Subject Privacy.** Subjects will be consented in a private room. Adequate time for questions will be provided.
6. **Data Confidentiality.** All records are maintained in password protected electronic files. Hard copies are filed in private offices.
7. **Study Documentation.** Documentation will be per established guidelines during the study (hard copy and electronic data capture). These files will be sampled annually.
8. **Study Coordination.** Quarterly debriefing will be conducted to ensure expectations are clear and if educational needs exist.

F. Limitations, potential problems and precautions taken.

We anticipate that certain patient groups (elderly, those with arthritis, obese) will report some degree of difficulty with use of the squatting assist device. To minimize the risk of patients dropping out because of difficulty using the squatting assist device, we will screen them in Period 1 where patients who self-report difficulty squatting will be excluded. The weight limit for Squatty Potty® is 350 lbs. - we will include only patients who weigh 300 pounds or less.

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