Electrical stimulation to evoke recto-colonic reflex for colonic motility

Funding Agency: VA RR&D

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Abstract

This study hopes to characterize the effects of minimally invasive electrical rectal stimulation on colonic motility in persons with neurogenic bowel dysfunction. Subjects will act as their own controls, with control data being obtained during subjects' typical bowel routines. Outcome measures include bowel emptying duration and amount of stool removed. These data will be compared to determine the efficacy of electrical stimulation to promote bowel emptying compared to patients' typical bowel routines, and to provide an effect size on the outcome measures of colonic motility for powering future studies.

We hypothesize that electrical rectal stimulation will produce increased colonic motility that results in defecation and that defecation time will be similar to subjects' typical bowel routines. The time required for defecation in response to their typical bowel routine and to minimally invasive electrical rectal stimulation will be monitored. Subjects will also be asked to report on sensations and comment on electrical stimulation.

List of Abbreviations

LSCDVAMC: Louis Stokes Cleveland DVA Medical Center

SVAMC: Syracuse VA Medical Center

SCI: spinal cord injury

EMG: electromyogram

AD: autonomic dysreflexia

NBD: neurogenic bowel dysfunction

FES: functional electrical stimulation

IRB: Institutional Review Board

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Protocol Title: Electrical stimulation to evoke recto-colonic reflex for colonic motility

1.0 Study Personnel

PI: Steven Brose, DO, Chief of the SVAMC SCI Unit

Co-Investigators: Dennis Bourbeau, PhD, Investigator and Biomedical Engineer at Cleveland FES center and LSCDVAMC.

2.0 Introduction

Loss of bowel function is a major concern for veterans with central nervous disorders, such as spinal cord injury (SCI). Over 42,000 veterans have SCI, representing more than 15% of the total American population with SCI. Following SCI, the colon is often unable to evacuate stools via peristaltic propulsion. Losing bowel function can cause constipation, gastro-intestinal complications, and fecal incontinence, severely impacting health and quality of life.

The standard of care for individuals with neurogenic bowel dysfunction involves the design of a bowel program for predictable and effective elimination of the bowels. A bowel program includes diet, fluid intake, activity, and pharmaceutical or mechanical rectal stimulation. Approximately 80% of individuals with neurogenic bowel dysfunction use digital stimulation of the rectum to reflexively activate the colon, improve colonic motility, and facilitate bowel evacuation. However, the bowel routine can require over an hour to evacuate the bowels and this process often requires the assistance of a caregiver, which adds to the cost of care and reduces independence. Restoring bowel function is considered a high priority by individuals with paraplegia, but it remains a critically unmet need requiring further development. The top priority for individuals with tetraplegia is reaching and hand function, but pelvic functions are still of high concern.

Digital rectal distension is the clinical standard for eliciting colon motility. The majority of individuals with neurogenic bowel dysfunction use digital rectal stimulation to mechanically distend the rectum and reflexively activate colon peristalsis, which loads stool into the rectum for bowel emptying. Digital rectal distension takes advantage of an existing reflex pathway affecting bowel function. The recto-colonic reflex has been well-studied in cats, dogs, and humans. Rectal distension activates mechanoreceptors innervating the rectum, which sends afferent information via small Aδ and C fibers to the sacral spinal cord. This input modulates a spinal reflex pathway that activates motor efferent drive to the colon, causing coordinated peristalsis and increasing colonic motility. Digital rectal stimulation is effective, but it requires an individual, or a caregiver, to reach into the individual's rectum with gloved fingers. Even with digital

rectal stimulation and other bowel program tools, the bowel routine still typically requires an hour or two to complete. Reliance on digital rectal stimulation is associated with lost independence, lost time, lost dignity, and increased caregiver costs. Substituting rectal distension for a method that does not include these drawbacks would provide positive social and psychological benefits.

We are currently developing approaches using electrical stimulation to improve colonic motility as an alternative to digital rectal stimulation and to take advantage of the recto-colic reflex. Recent preclinical experiments have provided supporting evidence that electrical stimulation of the rectum or distal colon can modulate this excitatory recto-colic reflex and potentially promote bowel emptying. We hope to quantify the effects of minimally invasive electrical rectal stimulation, in comparison to subjects' typical bowel emptying routine, on colonic activity in persons with neurogenic bowel dysfunction.

3.0 Objectives

This pilot study hopes to characterize the effects of minimally invasive electrical rectal stimulation on colonic motility in persons with neurogenic bowel dysfunction, as well as collect data to determine an effect size and so power future studies that measure colonic motility in response to electrical stimulation

Our hypothesis is that electrical rectal stimulation will produce increased colonic motility that results in defecation and that defecation time will be similar to subjects' typical bowel routines.

4.0 Resources and Personnel

All study actives will occur at the SVAMC, in the SCI inpatient clinic.

Recruitment of subjects will be done by the PI, who will identify potentially eligible participants receiving SCI treatment at the SVAMC. Once potential subjects are identified, informed consent will be obtained by a research assistant or nurse. Only a nurse approved on the study will be responsible for collecting data.

5.0 Study Procedures

5.1 Study Design

Experiments will be conducted in the SCI inpatient clinic in 10 individuals with neurogenic bowel dysfunction who have stable bowel routines. We will work with nursing staff on the study to maintain a consistent bowel emptying schedule for the subjects. We will not disrupt the patient's typical bowel emptying routine. Only the Research Nurse will be completing any research related procedures. Data will be collected from subjects over 6 weeks during their typical bowel routines. Then we will test minimally invasive electrical rectal stimulation via a rectal probe in a second 6-week period. Subjects will be instrumented with a rectal probe and stimulator inserted by the Research Nurse only for the duration of those bowel routines and effects are not expected to continue past the end of the experiment period. Subjects will return to their typical bowel routine at the end of the 6-week stimulation testing period. For patients >6 months post-SCI, the control period for the study will consist of their typical digital stim bowel routine. Nurses will log dig stim data as they usually do and this data will be used as control data for the study. During the experimental phase of the experiment, dig stim will be replaced with electrical stimulation. Use of electrical stim will not change the patients' bowel routine otherwise. There is no set schedule for the intervention because we are adapting to each patients' normal bowel routine. The only structure is that we have a defined control period using their normal routine, followed by a defined experimental period with the electrical stimulation. For a normal bowel routine, patients typically receive bowel intervention every other day in a typical week.

For subjects within 6 months of SCI diagnosis, but after the acute spinal shock phase, we will instead alternate between periods of control intervention (dig stim) and electrical stimulation. This will be done 3-7 times a week to optimize data acquisition, rather than having a defined control period followed by a defined experimental period. Neither the altered procedure nor the inclusion of patients who are <6 months post-SCI will affect the risk level of the study. Acute spinal shock is defined as the period immediately following an acute spinal cord injury. This phase resolves 72 hours post-injury and it is exceptionally rare that a patient in this phase of injury would be in the SCI, rather than the ICU.

Typical Bowel Routine
Typical bowel routines usually involve digital rectal stimulation conducted by the subject, their nurse, or their caregiver. An individual inserts a gloved finger through the anus into the rectum and mechanically distends the rectum by moving back and forth against the inside of the rectal wall for approximately 30 seconds. Time is allowed for the colon to move and evacuate some stools, then the process is repeated (typically 15-20 minutes later). Digital rectal stimulation is thus repeated until the colon contents are empty, usually marked by the appearance of mucus and no evidence of stools in the distal colon or rectum. Some subjects may also receive a mini-enema or other

suppository to aid in bowel emptying. Individual bowel routine schedules vary but are typically conducted 3-5 times a week.

Electrical Rectal Stimulation
A clinically standard rectal probe electrode will be inserted into the rectum to administer electrical stimulation. The probe electrode will only be in place to administer bouts of stimulation just as gloved fingers administer digital rectal distension, after which it will be removed to allow for bowel emptying. The probe electrode will be connected to a Digitimer stimulator DS7A, which is FDA-approved for electrical stimulation in human subjects and has been used in our previous, similar experiments for bladder function. Stimulation will either be 20 Hz constant frequency or burst pattern stimulation delivered as 5-50 pulses at 100-200 Hz once per second. We will first determine the stimulation amplitudes at which the subject can sense stimulation and at what limit they tolerate stimulation but do not wish to go higher for concern of discomfort. We will then apply stimulation within this range, not expected to exceed 40 mA, which is the typical range we see in similar applications of surface electrical stimulation. Stimulation will be administered continuously for the duration of the bowel routine. If stimulation does not increase colonic motility and promote defecation, as determined by each subject's baseline data on bowel emptying time, nurse experience, or clinician expertise, then we will cease stimulation for that day and return to the subject's typical bowel routine. If stimulation fails to increase colonic motility for bowel emptying on 3 or more occasions in a given subject, then we will stop the 6-week stimulation period and return that subject to their typical bowel routine.

The procedures in this study involve certain risks, which are similar to the risks of digital rectal stimulation, which is part of a participant's bowel routine. The incremental risks involved in performance of these studies are not significantly greater than those encountered during a standard bowel routine. However, these risks are outlined in the participant's consent form, along with explanations of what would be done to reduce the likelihood of adverse avents, and what would be done should any occur.

5.2 Recruitment Methods

Patients of the SCI unit will be recruited by word of mouth by Dr. Brose at the SVAMC. As many patients will be recruited as needed to enroll 10 subjects into the study. Eligibility will be assessed via chart review and patient interview by the PI. Those expressing interest will be referred to study staff who will explain the study, highlight that it is voluntary, and answer any questions.

Every effort will be made to recruit individuals that are representative of the US population. The units treating patients with spinal cord injuries, stroke, or multiple sclerosis at the SVAMC have a particularly high proportion of subjects from underrepresented minority groups. The majority of individuals with neurogenic bowel dysfunction that are available for the study are male. Therefore it is expected that the majority of experiments will be performed on men. Every effort will be made to include women who should at least represent their prevalence in the spinal cord injured

population. All candidates will be treated the same with strict adherence to the inclusion and exclusion criteria.

Individuals who do not speak English will not be recruited. However, it is not anticipated that non-English speaking potential participants will be encountered.

Participants will be paid $50 via check sent through the post upon completion or partial completion of the study.

5.3 Informed Consent Procedures

Informed consent will be obtained by a member of the research staff, after verbal explanation and provision of time for the subject to study the consent form and ask questions. The informed consent process will involve meeting with a potential subject in a quiet, private area (on the SCI Unit or in a physician's private office), finding out whether he or she is capable of giving consent, and discussing the purpose, risks, and benefits of participation. We will ensure that all subjects genuinely understand the study, that they are aware that participation is entirely voluntary, and that they can choose to discontinue participation at any time.

HIPAA authorization will be discussed with the potential participant at the time the patient is interviewed and a copy of the authorization will be given to them for their review. Specific information collected will include: Date of birth, date of spinal injury, level of spinal injury, gender, name, medical record number (social security number), current medications, previous bladder or urinary tract interventions, current medical status, and phone number. This information is being collected because these data are used to categorize individuals according to medical condition and allow investigation of medically related differences between the responses of different individuals. The participant's social security number will be collected in order to place appropriate documentation in the participant's medical record

5.4 Inclusion/Exclusion Criteria

Inclusion Criteria

- Neurogenic bowel dysfunction using digital rectal stimulation
- Neurologically stable
- Skeletally mature
- Adults 18 years or greater
- Multiple Sclerosis or Stroke or Suprasacral SCI
- Must be past acute spinal shock phase

Exclusion Criteria

- Active sepsis
- Open pressure sores on or around pelvis
- Significant colon trauma or colostomy
- History of Autonomic Dysreflexia

5.5 Study Evaluations

Data collection will include standard medical charting and documenting outcome measures, such as bowel emptying time as written in section 5.6 Data Analysis. No tests, questionnaires, or procedures will be conducted beyond the typical bowel routine or stimulation testing described in this protocol.

5.6 Data Analysis

This work is considered a pilot study. Data will be collected to determine an effect size and power future studies that measure colonic motility in response to electrical stimulation. Therefore, 10 subjects are chosen to provide sufficient data to power a future study.

Bowel emptying will be performed by a trained clinician, caregiver, or subject (whoever normally performs it for the subject) using standard technique. The bowel routine is typically conducted with digital rectal stimulation and/or the insertion of suppositories or similar chemical systems. The time that elapses between initial intervention and bowel emptying will be measured as bowel emptying time. We will also test electrical stimulation to modulate an excitatory recto-colic reflex by stimulating via a rectal probe electrode. These systems are clinically available for chronic constipation in other indications and are considered minimal risk. We have experience measuring bowel activity with these methods. Initial introduction of the rectal probe electrode may cause temporary distension of the rectum. To ensure that reflexive activity due to the probe does not confound our data, we will wait approximately 5-10 minutes for the colon to relax back to baseline activity before beginning the bowel routine with stimulation.

The primary outcome variable is bowel emptying time. Bowel emptying time data are not expected to follow a normal distribution. Therefore, the non-parametric Mann-Whitney rank-sum test with a significance of 0.05 will be used to compare bowel emptying times between typical bowel routines and electrical stimulation conditions

across subjects. We expect to observe a great deal of variability in bowel emptying times, which may require many observations and subjects to achieve statistical significance.

Analysis on de-identified data will be performed by study staff. De-Identified data from this study may be pooled with data collected by Dr. Bourbeau originating from a similar study of the same name currently approved at the Louis Stokes Cleveland DVA Medical Center.

5.7 Withdrawal of Subjects

A subject may choose to withdraw from participation in the study at any time. There are no potential risks from early withdrawal or removal from the study, as this is not a treatment procedure; it is one time feasibility study. They may also be withdrawn from the study at any time by the PI or research staff as per the PI's clinical judgement.

6.0 Reporting

In the event that the security of VA research-related information (physical or electronic data) is compromised, either by unauthorized use, disclosure, transmission, removal, theft, loss, or destruction, the PI and authorized research staff will report to the ACOS for Research, Privacy Officer, and Information Security Officer within 1 hour, as specified in Research & Development Policy 151-17.

7.0 Privacy and Confidentiality

Data Storage

All study files at the SVAMC will be kept in a locked file in a designated room in the SCI unit. Consent forms will be kept in a separate file apart from the data files. All research data (physical and electronic) will be anonymized using identifiers supplied by the experimenter. In this study, each participant will be assigned a subject number (e.g., Subject 001), which will be used to link all data provided by the participant. There will be no correspondence between the participant's subject number and other personally identifying information, such as names or contact information, which could link them to the study or their data. The subject number key will be locked away separately from any

data identifiable by subject number. Privacy for patient health information will be strictly adhered to by study staff. Information will be collected during an interview in a quiet and private area (on the SCI Unit, or in a physician's private office).

Because two VA sites will be involved in data analysis (LSCDVAMC and SVAMC), data will be transferred between these locations using secure, encrypted VA email to the PI, co-PI, or designated research staff. However, nothing beyond data sharing should be required between the two sites because they are operating off independent, locally-approved IRB protocols. **All data shared is de-identified**.

Data Disposal

In accordance with the VHA Records Control Schedule (RCS 10-1), the official research file is a temporary record, which is maintained by VHA for 6 years after cut off of the records (cut off being the end of the fiscal year in which the study closed).

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