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The effect of electrical stimulation on colonic transit following spinal cord injury in cats

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The effect of direct electrical stimulation on colinic transit and manometric recordings following spinal cord injury were assessed in five adult male cats. Intra-colonic catheters were surgically placed, stimulating electrodes were sutured to the colonic serosa and a laminectomy with spinal cord clamping at a T4 level was done to induce spinal cord injury (SCI). Twenty radiopaque markers were inserted through an intra-colonic catheter located 1 cm distal to the cecum and were monitored with daily fluoroscopy as a measure of colonic transit. Transit measurements were compared before SCI, after SCI and after SCI with electrical stimulation of 40 pps, 1 ms, and 0–50 mA. Colonic transit following SCI was significantly prolonged ($P<0.05$) when compared to the transit before SCI. Electrical stimulation following SCI improved colonic transit to values not significantly different from those before SCI. Spontaneous colonic phasic motor activity was similar both before and after SCI. Manometric defection patterns were also observed to be similar before SCI and after SCI with electrical stimulation. Based on our scoring criteria, the most frequent response to electrical stimulation was an abdominal contraction. These findings demonstrate that colonic transit is prolonged following SCI and that direct electrical stimulation of the colon following SCI improves colonic transit in an animal model.

Keywords: colon transit; constipation; spinal cord injury; neuroprosthetics; electrical stimulation

Introduction

Spinal cord injury (SCI) can result in significant gastrointestinal complications. These problems range from the esophagus[1] to the colon and rectum.[2] Constipation and fecal impaction are significant problems following SCI. Difficulty with bowel evacuation was found in 20% of SCI patients,[3] while fecal impaction comprised 45% of all gastrointestinal complications in another group of SCI patients.[4] The exact etiology of this difficult evacuation is uncertain. Prolonged colonic transit occurs after SCI but it is unclear how this relates to colonic motor activity and anorectal function. The treatment of this bowel dysfunction following SCI is difficult. Approaches often include digital stimulation, stool softeners and suppositories. Other treatment has included the use of an enema continence catheter but compliance was difficult.[5] The use of colostomy as an alternative therapy in SCI patients has also been evaluated and can be effective.[6–8] Unfortunately, this treatment presents yet another psychological adjustment to be made in the physical appearance of these often young SCI patients. Application of electrical stimulation is a promising approach for promotion of defecation following SCI. The use of electrical stimulation of the anterior sacral roots (S2–S4) has been described.[9–11] Six of 12 patients with cervical or thoracic SCI achieved complete rectal evaluation of feces using this approach.[10] This type of electrical stimulation, however, requires neurosurgery and deafferentiation of the sacral roots resulting in loss of reflex defecation. A potential alternative treatment would be direct electrical stimulation of the colon. This method could result in improved colonic transit and defecation without affecting other organ systems. In the present study, an animal (cat) model of SCI was used to assess the effect of direct electrical stimulation of the colon on transit following SCI.

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Methods

Five adult male cats weighing 4–6 kg were received from a federally licensed vendor. The animals were housed and used in a AAALAC accredited facility.

Institutional Care and Use Committee approval was obtained for the animal care and surgical procedures. The animals were housed in stainless steel cages and given a constant diet of two 5.5 oz cans of commercial cat food (Pro-Pet, Syracuse, NY) daily. As previously detailed,[12] two survival surgeries were performed on each animal: the first surgery for instrumentation (placement of intra-colonic catheters, urinary bladder catheter, intra-abdominal balloon catheter, colonic serosal electrodes) and the second surgery for SCI.

In brief, the first surgery for the instrumentation included placement of two intra-colonic silastic catheters for manometric recordings. Each catheter had two lumens. The colonic catheters were made from silastic, medical-grade tubing and consisted of two lumens each. The first colonic catheter was placed 1 cm distal to the cecum (approximately 27 cm proximal to the anus). One of the lumens (3/16 in O.D.) from this catheter extended 3 cm into the colon and was used for insertion of the radiopaque markers in addition to manometric recordings; the other lumen (2/16 in O.D.) extended 6 cm into the colon and was used solely for manometric recordings. The second colonic catheter had two lumens (each 2/16 in O.D.) with one lumen extending 3 cm and the second lumen extending 6 cm into the colon. This colonic catheter was placed 10 cm proximal to the anus. The two colonic catheters inserted into the colon were secured with purse-string sutures (3–0 nonabsorbable Prolene with a noncutting needle). The colonic catheters were fitted and secured with a silastic disk. A single-lumen, silastic, urinary bladder catheter (2/16 in O.D.) was inserted into the dome through a small incision and secured with purse string sutures (3–0 nonabsorbable Prolene with a noncutting needle). A silastic, medical-grade disc, which was located at the bladder/catheter interface, was used to further secure the catheter with simple interrupted sutures (3–0 nonabsorbable Prolene with a noncutting needle). The portion of the urinary bladder catheter which resided inside the urinary bladder did not extend to the urethra. This catheter was used to drain the urinary bladder after SCI and as an indirect measure of intra-abdominal pressure. Six electrodes each consisting of 50 stranded, 1 mil 316L VM, stainless steel wire (Cooner Wire Inc., Chatsworth, CA, USA) were sutured to the colonic serosa. Two elecrodes each were implanted in a semi-circular fashion around the colon at approximately 10 cm and 25 cm proximal to the anus. An additional electrode each was implanted longitudinally (parallel to colonic lumen) at approximately 5 cm and 20 cm proximal to the anus. The six electrodes and four catheters were advanced under the skin and exited percutaneously from the dorsum of the animal. The electrodes and catheters were placed in the pockets of the animal jacket (Alice King Medical Arts). The animals were allowed to recover for 7–14 days before the manometric and transit studies were performed.

Colonic transit was assessed before and after SCI with the use of radiopaque markers composed of polyvinyl chloride O-rings 1 mm × 4.5 mm (Konsyl Pharmaceuticals, Inc., Fort Worth, TX). Each circular marker was cut into four equal pieces. Using video fluoroscopy, twenty pieces of radiopaque marker were introduced into the colon through one of the lumens of the catheter located just distal to the cecum on day 1. An average of 41 35.8 and 34 cc saline was used to flush the markers through the tubing and into the cecum before SCI, after SCI and after SCI with stimulation transit studies, respectively. The amount of saline used was not found to be statistically different among these three groups. Fluoroscopy was performed daily for 5 days so the number of markers remaining in the colon could be monitored. Transit times were based on the number of markers extruded over a maximum of a 5 day period. The percentage of radiopaque markers extruded over a 5 day period was compared before SCI, after SCI and after SCI with electrical stimulation. Each of these colonic transit studies was duplicated for a total of six transit studies per animal. Both transit studies after SCI without stimulation were conducted before the two transit studies with stimulation in order to obtain a baseline value of colonic transit after SCI without the effects of electrical stimulation. Animals that had not defecated by day 5 were given water enemas to evaluate their bowel and avoid fecal impaction. Of all the animals evaluated, one required an enema after the completion of a transit study. Eleven days passed before this animal was further evaluated.

Colonic manometric studies were performed using water-filled intra-colonic catheters, Motorola pressure sensors (Phoenix, AZ, USA), Gould universal amplifiers (Cleveland, OH, USA) and a Grass 8-channel strip chart recorder (West Warwick, RI, USA). The urinary bladder pressure and intra-abdominal pressure were also simultaneously recorded with the same equipment. The animals were not sedated or anesthetized for any manometric recordings. Recordings were performed after a 12 h overnight fast. An initial 3 h recording was performed after which the animal was then fed a 5.5 oz can of soft commercial cat food over a 15 min period followed by a second 3 h recording.

The second surgery for spinal cord injury was performed approximately 8 weeks after the first surgery. A laminectomy was performed at T4 through a superior (dorsal) thoracic incision. The cord was clamped at T4 with a hemostate for 30 s. With this technique, no animal regained motor function of the hind limbs for the duration of the study. Following a 7–14 day recovery from SCI, the animals then underwent repeat colonic transit and manometry studies to determine the effect of SCI on baseline colonic transit and intra-colonic pressures.

The effect of electrical stimulation on intra-colonic pressures and on colonic transit after SCI was then

determined. An isolated constant current S48 Grass stimulator (Quincy, MA, USA) was used. Frequency (10,40 pps), pulse duration (0.1,1.0 ms), and current (0 – 50 mA) were systematically varied for each pair of electrodes to determine the parameters and the electrodes which could induce defecation in each animal. These ranges of parameters were used in previous studies involving the urinary bladder in SCI.[13–15] Preliminary stimulation trials were performed twice daily (morning and afternoon) on two separate days. Three pairs of electrodes were located semi-circularly 10 cm proximal to the anus, semi-circularly 25 cm proximal to the anus, or longitudinally. Stimulation protocols consisted of selectively activating each pair of electrodes individually. All stimulations were bipolar with one electrode of each pair connected to the positive pole and the second electrode of each pair connected to the negative pole. A transit study was then performed using the previously determined optimal stimulation parameters and electrode sites for that animal which were found to induce defecation. Electrical stimulation during this transit study was performed once each morning and once each afternoon for a total stimulation time of 120 s per day.

Based on post-mortum evaluations, the approximate length for the stimulating portion of each semi-circular electrode was taken to the 6 cm which resulted in a calculated area of 0.048 cm^2. Of this area, approximately half of it was estimated to be exposed due to the contract amongst the individual strands. As a result, at a current of 45 mA and at a pulse width of 1 ms, the estimated charge injection density was calculated to be 37.5 $\mu C/cm^2$. For the longitudinal electrodes, the length of 10 cm was used and a similar calculation estimated the maximum charge injection density of 23 $\mu C/cm^2$.

Spontaneous and stimulation induced colonic and abdominal responses were scored using a criterion based scale for the involvement of abdominal skeletal muscles, colonic contractions and bladder contractions. The criteria for this scale was as follows: (1) a colonic contraction was identified as an increase in colonic pressure of 10 cm H_2O above respiratory baseline in any of the colonic catheters without an increase in bladder pressure; (2) a bladder contraction was identified as an increase in bladder pressure of 10 cm H_2O above respiratory baseline without an increase in colonic pressure; (3) an abdominal contraction was identified as an equal increase of 10 cm H_2O above respiratory baseline in colon pressure and in bladder pressure; (4) an abdominal contraction with a corresponding colon contraction was identified as an increase in both bladder and colonic pressures of 10 cm H_2O above respiratory baseline with the greatest pressure increase recorded from the colon; (5) an abdominal contraction with a corresponding bladder contraction was identified when there was an increase in both colonic and bladder pressures of 10 cm H_2O above respiratory baseline with the greatest pressure increase recorded from the bladder; and (6) an undetermined contraction was identified when any of the individual pressure records were off scale.

ANOVA was used for statistical analysis to determine the significance of the independent variable (current) on the dependent variable (transit time). Bonferroni's procedure was used as a *post-hoc* test for making all possible pairwise contrasts among the means of the transit data.

Results

The colonic transit studies before SCI, after SCI and after SCI with electrical stimulation are demonstrated in Figure 1. Colonic transit time following SCI (SCI) was significantly ($P<0.05$) prolonged when compared to the transit time before SCI (PreSCI). Before SCI, at least 80% of the markers were extruded within 3 days. After SCI, drastically delayed transit times in excess of 5 days were observed. Electrical stimulation of the colon (SCI + Stim) following SCI improved colonic

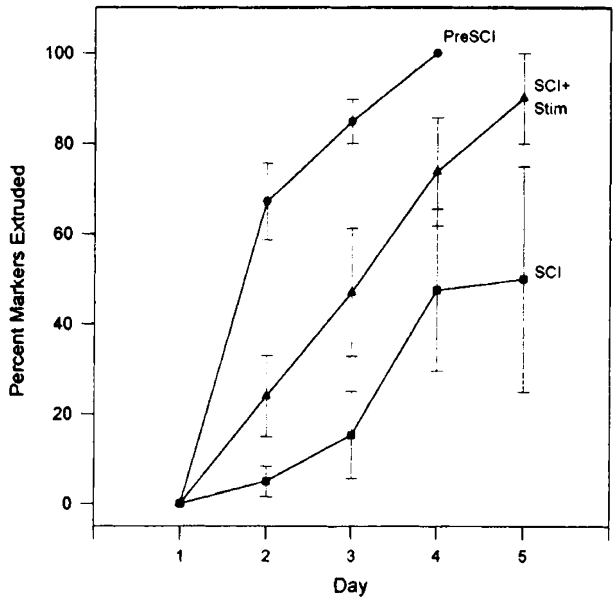

Figure 1 Graphic representation of the percentage of the markers over time. Video fluoroscopy was used to determine the percentage of markers extruded from non-SCI animals without stimulation (PreSCI); T4 SCI animals without stimulation (SCI); and T4 SCI animals receiving daily stimulation (SCI + Stim). The stimulation protocols were optimized for each animal but remained consistent throughout the 5 day trial. Day one corresponds to the day the markers were inserted. Colonic transit following SCI (SCI) was significantly prolonged ($P<0.05$) when compared to the transit before SCI (PreSCI). Colonic transit after SCI with electrical stimulation (SCI + Stim) improved colonic transit to values not significantly different from those before SCI. The data are displayed as mean ± SE

transit time to values not significantly different from those before SCI. For all animals, the stimulation protocol found most effective consisted of a frequency of 40 pps and a pulse width of 1 ms. The stimulation current was optimized for each animal with the most effective current typically between 25–35 mA with a range of 5–50 mA. In all five animals, the electrode pair which was most effective at promoting defecation was located semi-circularly 10 cm proximal to the anus.

Figure 2 demonstrates representative spontaneous colonic phasic motor activity before and after SCI. The phasic activity appears similar in amplitude, frequency and duration before and after SCI. Two types of colonic contractions were identified — short duration, high frequency and long duration, low frequency. The short duration contractions lasted approximately 25 s (range 20–30 sec) with a frequency of approximately one contraction every 35 s. The long duration contractions were defined as having typical durations of 50 s (range 40–60 s) with a frequency of approximately one contraction every 15 min. The amplitudes for both types of contraction were approximately 25 cm H_2O (range 15–35 cm H_2O). No significant differences were seen in either type of contraction before SCI, after SCI and after SCI with stimulation. A representative defecation pattern recorded before SCI without stimulation (Figure 3A) was similar to that recorded after SCI with stimulation (Figure 3B). The time scales for Figure 3A and B are different due to increased length of recording necessary for spontaneous defecation compared to stimulated defecation. During defecation, increases in abdominal pressures, as recorded by increases in urinary bladder pressure, were observed both before and after SCI.

Both spontaneous and stimulation induced contractions were scored using the criterion based scale described above. A total of 380 spontaneous events were scored: 38% were colonic contractions, 26% were bladder contractions, 26% were abdominal contractions, 3% were abdominal and colonic contractions, 4% were abdominal and bladder contractions, and 3% were undetermined. In response to 124 scored stimulations, 3% induced colonic contractions, 9% induced bladder contractions, 38% induced abdominal contractions, 4% induced abdominal and colonic contractions, 33% induced abdominal and bladder contractions and 13% of the responses were undetermined.

Discussion

Prolonged colonic transit following SCI has been demonstrated in several human studies, however the region of colon involved is uncertain. Delayed transit has been found in the rectosigmoid colon[16] and in both the left colon and rectosigmoid colon.[17] Another study found prolonged transit in the left colon and rectum but also a minor degree of transit delay at the level of the right colon,[18] while prolonged colonic transit involving the entire colon was also demonstrated.[19] The delay in transit following SCI seems to involve the left colon and rectosigmoid colon with some evidence for involvement of the right colon as well. Though the present study did not address regional colonic transit, the total colonic transit in this animal model assessed with radiopaque markers was significantly delayed following SCI when compared to values obtained before SCI. Direct electrical stimulation of the colon resulted in improved colonic transit to values that were not significantly different from baseline. The electrical stimulation could potentially improve colonic motility or effectively increase intra-abdominal pressure both of which could aid in defecation and in improved colonic transit. Though the mechanism of this improved transit remains unclear, these results suggest that direct electrical stimulation could possibly provide a benefit in SCI defecation.

The electrical stimulation parameters which reproducibly induced defecation and improved colonic transit involved the electrodes located 10 cm proximal

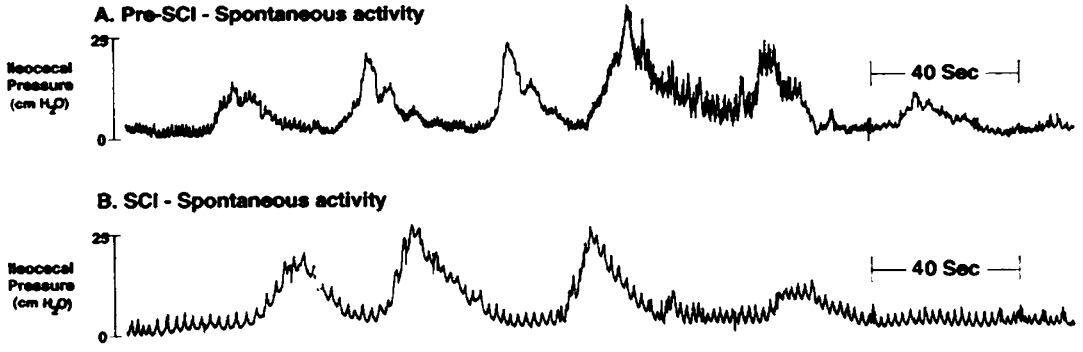

Figure 2 Representative colonic phasic motor activity from (**A**) pre-SCI animal and (**B**) T4 SCI animal which demonstrates a similar amplitude and frequency of baseline phasic motor activity

to the anus oriented in a semicircular fashion with stimulation parameters of 1.0 ms, 40 pps and 5–50 mA. The region of colon that was electrically stimulated appears to play a role as the electrodes 10 cm proximal to the anus resulted in defecation whereas the electrodes 25 cm proximal to the anus were unsuccessful. The orientation of these electrodes also appeared to be important as the semicircular electrodes were more effective than the longitudinal electrodes. The frequency and pulse duration parameters tested in this study were obtained from previous work[13–15] and the maximum current used was limited by the electrode configuration.

The mechanism of improved colonic transit with the use of electrical stimulation is uncertain but a resultant change in colonic motility or in intra-abdominal pressure would be a logical thought. The colonic phasic motor activity before and after SCI appears similar in amplitude, frequency, and duration. Similar findings are observed when comparing the representative defecation patterns before SCI without stimulation and after SCI with stimulation as well as the frequency of long-duration contractions before SCI and after SCI and after SCI with stimulation. These findings suggest the frequency, amplitude and duration of both types of colonic contractions are unaffected by SCI.

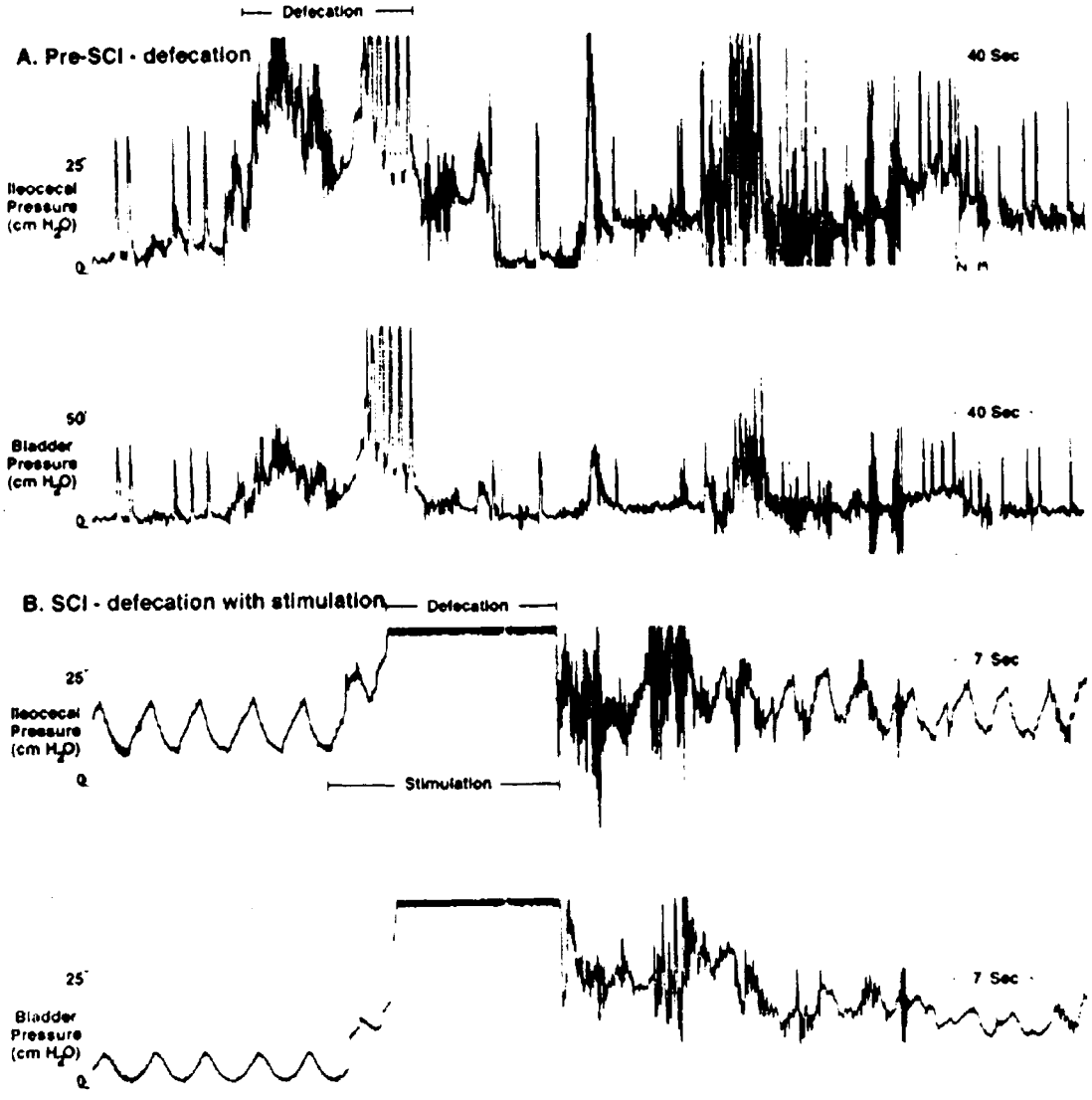

Figure 3 (**A**) Ileocecal and bladder pressure changes recorded during spontaneous defecation in a non-SCI cat without stimulation. The time scale is 40 s. (**B**) Ileocecal and bladder pressure changes recorded during stimulation induced defecation in an SCI cat using semi-circular electrodes located 10 cm proximal to the anus. Stimulation was at 35 mA, 40 pps, 1 ms for a total stimulation time of 60 s. The time scale is 7 s

Prior human studies also did not universally demonstrate abnormal colonic motor activity in SCI. For example, resting colonic motor activity in patients with SCI was evaluated by Connell *et al*[20] and the motor activity was reduced in patients with spinal cord transection above T9; while it was found to be increased in patients with transections at T9 or below. The baseline motor activity and myoelectrical activity of nine patients with thoracic SCI was similar to the colonic activity found in asymptomatic volunteers.[21] Another study found the resting myoelectrical activity of the colon in SCI patients to be significantly greater than that of control patients.[22] Our present finding of prolonged colonic transit and unchanged colonic motor activity in SCI cats is compatible with previous human studies and would suggest the baseline colonic motor activity of SCI patients is at least similar to control patients if not increased. Though the amplitude and frequency of contractions appear unchanged the coordination of colonic contractions following SCI remains unknown. The uncoordinated colonic contractions of normal frequency and amplitude may ultimately prove to be the colonic motor abnormality in SCI resulting in constipation.

Another possibility of the improved colonic transit after electrical stimulation could involve intra-abdominal pressure. Figure 3 demonstrates manometric defecation patterns with similar increases in intracolonic pressure and in intra-abdominal pressure as measured by increases in urinary bladder pressure when comparing spontaneous defecation before SCI to defecation induced with electrical stimulation after SCI. This observation would suggest that intra-abdominal pressure may play an important role in normal defecation and ineffective attempts to increase this pressure may contribute to the delayed transit and constipation seen following SCI. Further supporting this possibility is the increased intra-abdominal pressure with stimulation as reflected in the criterion based scale. The most frequent response following stimulation was an abdominal contraction (with equal increases in colon and in bladder pressure or increases in colon pressure with even greater increases in bladder pressure) occurring in 38% of the contractions.

The results of this study are promising but other considerations should be addressed. This project was a pilot study evaluating the effect of electrical stimulation on colonic transit of five SCI cats. The number of animals is small and larger numbers are needed to further evaluate these results. The SCI in this model was acute with 7–14 days of recovery before transit studies were initiated. Certainly the duration of SCI could be an important variable as injuries of longer duration could yield different results. Also, the electrical stimulation was performed following the baseline SCI transit studies. The effect of stimulation immediately after SCI was not studied and again could result in differences not seen in this study. Variability was seen in the electrical stimulation parameters used and in the defecatory responses to the stimulation. The variability in the stimulation parameters was seen in the range of current used and may have been due to differences in electrode placement (both location and depth) or electrode wire breakage. These electrode placement and breakage issues could also have resulted in stimulation differences between longitudinally and semi-circularly oriented electrodes. The defacation responses to stimulation also varied during the study. The differences in the amount of stool produced and its consistency may have been due to the lack of stool in the distal colon at the time of stimulation or ineffectiveness of the stimulation. A standardized method of defecation such as a water-filled balloon in the distal colon or manual palpation of the abdomen would be helpful to assess the functional effectiveness of the electrical stimulation. Despite these considerations, the results of this study were encouraging and warrant additional studies to further assess the colonic motor activity and transit following SCI.

Future studies are needed to assess phasic motor activity and colonic tone after SCI as this physiology may provide valuable insights into colonic transit and defecation in SCI. Another important variable which needs further investigation is the effect of different levels of SCI on colonic transit, colonic motor activity and defecation as well as further defining the role of intra-abdominal pressure in SCI defecation. This data will be useful in assessing the full impact of direct electrical stimulation of the colon following SCI. Because the mechanism of constipation following SCI has not been fully defined, the best treatment options also remain uncertain but electrical stimulation does provide a possible alternative to present therapies. In conclusion, this study has demonstrated that colonic transit is prolonged following SCI and that direct electrical stimulation of the colon following SCI improves colonic transit in an animal model. These findings support further evaluation of electrical stimulation as a potential treatment option for constipation in patients with SCI.

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