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Lower Thoracic Spinal Cord Stimulation to Restore Cough in Patients with Spinal Cord Injury: Results of a National Institutes of Health-Sponsored Clinical Trial. Part II: Clinical Outcomes

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Abstract

Objective—To evaluate the clinical effects of spinal cord stimulation (SCS) to restore cough in subjects with cervical spinal cord injury.

Design—Clinical trial assessing the clinical outcomes and side effects associated with the cough system.

Setting—Out-patient hospital or residence

Participants—Subjects (N = 9; 8 men, 1 woman) with cervical spinal cord injury

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Abstracts/Presentations:

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Clinical Trial Registration Number: NCT00116337

Intervention(s)—SCS was performed at home by either the subjects themselves or caregivers on a chronic basis and as needed for secretion management.

Main Outcome Measure(s)—Ease in raising secretions, requirement for trained caregiver support related to secretion management and incidence of acute respiratory tract infections.

Results—The degree of difficulty in raising secretions improved markedly, and the need for alternative methods of secretion removal was virtually eliminated. Subject life quality related to respiratory care improved with subjects reporting greater control of breathing problems and enhanced mobility. The incidence of acute respiratory tract infections fell from 2.0 ± 0.5 to 0.7 ± 0.4 events/subject year ($p < 0.01$), and mean level of trained caregiver support related to secretion management measured over a 2 week period decreased from 16.9 ± 7.9 to 2.1 ± 1.6 and 0.4 ± 0.3 times/week ($p < 0.01$) at 28 and 40 weeks following implantation of the device, respectively. Three subjects developed mild hemodynamic effects which abated completely with continued SCS. Subjects experienced mild leg jerks during SCS, which were well tolerated. There were no instances of bowel or bladder leakage.

Conclusion(s)—Restoration of cough via SCS is safe and efficacious. This method improves life quality and has the potential to reduce the morbidity and mortality associated with recurrent respiratory tract infections in this patient population.

Keywords

Electric Stimulation; Quadriplegia; Cough; Respiratory Muscles; Spinal Cord Injuries

Introduction

Paralysis of the expiratory intercostal and abdominal muscles in cervical and high thoracic spinal cord injury (SCI) results in impaired ability to effectively clear airway secretions. In a companion paper, we demonstrated that lower thoracic spinal cord stimulation (SCS) results in near maximal expiratory muscle activation and the generation of high peak flow rates and airway pressures characteristic of a normal cough in patients with SCI. The stimulus parameters necessary to achieve optimal expiratory muscle activation were also presented. In this paper, we report the clinical effectiveness of this technique as assessed by the impact of cough restoration on severity and frequency of conventional methods of secretion clearance, difficulty in raising sputum, life quality, need for caregiver support and occurrence of acute respiratory tract infections. Side effects and complications observed during this clinical trial are also described.

Methods

This investigation was approved by the Institutional Review Board, the National Institute of Neurological Disorders and Stroke and the Food and Drug Administration. Informed consent was obtained from each subject before enrollment in the study. All 9 subjects suffered from some form of traumatic injury to their cervical spinal cord. Each had significant paresis of their expiratory muscles and had difficulty mobilizing secretions and therefore underwent implantation of the SCS cough system (see companion paper for further details).

Approximately 3 weeks following implantation of the SCS system, all subjects returned to the hospital for the initial application of electrical stimulation on an out-patient basis. At this time, cardiac rate and rhythm, oxygen saturation and blood pressure were monitored. The effects of stimulation of each electrode lead alone and in combinations were assessed. Since combined use of 3 leads did not result in greater pressure generation than 2 leads, subjects were instructed

to apply chronic stimulation with a 2 lead combination. Four of the 9 subjects were able to trigger the system themselves with either upper extremity motion or mouth stick.

While lower thoracic SCS results in large airway pressures and high peak flow rates, optimal secretion or foreign body removal requires coordination of expiratory muscle contraction with other phases of the cough reflex (1,2). Subjects were trained, therefore, to relax, inspire, and then close their glottis (hold their breath) just prior to expiratory muscle activation and, in turn, within 1 sec after the stimulus is applied, to open their glottis.

All subjects were instructed to use the cough system every 15–30 sec for 10–15 min, 2–3 times/day on a chronic basis, as tolerated and also as needed for secretion management. This protocol was devised to maintain the strength of the expiratory muscles and prevent atrophy and also to provide prophylactic airway clearance. Based upon previous work (3–7), it has been determined that short periods of high intensity stimulation results in the greatest muscle bulk and force generating capacity. Consequently, near supramaximal stimulus amplitude (20–40V) and frequency levels (30–50Hz) (lowest effective stimulus amplitude and frequency resulting in near maximal increases in airway pressure) were prescribed for chronic use, as tolerated. Cough intensity increases with the depth of the prior inhalation (8). When used to train the expiratory muscles, therefore, subjects were instructed to maximally fill their lungs with air, i.e. inspire to total lung capacity (TLC). When used intermittently for secretion clearance, the depth of inspiration was at the subject's discretion.

In addition to the wide range of stimulus output parameters, the Finetech stimulator¹ allows for 9 different settings of stimulus paradigms. For example, different channels could be set for different strengths of cough intensity or duration of stimulation. In addition, stimulation could be applied every 2 or more seconds for a series of cough efforts. Duration of stimulation generally ranged between 0.4 and 0.6 sec. When used for airway clearance management, the selection of the specific stimulus paradigm was determined by subject preference.

At the time of study enrollment and at 28 and 40 weeks following implantation of the cough system, assessments were made concerning each subject's respiratory care needs and history including specific information related to secretion management and their impact on the subject's life quality. This was performed utilizing questionnaires related to cough and secretion removal.

A suctioning / assisted cough and sputum index was constructed (Figure 1) to characterize the severity of episodes requiring secretion removal and need for bronchodilator medications. Since a more effective cough mechanism may reduce stress, increase time for social activities, allow pursuit of outside interests and improve sense of well-being for the subject, life quality assessments were also performed. There are no gold standard quality of life assessments in the field of spinal cord injury (9–13), however, and no general consensus concerning optimal measuring instruments (13,14). Moreover, there are no instruments which relate specifically to secretion management. Therefore, a life quality assessment which queries issues specifically related to breathing, cough and suctioning was developed in attempt to more accurately reflect the potential impact of an improved cough mechanism (Figure 2).

Since these questionnaires may have been biased toward pre-conceived potential effects of the cough implant, each subject was also asked the following open ended question: "What was the most significant effect of the cough implant on your life?"

Suppliers

1. Finetech Medical Ltd., Welwyn Garden City, Hertfordshire, UK

The incidence of acute respiratory tract infections, defined by a change in the character, color or amount of respiratory secretions and requiring antibiotic administration, was tracked over the 2 year period prior to implantation of the cough system. The occurrence of respiratory tract infections was determined by subject history and corroborated by review of medical records, when available. Following implantation of the cough system, the incidence of acute respiratory tract infections was tracked continually.

The degree of caregiver support was determined by the number of times it was necessary for a caregiver to provide the subject with an assistive means of secretion clearance, such as suctioning, manually assisted cough or in-exsufflator use. This was determined prospectively over the 2 week period prior to implantation of the cough system and re-evaluated over a 2 week period following implantation of the cough system at the 28 and 40 week time points.

The data prior to implantation were compared to data obtained following implantation of the cough system using a non-parametric analogue (Freidman Test) to the standard repeated measures ANOVA. Statistical significance was assumed at $p < 0.01$. This alpha level was chosen as a correlation for inflated type I error rates due to multiple comparisons. Results are reported as mean $\pm$ SE.

Results

Questionnaire Responses

The mean results of the suctioning / assisted cough and sputum index are provided in Figure 1. With the exception of the need for aerosolized bronchodilator therapy (question #4), which was rare in this patient group, there was significant improvement in each of the assessed parameters at 28 weeks and maintained at 40 weeks following implantation of the cough system. The degree of difficulty in raising secretions (question #3) was reduced from between moderate and marked, to between mild and no difficulty ($p < 0.01$). This response was corroborated by the response to question #5 revealing moderate (week #28) to marked (week #40) improvement in the ease of raising secretions with use of the cough system ($p < 0.01$). The need for suctioning or some form of assisted cough (question #1) decreased from occasional (3–5 times/day) to between none and rare ($p < 0.01$) while the severity of cough episodes decreased from moderate (had to stop activity for secretion removal) to between mild (did not interfere with daily activity) and unaware of need ($p < 0.01$).

Concerning subject life quality (Figure 2), there were significant improvements in that their overall physical condition or medical treatment had less interference with family life (question #1), need for cough interfered less with daily activities (question #3), there was less requirement for suctioning or some form of assisted cough (question #4), less embarrassment by coughing or respiratory problem (question #7) and greater control of their breathing problems (question #8) at week #28, $p < 0.01$ for each and maintained at week #40 ($p < 0.01$ for each). There were also significant reductions in subjects' perceptions of financial difficulties (question #2) and level of stress related to need for coughing assistance (question #6) ($p < 0.01$ for each). The improvements in overall health (question #9) and overall life quality (question #10) were not significantly different than baseline values. Two of the four subjects with tracheostomy tubes at the time of study entrance were able to be decannulated.

The mean level of trained caregiver support related to secretion management measured over a period of 2 weeks decreased from 16.9 ± 7.9 times/week to 2.1 ± 1.6 and 0.4 ± 0.3 times/week at 28 weeks and 40 weeks following implantation of the device, respectively ($p < 0.01$ for each compared to Initial). Moreover, during the mean 20.0 ± 3.7 months of follow-up following implantation of the cough system, the incidence of acute respiratory tract infections significantly fell from 2.0 ± 0.5 events/ subject year to 0.7 ± 0.4 events/ subject year ($p < 0.01$).

The response to the question concerning the most significant effect of the cough system demonstrated an additional benefit in that 5 of the 9 subjects reported an improvement in mobility since they could now travel without their caregivers (Table 1). In fact, since 4 of the subjects were able to trigger the device themselves, they did not require any assistance with secretion removal. Four of the remaining subjects also developed greater independence since the cough system could be triggered by non-trained individuals and therefore did not require the presence of their usual caregivers. Subject #1 reported that he felt “more comfortable traveling alone,” and Subject #9 commented, “It tremendously increased my independence.”

Side Effects

Hemodynamic Effects—Three subjects developed increases in blood pressure and decreases in pulse rate in association with the initial application of SCS. In these subjects, mean initial systolic blood pressure was 107.3 ± 6.7 mmHg and increased to 160.3 ± 9.9 mmHg ($p < 0.05$). Mean initial diastolic blood pressure was 67.3 ± 3.5 mmHg and increased to 84.0 ± 4.7 mmHg ($p < 0.05$) following SCS. Mean heart rate decreased from 78.0 ± 12.8 to 63.3 ± 11.4 beats/min (NS). These changes were not associated with any symptoms; specifically, no subjects complained of headaches, flushing or sweating. In these subjects, SCS was not repeated until blood pressure and pulse rate returned to near baseline values. These changes resolved within a mean 7.1 ± 0.4 min following cessation of stimulation. When the time course of recovery was determined, SCS was then applied at intervals sufficient to allow resolution of hemodynamic effects. With the application of chronic daily stimulation, these changes gradually diminished such that SCS was not associated with any hemodynamic effects within several weeks despite the frequent application of SCS. In the remaining 6 subjects, SCS was never associated with any hemodynamic change.

Back and Leg Muscle Contraction—SCS resulted in some contraction of the thigh muscles during supramaximal stimulation, best characterized as leg jerks. This occurred in each subject during stimulation at the L1 site. This motion was significantly reduced or eliminated by reducing stimulus amplitude. Stimulation at the T11 level resulted in mild or no visible leg jerks. There was no apparent leg movement with T9 stimulation. In all instances, leg movement was well tolerated and did not result in any physical discomfort. Some straightening of the back, attributable to paraspinal muscle contraction, was also observed in some subjects. This motion was bothersome in only one subject but lessened significantly by reductions in stimulus amplitude.

Importantly, there were no instances of bowel or bladder leakage. It should be noted that 8 of the 9 subjects had an in-dwelling bladder catheter. While not measured quantitatively, there were no subjective increases in urine flow in any of the subjects.

Complications

Implant failures—Of the 27 leads implanted, 2 leads were not functional, one lead in each of 2 subjects. Each of these leads was functional when tested intra-operatively. However, they were non-functional during the initial application of SCS post-operatively. The cause of these lead failures is not certain but may relate to wire breakage during the final stages of the surgical procedure or receiver failure. Since optimal stimulation could be achieved with stimulation at 2 sites, lead failure did not significantly affect airway pressure generation nor cough effectiveness.

Infection—There were no post-operative infections. However, one subject developed skin breakdown within several cm of the implanted receiver 22 months following surgical implantation. This led to the development of infection at the receiver site necessitating its surgical removal. The implanted leads and connecting wires were left in place. Since this

subject derived significant clinical benefit from the cough system, he was very eager to have the receiver replaced.

Discussion

This study represents the first demonstration of restoration of an effective cough system providing significant long-term clinical benefit in patients with spinal cord injury. Consistent with the supposition that the increased risk of respiratory infection is secondary to expiratory muscle paralysis and resultant loss of an effective cough mechanism, the results of this investigation indicate that the occurrence of respiratory infections can be significantly reduced by restoration of an effective cough via electrical activation of the expiratory muscles. This is a critically important finding as respiratory tract infections remain a major cause of morbidity and mortality in subjects with SCI (15–26). This technique therefore has the potential to reduce the need for hospitalization, use of antibiotics and other therapeutic modalities, and associated discomfort, inconvenience and cost. Moreover, the use of SCS may positively impact survival in selected patients with SCI. As an additional benefit, the battery life of the cough system will allow for effective secretion clearance without the need for electrically dependent suction equipment in the event of a natural disaster and loss of power. It is likely that patients with any spinal cord level injury resulting in significant paresis of their expiratory muscles and difficulty managing secretions may benefit from this technique.

Use of the cough system also significantly reduced and, in some cases, eliminated the need for caregiver assistance for secretion management and the need for other methods of secretion removal. These benefits contributed to increases in the degree of subject mobility and also have the potential to significantly reduce health care costs. Other benefits included significant reductions in the immediate need to expel secretions, reductions in the difficulty of raising secretions and marked improvement in the ease with which secretions could be expelled. In terms of life quality, implementation of the cough system reduced the interference of airway clearance management with daily activities and family life, reduced embarrassment and level of stress associated with coughing assistance and allowed for greater overall control of respiratory issues.

Side Effects

The use of SCS to restore cough was associated with some side effects, including increases in blood pressure and reductions in heart rate, suggesting autonomic dysreflexia (27). This effect was limited to the early phase of the conditioning program, occurred in only 3 of our subject and was not associated with any symptoms. It is well known that autonomic stimulation precipitated by peripheral stimuli such as bladder distention, urinary tract infection and other forms of functional electrical stimulation can result in classic autonomic dysfunction associated with marked increases in blood pressure, reductions in heart rate and symptoms of headache, flushing and sweating (27). Our approach to reducing the frequency of application of stimulation and allowing return of these cardiovascular variables to near baseline levels ultimately resulted in accommodation to the stimulus such that over the ensuing weeks, this response was no longer observed. During the early application of the technique, therefore, it is important that these parameters be monitored to determine the appropriate safe interval of SCS.

Other side effects were mild straightening of the back and leg jerking. This was not an unexpected finding since lower thoracic SCS results in a non-specific stimulus to the lower thoracic and lumbar roots innervating the muscles of the lower extremity and paraspinal muscles (28). Not surprisingly, leg jerks were most pronounced with stimulation of the L1 lead. Even with the application of supramaximal stimulus parameters, however, none of the subjects experienced any pain or discomfort. This side effect was significantly reduced or

eliminated, however, by reducing stimulus amplitude and/or limiting stimulation to the T9 and T11 levels, which resulted in similar levels of airway pressure generation.

Methodological Concerns

It is important to note that the assessment performed in the present study does not represent a true quality of life (QOL) evaluation. Unfortunately, most previous assessments of health-related QOL are limited since they are not specific to patients with SCI. While such tests are under development (13), the effects of lack of an effective cough mechanism have not been specifically addressed. Consequently, there are no valid and reliable QOL testing instruments to assess this parameter. Nonetheless, the questionnaires developed for this pilot study provide a reasonable estimate of the clinical impact of restoration of an effective cough in subjects with SCI.

While the results of this study demonstrate significant reductions in the incidence of respiratory tract infection and caregiver support, we cannot exclude the possibility of selection bias in terms of subject recruitment. It is possible, for example, that patients with the greatest difficulty with secretion management and more frequent infections more actively sought study participation. Nonetheless, each of these subjects, without exception, derived significant clinical benefits with use of the cough system. It is worth noting that two of our subjects who required very infrequent assistance with secretion management prior to the application of SCS, became aware of much greater ease in clearing their throats and felt that their chests were more clear. In addition, most subjects used the device to prevent choking while eating or drinking. Some subjects also used SCS to blow their noses. This suggests that even patients without the need for frequent use of methods to expel secretions can also derive significant benefit.

While study enrollment was open to both high thoracic and cervical spinal cord injured patients, all study participants had cervical spinal cord injuries. This may be reflective of the fact that patients with cervical spinal cord injuries have virtually no expiratory muscle function and therefore would have a greater need for cough restoration (29,30). Patients with thoracic spinal cord injuries, in contrast, are more likely to have some residual expiratory muscle function and, therefore, a more effective cough.

Comparison to other Methods of Secretion Removal

Other methods of secretion management include gravity, active suctioning with a catheter connected to a suction device, manually assisted coughing whereby external force is applied to the abdominal wall (31,32), and use of a mechanical insufflation-exsufflation device that applies a large positive pressure followed by a large negative pressure to the airway (33–35). While somewhat effective, each of these methods has significant limitations. These techniques are labor intensive, require the presence of trained personnel, specialized equipment and provider-patient coordination and are generally uncomfortable.

Despite the clinical benefits of SCS described in the present study, however, it is not certain that this technique is necessarily more effective than other methods of secretion management, such as the insufflator-exsufflator device (33–35). Nonetheless, this latter device is bulky, requires an external power source and trained caregivers, all of which significantly limit mobility. Moreover, restoration of the missing component of a normal cough reflex by electrical stimulation techniques is more physiologic and therefore likely to be a more efficacious method.

In summary, SCS is an effective method of airway clearance management resulting in a positive clinical impact in patients with SCI. This technique results in significant reductions in the incidence of acute respiratory tract infections and need for caregiver support and improves life

quality related to secretion management. Moreover, application of this technique is relatively safe, being associated with only few side effects. Further study will be necessary to confirm efficacy and safety and evaluate methods to implant electrodes less invasively.

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List of Abbreviations

SCI	spinal cord injury
SCS	spinal cord stimulation
TLC	total lung capacity
QOL	quality of life

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Suctioning / Assisted Cough and Sputum Index

1. Suction / assisted cough frequency

How frequent were your needs for suctioning/assisted cough on a typical day during the past week?

- 0 - None – Unaware of need
- 1 - Rare – 1-2 times / day
- 2 - Occasional – 3-5 times / day
- 3 - Frequent – 6-12 times / day
- 4 - Almost Constant – > 12 times / day

2. Suction / assisted cough episodes: Severity

How severe were your suctioning/assisted cough episodes on a typical day during this past week?

- 0 - None – Unaware of need
- 1 - Mild – Did not interfere with usual daily activity
- 2 - Moderate – Must stop activity during need for suctioning
- 3 - Marked – Must stop activity for brief period (10 - 30 min) after need for suctioning
- 4 - Severe – Must stop activity for prolonged (> 30 min) period after need for suctioning, may be accompanied by dizziness, headache and/or pain in upper chest

3. Difficulty in raising sputum?

- 0 - None – No sputum
- 1 - Mild – Rarely have difficulty
- 2 - Moderate – Occasional difficulty
- 3 - Marked – Frequent difficulty
- 4 - Severe – Usually have great difficulty

4. Need for aerosol bronchodilator on a typical day during the past week?

- 0 - Never – Not needed
- 1 - Rarely – 1-2 times / day
- 2 - Occasionally – 3-4 times / day
- 3 - Frequently – 5-6 times / day
- 4 - Very frequently – > 6 times / day

5. Ease in raising sputum

Indicate any changes in the ease with which you raise sputum on typical day over the past week using SCS as compared to previous methods.

- 3 - Marked Improvement
- 2 - Moderate Improvement
- 1 - Slight Improvement
- 0 - No change
- 1 - Slightly Worse
- 2 - Moderately Worse
- 3 - Markedly Worse

* p < 0.01 compared to Initial

Figure 1.

Subject responses to frequency of need for conventional means of secretion clearance, severity of cough episodes, difficulty in raising secretions, need for aerosol bronchodilator medications and ease in raising sputum. With the exception of need for bronchodilator medication, there were significant improvements in all other parameters of secretion management at week #28. This improvement was maintained at week #40.

Life Quality Assessment

Figure 2.

Subject responses to life quality assessment related to secretion management. There was significant improvement in most parameters at week #28 and week #40 ($p < 0.01$). Improvements in overall health and life quality, however, were not statistically significant.

Figure 3.

There were significant reductions in the need for caregiver support (upper panel) and significant reductions in the incidence of acute respiratory tract infections (lower panel) following use of the cough system. See text for further explanation.

Table 1**Most Significant Effect of the Cough System**

Subject	Comments
1	I feel more comfortable traveling alone to go shopping or visit family since I don't have to have someone around to provide a cough assist.
2	I rarely need suctioning anymore.
3	I am able to quickly raise all my secretions. I can travel more easily since I don't need a machine for suctioning.
4	I always had difficulty clearing my throat and raising secretions. Now, they come up instantly.
5	I'm able to hack up secretions when I need to, without any difficulty.
6	This improved my mobility. I'm able to travel without my caregiver. I no longer need the CoughAssist device, which I was using 10 times/day.
7	I no longer need the CoughAssist device or suctioning. This method is more natural and effective.
8	I can travel more easily now. Before, I was always afraid to be away from someone who could provide a cough assist.
9	It tremendously increased my independence. I can travel alone now.