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Current Barriers and Ethical Considerations for Clinical Implementation of Epidural Stimulation for Functional Improvement after Spinal Cord Injury

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Abstract:	Context/Objective: To determine current barriers for clinical implementation of epidural stimulation for functional improvement after spinal cord injury and highlight applicable ethical constructs to approach future research. Design: Survey of spinal cord injury medicine physicians, January 2019. Setting: Spinal cord injury model systems hospital sites across the United States. Participants: Spinal cord injury medicine physicians Interventions: NA Outcome Measures: Physician-identified current barriers to clinical implementation of epidural stimulation. Results: The response rate for the survey was 54.6% (n=42), with the majority of physicians (61.9%) having been asked by patients with spinal cord injuries about epidural stimulation. Numerous current barriers to clinical implementation were identified, including need for additional efficacy studies (92.9%), lack of clear guidelines on stimulation parameters (83.3%), and inability to identify which patients will benefit (76.2%). Conclusions: With multiple barriers to clinical implementation currently identified, evaluating this research with an eye toward the ethical construct of equipoise is increasingly relevant. Addressing these barriers may require modifications in both physician expectations and how researchers approach this work.

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Context/Objective: To determine current barriers for clinical implementation of epidural stimulation for functional improvement after spinal cord injury and highlight applicable ethical constructs to approach future research.

Design: Survey of spinal cord injury medicine physicians, January 2019.

Setting: Spinal cord injury model systems hospital sites across the United States.

Participants: Spinal cord injury medicine physicians

Interventions: NA

Outcome Measures: Physician-identified current barriers to clinical implementation of epidural stimulation.

Results: The response rate for the survey was 54.6% (n=42), with the majority of physicians (61.9%) having been asked by patients with spinal cord injuries about epidural stimulation. Numerous current barriers to clinical implementation were identified, including need for additional efficacy studies (92.9%), lack of clear guidelines on stimulation parameters (83.3%), and inability to identify which patients will benefit (76.2%).

Conclusions: With multiple barriers to clinical implementation currently identified, evaluating this research with an eye toward the ethical construct of equipoise is increasingly relevant. Addressing these barriers may require modifications in both physician expectations and how researchers approach this work.

Introduction:

Implanted epidural stimulators have been tested for functional improvement after spinal cord injury (SCI) in only a handful of small trials over the past 10 years. While their numbers are limited, studies demonstrate early evidence for a surprising breadth of dramatic functional improvements following chronic SCI. In recent reports, patients with long-standing, clinically complete motor paralysis underwent implantation with epidural stimulators and subsequently demonstrated restored volitional standing and walking.[1] Similar studies have replicated this improved motor function below the level of the spinal lesion,[2-6] while others have provided early evidence for epidural stimulation's role in restoration of neurogenic bladder function[7] and orthostatic hypotension control.[8,9]

As opposed to other potential treatments for functional restoration after SCI, such as novel medications[10] or stem cells[11], implanted epidural stimulators are unique in that they have been FDA-approved for chronic pain for the past 30 years. This history provides significant safety data, with serious adverse events such as spinal epidural hematomas occurring in less than 0.2% of cases.[12] Combined with the potential for functional improvement, this raises the issue of when these stimulators will be appropriate for wider clinical adoption for this purpose. While efficacy must be proven, optimal timing centers on when an adequate threshold for evidence is met. Given the non-benign nature of surgical implantation and lack of randomized controlled trials demonstrating efficacy, it is reasonable to exercise caution. However, an overly cautious position could prevent patients from obtaining a potentially beneficial therapy. When considering this balance, the ethical construct of equipoise is helpful. Equipoise exists when there is genuine uncertainty in the medical community concerning whether the intervention being tested is better than the standard of care.[13]

As physician engagement will be key in clinical implementation of this technology, the goal of this study was to survey physicians' views of epidural stimulation for functional improvement after SCI. Specifically, we aimed to identify current barriers towards clinical implementation with hopes of spurring discussion of how epidural stimulation technology can be utilized in a responsible manner.

Methods

To investigate physician-perceived potential barriers to the clinical use of epidural stimulation for functional improvement after SCI, a brief, unique survey was developed (Supplemental Figure 1). Initial pilot testing was completed with SCI medicine physicians prior to wider dissemination, and institutional review board approval was attained from [redacted] IRB. Physicians who identified as SCI medicine trained and were associated with one of the United States Spinal Cord Injury Model Systems hospitals (a research and clinical designation of excellence) were sent the survey in January 2019 via email through a secure online platform (REDCap). Physicians who did not initially respond were sent a single follow-up email after one week. Descriptive statistics were utilized to identify and report frequencies of each response.

Results

Eighty-one surveys were sent to SCI medicine physicians, four of which were returned due to inactive email addresses. Responses were received from 42 physicians (response rate of 54.6%).

Of respondents, 61.9% of physicians had been asked by a patient about having an epidural stimulator implanted for functional improvement (a median of five patients per physician). Physicians noted that their patients may have obtained information regarding epidural stimulation from a variety of sources including 84.6% from news media stories, 76.9% from internet searches, 50% from family/friends/peers with SCI, and 3.9% from other sources. 7.7% of respondents indicated that they were unsure where the patient received their information or did not ask.

<<Figure 1 about here>>

The majority of physicians felt that epidural stimulator implants were somewhat or quite safe for individuals with SCI (Figure 1). Notably, 31.7% of respondents indicated that they were unsure or that it

depended on the individual patient. Physicians identified multiple current barriers to wider clinical implementation of epidural stimulators for patients with SCI from a list of pre-populated options (Table 1), including need for further studies showing efficacy and greater knowledge of stimulation parameters.

<<Table 1 about here>>

When proposed a future scenario where epidural stimulators are clinically available for functional improvement after SCI, 95.2% of respondents felt that the stimulator parameters (frequency, amplitude of stimulation, location of active electrodes on the array, etc.) should be controlled by physicians trained in their use, similar to intrathecal baclofen pumps. 42.9% of respondents felt that these parameters ought to be controlled by patients, within limits preprogrammed into the device based on the targeted function to be restored (i.e., only able to activate an electrode array that has been shown to work for motor function restoration if that is the intended treatment goal). 38.1% of respondents felt that patients should be given control of all stimulation parameters within preprogrammed safety limits and 21.4% noted that manufacturer device representatives should control these parameters.

Discussion

Most SCI physicians have been asked by their patients about epidural stimulators, noting that they believe that their patients' information tended to be from internet searches or the news media. As the media continues to cover epidural stimulation studies, it is anticipated that the number of patients asking about this will grow with time. Additionally, physicians perceive there to be multiple barriers to the clinical implementation of epidural stimulators, though there are no pre-existing concerns from the clinical community regarding safety. Given the experimental nature of these devices for this purpose, this caution is likely warranted. Greatest among the identified barriers were demonstration of further efficacy and clear guidelines on stimulation device parameters. From a clinical standpoint, identifying which patients will potentially benefit and establishing targeted therapy programs will be key towards advancing this

technology. Epidural stimulators have an established infrastructure for implantation and management, with device representatives performing the majority of the parameter adjustments. Given that this survey found only 21% of SCI medicine physicians felt these device representatives should control the stimulation parameters, new paradigms for adjustment and optimization of stimulation paradigms[6] could be appropriate.

Ethical Perspective

While all burgeoning medical treatments must ethically address potential issues in clinical implementation, epidural stimulation for functional improvement after SCI may challenge our classic structures. With growing evidence of efficacy and a standard of care riddled with high risks for urinary tract infections, pressure injuries, immobility, and cardiovascular disease[14], we may soon be at a tipping point for equipoise. An additional key general ethical concern with all new research is ensuring the intervention is safe and that the potential risks are accurately characterized, allowing patients to make informed decisions on if the benefits outweigh the associated risks. Preliminary data suggests impressive efficacy for these devices to couple with robust existing safety data for the alternative indication of chronic pain. Based on this, these devices may provide notable benefit for a significant number of patients with SCI.

Given the number of SCI patients asking their physicians about epidural stimulation from our survey, there is a clear potential interest/demand for this technology. Currently, supply is limited to research settings. However, a growing number of options for implantation at overseas, for-profit institutions looms to address this demand. Failure to balance the ongoing need for rigorous research with the needs of the community affected by SCI in a timely manner could drive individuals with SCI to seek options for implantation abroad and outside of traditional research studies- necessitating a recent warning from advocacy groups.[15]

Given these considerations, how might we tactfully move forward?

For SCI medicine physicians, we may need to rethink our traditional research standards to accommodate this unique technology. If these devices are safe and the question becomes, not *if* but *how* they will benefit our specific patients, we are not in proper equipoise. For this scenario of epidural stimulation, clinicians may need to compromise from perfect evidence to allow the most good for our patients. The alternative current standard of care promises ongoing, well-known medical complications, so the time may rapidly be approaching where thorough discussions with our patients on potential risks and benefits of these devices become common.

For SCI researchers expanding this exciting research, the clinical community asks for ongoing studies with greater numbers of subjects focused on efficacy as demonstrated by quantitative endpoints. Further addressing identified barriers from this survey should include more open dialogue on device parameter settings and post-implant therapy. These will maximize the potential clinical benefit when the research findings are implemented, ultimately benefitting the most patients.

Limitations

Survey questions erred on the side of brevity, leaving some interpretation to the respondent. This was done to minimize external bias, though may have left some respondents with suboptimal direction on the intention of a given question. This survey was aimed at assessing SCI physicians' views, and as such, responses on where patients may have obtained their epidural stimulation data may be less accurate than asking these individuals directly. As it was posited, the results reflect physician views of this issue.

Conclusions

Physicians currently identify multiple barriers to clinical implement of epidural stimulation for functional improvement after SCI. Addressing these barriers may require modifications in both physician expectations and how researchers approach their important work.

Acknowledgments

None

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Figure Legend

Figure 1: Response to question "How safe do you think epidural stimulation implants are in general for individuals with SCI?"

Tables

Additional research studies needed to show efficacy	92.9%
Lack of clear guidelines on stimulation parameters	83.3%
Lack of knowledge on which patients will benefit	76.2%
Targeted therapy protocols for post-op functional training	69.1%
Limited locations available to provide the surgery	69.1%
Monetary cost associated with the device	54.8%
Monetary cost associated with the surgical implantation	54.8%
Monetary cost associated with the device management	42.9%
Other*	14.3%

Table 1: Physician-perceived barriers to wider implementation of epidural stimulators for patients with SCI. * Themes of additional write in comments for those who selected "Other" included cost of post-implant therapy, potential disqualification from future studies with stronger evidence, and lack of transparent existing data/protocols.

Figure 1

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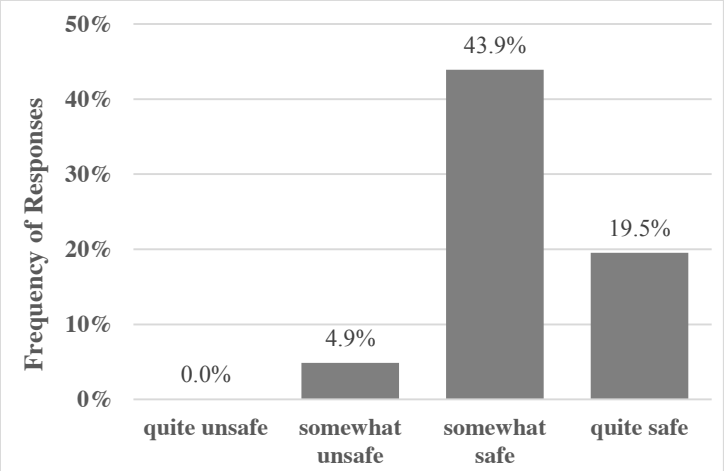

List and description of supplementary files [mandatory when a paper includes supplementary material]