Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial

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Summary

Background Spinal cord stimulation has been an established treatment for chronic back and leg pain for more than 50 years; however, outcomes are variable and unpredictable, and objective evidence of the mechanism of action is needed. A novel spinal cord stimulation system provides the first in vivo, real-time, continuous objective measure of spinal cord activation in response to therapy via recorded evoked compound action potentials (ECAPs) in patients during daily use. These ECAPs are also used to optimise programming and deliver closed-loop spinal cord stimulation by adjusting the stimulation current to maintain activation within patients' therapeutic window. We aimed to examine pain relief and the extent of spinal cord activation with ECAP-controlled closed-loop versus fixed-output, open-loop spinal cord stimulation for the treatment of chronic back and leg pain.

Methods This multicentre, double-blind, parallel-arm, randomised controlled trial was done at 13 specialist clinics, academic centres, and hospitals in the USA. Patients with chronic, intractable pain of the back and legs (Visual Analog Scale [VAS] pain score ≥60 mm; Oswestry Disability Index [ODI] score 41–80) who were refractory to conservative therapy, on stable pain medications, had no previous experience with spinal cord stimulation, and were appropriate candidates for a spinal cord stimulation trial were screened. Eligible patients were randomly assigned (1:1) to receive ECAP-controlled closed-loop spinal cord stimulation (investigational group) or fixed-output, open-loop spinal cord stimulation (control group). The randomisation sequence was computer generated with permuted blocks of size 4 and 6 and stratified by site. Patients, investigators, and site staff were masked to the treatment assignment. The primary outcome was the proportion of patients with a reduction of 50% or more in overall back and leg pain with no increase in pain medications. Non-inferiority (δ=10%) followed by superiority were tested in the intention-to-treat population at 3 months (primary analysis) and 12 months (additional prespecified analysis) after the permanent implant. This study is registered with ClinicalTrials.gov, NCT02924129, and is ongoing.

Findings Between Feb 21, 2017, and Feb 20, 2018, 134 patients were enrolled and randomly assigned (67 to each treatment group). The intention-to-treat analysis comprised 125 patients at 3 months (62 in the closed-loop group and 63 in the open-loop group) and 118 patients at 12 months (59 in the closed-loop group and 59 in the open-loop group). The primary outcome was achieved in a greater proportion of patients in the closed-loop group than in the open-loop group at 3 months (51 [82·3%] of 62 patients *vs* 38 [60·3%] of 63 patients; difference 21·9%, 95% CI 6·6–37·3; p=0·0052) and at 12 months (49 [83·1%] of 59 patients *vs* 36 [61·0%] of 59 patients; difference 22·0%, 6·3–37·7; p=0·0060). We observed no differences in safety profiles between the two groups. The most frequently reported study-related adverse events in both groups were lead migration (nine [7%] patients), implantable pulse generator pocket pain (five [4%]), and muscle spasm or cramp (three [2%]).

Interpretation ECAP-controlled closed-loop stimulation provided significantly greater and more clinically meaningful pain relief up to 12 months than open-loop spinal cord stimulation. Greater spinal cord activation seen in the closed-loop group suggests a mechanistic explanation for the superior results, which aligns with the putative mechanism of action for spinal cord stimulation and warrants further investigation.

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Introduction

Spinal cord stimulation for pain control was initiated after the landmark report of the gate control theory of pain by Melzack and Wall in 1965.[1] This report, coupled with advances in implantable pacemaker technology, enabled direct delivery of electrical current to the dorsal columns of the spinal cord as a novel approach to achieve pain relief. Although the closely allied field of cardiac electrophysiology rapidly advanced to include feedback regulation mechanisms within cardiac pacemakers that sense heart rate

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See Comment page 103

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Research in context

Evidence before this study

The two randomised controlled trials in patients with failed back surgery syndrome that established spinal cord stimulation as a safe and effective treatment option for chronic back and leg pain include the 2007 PROCESS study by Kumar and colleagues comparing spinal cord stimulation with conventional medical management and the 2005 study by North and colleagues comparing spinal cord stimulation with repeat lumbosacral spine surgery. These studies showed that, compared with other treatment options, spinal cord stimulation led to significant improvement in pain, defined as 50% or greater reduction in pain (responder rate) as per the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines. The general benchmark for effectiveness in spinal cord stimulation has been approximately 50% of patients with pain relief of 50% or more. Responder rates in these studies were approximately 50% for spinal cord stimulation compared with less than 20% for conventional medical management and reoperation at long-term follow-up. A 2014 systematic literature review and meta-analysis of spinal cord stimulation done by Taylor and colleagues found the mean level of pain relief with spinal cord stimulation, defined by a responder rate of 50% or more or another subjective cutoff (eg, "satisfactory", "good", or "excellent" pain relief), to be 58% for patients with chronic back and leg pain irrespective of previous back surgery.
We searched PubMed and Google Scholar for studies of at least 20 patients and with at least 3 months of follow-up with spinal cord stimulation of any type for chronic pain of the back and legs, or both, published between January, 2014, and February, 2019. Four randomised controlled trials reporting responder rates were identified. The range of responder rates in these studies was 13·6% to 76·5%. An initial prospective, multicentre, single-arm study of a new stimulation system based on ECAP-controlled closed-loop spinal cord stimulation provided preliminary evidence of its effectiveness. This spinal cord stimulation system records in-vivo human spinal cord electrophysiology continuously in real-time through ECAPs and uses this objective measure to automatically adjust the stimulation current to maintain a consistent level of spinal cord activation within each patient's therapeutic range of activation (ie, closed-loop spinal cord stimulation). Responder rates exceeded 76% for ECAP-controlled closed-loop spinal cord stimulation at the 12-month follow-up, which are higher than rates previously reported for other spinal cord stimulation systems.

Added value of this study

We report the results of the first double-blind randomised controlled trial to compare ECAP-controlled closed-loop spinal cord stimulation with fixed-output, open-loop spinal cord stimulation and to measure spinal cord activation in both groups. We observed significantly better responder rates with closed-loop spinal cord stimulation than with open-loop spinal cord stimulation at the 12-month follow-up. Additionally, closed-loop spinal cord stimulation provided greater improvement than open-loop spinal cord stimulation in all patient-reported outcomes collected as per IMMPACT recommendations. Greater rates of improvement in these subjective outcomes coincided with higher, more consistent spinal cord activation within patients' therapeutic range of activation in the closed-loop group compared with those in the open-loop group.

Implications of all the available evidence

This study shows that the neural response to stimulation can be successfully measured and associated with clinical outcomes. This study has important practical implications as it has shown that spinal cord activation can be used to identify and target a patient-specific therapeutic window to improve care.
The potential clinical usefulness of this technology is promising and might provide the foundation for an individualised mechanism-based treatment approach for more effective therapy, as well as monitor the health of the spinal cord and the effects of treatment over time. Not only would this be revolutionary for the field of spinal cord stimulation but it would also have broad application to the field of neuromodulation, including therapies such as vagal nerve, sacral nerve, and deep brain stimulation.

and other features of the electrocardiogram, similar technological advances have not been available for spinal cord stimulation systems until now. Neurostimulation differs from other types of electrical stimulation in that it requires a high degree of stimulation selectivity[2] to activate only those nerve fibres that create therapeutic benefit (ie, Aβ fibres in the dorsal column that innervate the cutaneous receptors) and to avoid those nerve fibres that produce undesirable side-effects (eg, nociceptors[2,3]). Since the inception of spinal cord stimulation more than half a century ago, electricity has been delivered to the spinal cord without continuous measurement of the nerve fibre response in patients during daily use. A small response from few fibres,[4] each contributing even smaller single-fibre action potentials,[5] combined with large stimulus artefacts,[6] posed substantial engineering challenges.

The electrically evoked activation of the dorsal column Aβ fibres have antidromic and orthodromic inhibitory effects, which in turn drive the modulatory role of spinal cord stimulation over the dorsal columns, leading to the clinical effect of pain relief.[7] Electrical stimulation of sufficient amplitude induces membrane depolarisation and repolarisation of a single fibre, generating an action potential. Evoked compound action potentials (ECAPs) are the sum of multiple action potentials that result from activation of multiple nerve fibres by an electrical stimulus (appendix p 2). In spinal cord stimulation, the ECAP is a direct measure of spinal cord fibre activation

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that leads to pain inhibition through modulation of pain processing in the spinal grey matter.

Effective non-opioid treatment options are urgently needed for chronic back and leg pain. Global prevalence of low back pain is greater than 576 million, with an incidence of approximately 246 million per year, and is one of the top three causes of disability.[8] The prevalence of lower back and leg pain is approximately 187 million and the incidence is 79 million per year.[8] Spinal cord stimulation is an established treatment for refractory chronic back and leg pain. Treatment success, defined as pain relief of 50% or more, is typically reported in 50% of patients,[9–11] with studies based on new stimulation systems providing somewhat greater degrees of relief.[12] However, clinical use of spinal cord stimulation is limited by whether patients respond or if efficacy is lost over time.[13,14]

A major challenge in spinal cord stimulation is the ever-changing distance between the stimulating electrodes relative to their spinal cord target. The electrode is fixed in the epidural space, whereas the spinal cord changes position within the cerebrospinal fluid with every movement, including the cardiorespiratory cycle (eg, breathing, heartbeat), coughing, or changes in body position (eg, standing, sitting, and lying down). Small changes in the distance between the electrode and spinal cord result in large changes in the current reaching the spinal cord, because the density of the current with spinal cord stimulation varies with the inverse of the distance between the electrode and spinal cord squared.[4] Therefore, at a fixed spinal cord stimulation output level, the degree of spinal cord activation varies widely.

Available spinal cord stimulation systems, regardless of the stimulation parameters, are open-loop systems and incapable of measuring spinal cord activation or varying stimulation output on the basis of such measurement. For these systems, the stimulation is fixed according to in-clinic programmed settings. There is a feed-forward system[15] with an accelerometer located in the pulse generator, distant from the electrode to spinal cord interface, that uses pre-programmed, fixed output stimulation programs based on gross postural changes.[16] In all cases, however, the stimulation output does not vary on the basis of how much current is reaching the spinal cord, which can result in substantial variation in spinal cord activation. To manage variance in stimulation, patients generally reduce the stimulation amplitude with a remote control, which improves tolerability of stimulation and reduces the incidence of overstimulation, but also reduces the amount of analgesia that can be achieved.[3]

To address these limitations, a novel neuromodulation system has been developed that is able to record in-vivo human spinal cord electrophysiology continuously in real time.[17,18] An ECAP is measured for each stimulation pulse delivered, which reflects the degree of spinal cord activation elicited by spinal cord stimulation. The system can operate in a fixed-output, open-loop (plus ECAP measurement) mode or an ECAP-controlled, closed-loop mode. In open-loop spinal cord stimulation, the system measures ECAPs, which can be used to determine optimal stimulation settings but are not used to automatically adjust stimulation current to maintain a target response. In closed-loop spinal cord stimulation, the difference between the measured ECAP and the target ECAP amplitude is minimised by automatically adjusting the stimulation current to maintain consistent spinal cord activation within the individuals' therapeutic window (figure 1). Through real-time modulation of the output current, the closed-loop system maintains consistent spinal cord activation with corresponding inhibition of pain processing pathways, and thus maximises the therapeutic effect.

The initial effectiveness of ECAP-controlled closed-loop spinal cord stimulation was evaluated in a prospective, multicentre, single-arm study. The long-term results showed sustained, high rates of pain reduction and significant improvements in functional disability, quality of life, and sleep quality (ACTRN12615000713594).[19]

We present the 12-month safety and efficacy results of the first double-blind, randomised controlled trial comparing ECAP-controlled closed-loop spinal cord stimulation with fixed-output, open-loop spinal cord stimulation for the treatment of chronic back and leg pain. This study is, to the best of our knowledge, the first to record in-vivo human spinal cord electrophysiology in both stimulation modes. We examined the association between pain relief and the extent of spinal cord activation.

Methods

Study design and participants

This multicentre, double-blind, parallel-arm, randomised controlled trial was done at 13 investigation sites—specialist clinics, academic centres, and hospitals—throughout the USA under an Investigational Device Exemption to gain approval from the US Food and Drug Administration (FDA). The protocol (published previously[20]) was approved by each participating site's institutional review board. This study was done in accordance with FDA regulatory requirements, Good Clinical Practice guidelines, and the ethical principles of the Declaration of Helsinki.

Patients aged 18–80 years who provided written informed consent were screened for enrolment according to the following key eligibility criteria: chronic, intractable pain of the back and legs refractory to conservative therapy; candidate for a spinal cord stimulation trial; overall, back, and leg pain scores on the Visual Analog Scale (VAS) of 60 mm or greater (out of 100 mm for worst imaginable pain); Oswestry Disability Index (ODI) score of 41–80; stable pain medications; and no previous experience with spinal cord stimulation (appendix pp 3–4). Patients with and without previous back surgery were eligible. An independent medical monitor confirmed that inclusion and exclusion criteria were interpreted consistently before enrolment of patients.

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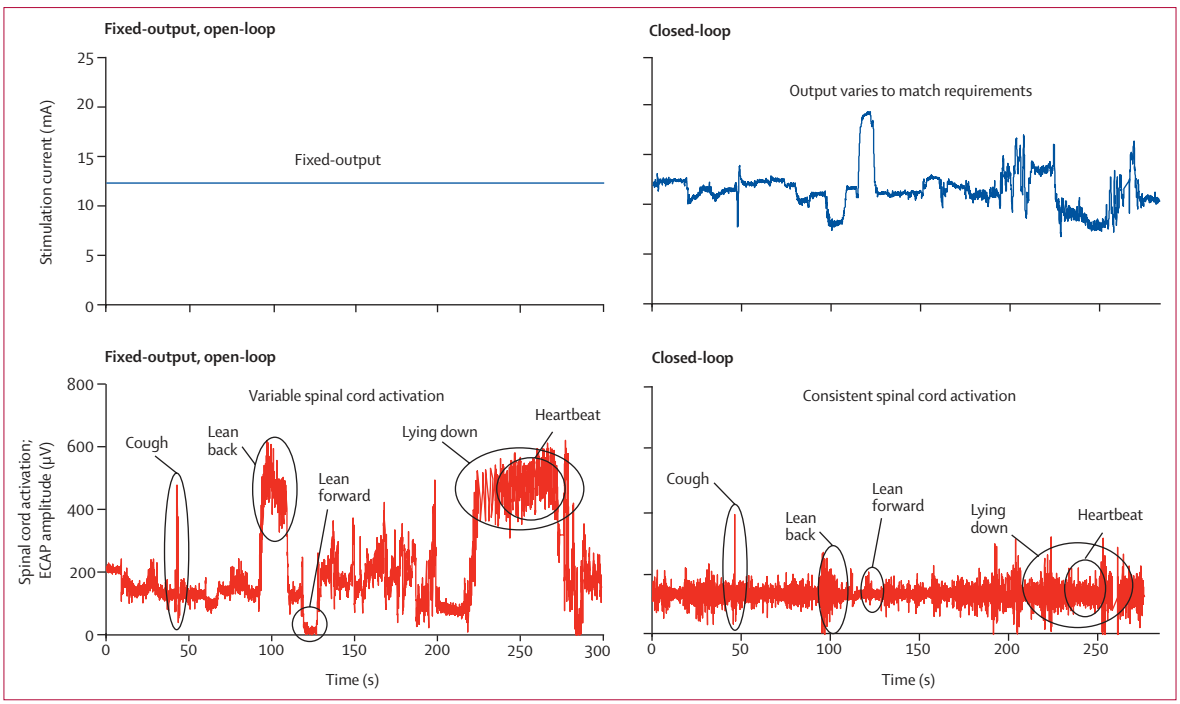


Figure 1: **Fixed-output, open-loop spinal cord stimulation versus closed-loop spinal cord stimulation**
Patient's involuntary physiological and voluntary movements change the separation between the electrode and the spinal cord. Fixed-output, open-loop spinal cord stimulation delivers a fixed output of stimulation current. The control therapy in this study additionally measures the neurophysiological response to stimulation (ie, spinal cord activation level through ECAPs). However, this response is not utilised to automatically adjust stimulation current to maintain a target response. As a consequence, the stimulation delivered to the patient might be lower (eg, no or minimal spinal cord activation) or higher (eg, activation of nociceptors) than required to achieve consistent spinal cord activation. Currently available spinal cord stimulation systems do not measure a neurophysiological response to stimulation and thus activation of the spinal cord is unknown. In closed-loop spinal cord stimulation, the stimulation current is automatically adjusted in real time through feedback of the measured neurophysiological response to stimulation to maintain the target response. Therefore, the objective of closed-loop spinal cord stimulation is to match the patient's requirements to produce consistent activation. ECAPs=evoked compound action potentials.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive ECAP-controlled, closed-loop spinal cord stimulation (investigational group) or fixed-output, open-loop spinal cord stimulation (control group). The randomisation scheme was generated by an independent statistician by use of permuted blocks of size four and six, stratified by site to ensure within-site balance, and uploaded to a secure database. The randomisation assignments were generated by the database at the time of the temporary spinal cord stimulation trial procedure, after lead placement. Treatment allocation was concealed from the patients, investigator, and site staff (appendix p 5). Aside from the difference in stimulation modes, patients in both treatment groups recieved the same care, with the device, implant procedure, and programming process being the same for both groups. An assessment of masking was completed to determine whether patients or investigators became unmasked to treatment assignment (appendix p 5).

Procedures

Randomly assigned patients underwent a temporary spinal cord stimulation trial lasting 2–11 days. Patients who received a reduction of 50% or greater in overall back and leg pain VAS during the trial were approved to receive a permanent implant. Follow-up was done at 1, 3, 6, 9, and 12 months and biannually thereafter for up to 3 years following the permanent implant procedure. Following the 24-month visit, a self-selected crossover was offered.

The trial and implant procedures were done according to usual practice. Two percutaneous leads were placed in the epidural space over the dorsal column at the thoracic vertebral level associated with pain and connected to the external trial stimulator (during the trial phase) or the stimulator implanted in a subcutaneous pocket (for the permanent implant).

The same neuromodulation system (Evoke System, Saluda Medical, Sydney, Australia) served as the investigational and control device, as it offered both ECAP-controlled closed-loop spinal cord stimulation and fixed-output, open-loop spinal cord stimulation. For both treatment groups, real-time spinal cord activation was ascertained from measured ECAPs and stored.

Programming was done by sponsor field clinical engineers with documented oversight from the investigators in accordance with FDA guidelines[21] in the same manner for both treatment groups using ECAP measurement and patient feedback (appendix p 6). Adjustments were permitted for both groups as needed to optimise therapy.

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