Interventional Pain Medicine 2 (2023) 100274

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

Trial or not trial in the practice of spinal cord stimulation. That's the question

The complex interplay of clinical and psychosocial factors that determine patients' eligibility for the implantation of spinal cord stimulation systems (SCS), for chronic pain control has led to selection criteria generally being based only on clinical and functional variables, mainly subjective, with wide differences between implant centers. The available guidelines [1–4] are not sufficiently explicit in their recommendations and certainly do not address the great heterogeneity of patients seen in daily clinical practice. Therefore, traditionally, it has been recommended to implant the SCS device in two phases, without an exact definition of the duration of the trial phase, but with the aim of identifying those patients who would benefit from the definitive implant, evaluating the ability of the device to cover the patient's expectations, meaning pain area and the level of associated paresthesia [5]. However, a 50% improvement in the long term has been demonstrated both in patients implanted after a satisfactory trial phase and in patients implanted in a single stage [6,7], and that false positive and false negative results can lead to long-term treatment failures [5].

In addition to the aspects previously outlined, the most common causes for the failure of the SCS trial phase were, the possible infection of the implant by the externalization of the electrode and its connection to the temporary battery [8,9], and the displacement and migration of the electrodes [10], due to the dressing detaching and, therefore pulling the electrode out of the target position set for the trial phase.

All these reasons make it clear that it is necessary to look for new alternatives that avoid the specific risks of the trial phase without diminishing the efficiency criterion that must mark at all times the process of implanting SCS in patients with chronic pain. In this sense, different authors [7,11,12], hypothesize that performing an implant in a single stage, is not only safer for the patient, but also cost-effective, since the trial phase requires the duplication of procedures, thus consuming more health resources and its consequent associated cost [13].

The studies published to date have questioned the prognostic value of the trial phase [14,15], given that its realization is based on expert opinion, and despite its habitual use, it does not have a consistent level of evidence.

In this issue of the journal is published the article of De Negri et al. [16]. in which a single-stage SCS procedure, and subsequent evaluation at 3 and up to 12 months with an average follow-up of 408 days, is presented as a real world practice. In this study, patients were tested on-table prior to immediate implantation. The authors do not give more information on how the test was performed, its duration, or the objective of symptomatic control posed to the patient. A mean 5.0 ± 2.1-point improvement (from 8.1 to 3.1; n. 109) in overall pain was reported at 3 months post-implantation and sustained at 12 months follow-up. Weinand et al. [17], conducted a study to compare the results of a short (15 minutes intraoperative) and prolonged (5 days) trial phase, concluding that their predictive value is equivalent. The test, both short and long in time, appears to have equivalent predictive value for the long-term outcome of SCS in the control of chronic low back and/or lower extremity pain. Colombo et al. [18], evaluated the long-term clinical efficacy of SCS in patients who had a trial phase and in patients who, on the contrary, underwent an immediate permanent implant. Pain reduction, as measured by variation in visual analogue scale (VAS) score, was greater in patients who underwent a permanent implant directly without a trial phase (59.5% vs. 71.4%).The recent articles from Eldabe et al. [11,12], and more importantly that of Chadwick et al. [19], quarantine our way of working so far. Results[196] indicate an overwhelming preference among patients for a single-time SCS implantation procedure. The reasons for this preference include among others, time savings (outside of work, in the hospital, attending appointments); avoiding the worry of having "loose cables" and their possible complications; and saving health resources (time of doctors and other staff, medical devices and materials). In addition, the advantage of having a single surgical intervention and a recovery period.

The evidence accumulated in the different published clinical studies undoubtedly leads us to propose a new scenario of the global management of SCS implantation in patients with chronic pain. Clinical practice reinforces the need to redefine the characteristics of patients who can select responders to SCS therapy [20]. Recently, a tool for assessing patients to be implanted (scstool.org) has been created based on a consensus at European level [21]. This tool allows, in four cases (PSPS, ischemic pain, CRPS and peripheral neuropathic pain), to assess the probability of success of the therapy from a clinical and psychological point of view. But there are also unknowns, how to assess, and what to do with those patients in whom there is a higher risk of failure after implantation, or with pathologies not included in this assessment tool, but who frequently benefit from stimulation.

In a recent article, Pahapill et al. [22], attempt to find an answer to the selection of the right candidate for SCS, performing magnetic resonance imaging scans of functional anatomical connectivity and at rest (rs) in all cases of Persistent Spinal Pain Syndrome (PSPS) before your planned surgery for implantation of a permanent SCS system. The authors specifically present a quantitative and objective measure of chronic pain specific to PSPS patients, reporting a report of altered functional internetwork connectivity involving emotion/reward brain circuits that is related to individual patients' pain scores with a negative correlation.

The efficacy of functional magnetic resonance imaging to be sensitive to the detection and identification of functional brain networks, is definitely a candidate area to provide information to predict the

https://doi.org/10.1016/j.inpm.2023.100274
Received 3 August 2023; Accepted 4 August 2023
Available online 31 August 2023

outcomes of SCS implantation [23], or to show pairwise brain areas, and volumetric changes in left putamen [23], or gray and white matter [24], suggesting the reversibility of brain alterations after chronic pain treatment using SCS.

Smart or closed-loop neuromodulation [25] allows for personalized and adjustable neuromodulation that usually incorporates the recording of a biomarker, followed by the implementation of an algorithm that decides the timing (when?) and energy (how much?) of the stimulation. Closed-loop neuromodulation has been shown to have greater benefits compared to open-loop neuromodulation in the management of patients with chronic pain [26–28]. However, an important aspect of the technique is the selection of an appropriate biomarker, preferably neural. Neurochemical detection can provide high-resolution biomarker monitoring for various neurological disorders, as well as offer deeper insight into neurological mechanisms. The chemicals of interest that are measured can be ions such as potassium (K+), sodium (Na+), calcium (Ca2+), chloride (Cl-), hydrogen (H+) or neurotransmitters such as dopamine, serotonin and glutamate [29].

Recent research reveals that the implantation of a SCS in patients with chronic pain can have effects at the level of expression and release of proteins. Lind et al. [30] observed alterations in 86 proteins with the use of DBS. The most relevant were Gelosin, Clusterin, VEGF, Angiotendinogen, Amyloid Beta Protein A4, Apoprotein E, Apoprotein C1, DKK3, Mimecan and Secretogranin 1. Other studies also postulate a decrease in vascular endothelial growth factor (VEGF) in patients with neuropathic pain with functioning DBS [31]. Also, the implantation of the neurostimulator has been linked to changes in metalloproteinases. Specifically, MMP-2 levels increased after one month after implantation and remained high 3 months after implantation, but no change was observed in MMP-9 [32]. On the other hand, the implantation of DBS leads to an increase in the local production in the spinal cord of neurotransmitters such as serotonin, substance P, acetylcholine, glycin and GABA, with simultaneous decreases of amino acids glutamate and aspartate [30].

We carried out a research work [33], to determine the gene and protein expression of markers of the opioid system (mu, kapa and delta receptors and opioid peptides (proenkephalin (**PENK**))dynorphin), the cannabinoid system (CB1 and CB2 receptors) and the inflammatory process (interleukin 1beta, TNFalpha) before and at various times after neurostimulation in lymphocytes and plasma of these patients. A positive correlation was observed between changes in VAS scores and PENK, as PENK changes increased, so did pain intensity.

Therefore, there is growing evidence in the literature, both clinical and experimental, on the existence of potent adaptive interactions between the central and peripheral aspects of the neuroimmune system in the genesis and maintenance of chronic neuropathic pain in the extremities and nociceptive back pain and the possible interaction caused by SCS [34]. All of the findings presented above may have important implications for the potential applications of neurostimulation. as anti-inflammatory therapy and the role of molecular profiling as a pre-implant detection modality and validation of post-implant results. Therefore, clinical and experimental research conducted in the future is highly justified in this particular new field of neuromodulation.

As a final reflection we must conclude that the evidence indicates that, although there may be some diagnostic utility of a trial phase for the implantation of SCS, compared to a strategy without detection, there is no benefit in the result, in the medium and long term, of the patient, in addition to supposing an increase in costs that represents a poor value for money. Undoubtedly, technological advances will provide us tools [35], that allow optimized selection based on objective data together with the communication received from the patient, which will allow predicting the suitability of the candidate in the screening phase, as well as providing objective data on the effectiveness of the SCS system during its operation, being able to correlate them with the patient's clinical symptoms.

References

[1] National Institute for Health and Clinical Excellence. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. 2008. Retrieved from, https://www.nice.org.uk/guidance/ta159.

[2] Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, Levy RM, Backonja M, Baron R, Harke H, Loeser JD, Treede RD, Turk DC, Wells CD. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154(11):2249–61.

[3] Deer TR, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, Levy RM, Abejon D, Buchser E, Burton A, Buvanendran A, Candido K, Caraway D, Cousins M, DeJongste M, Diwan S, Eldabe S, Gatzinsky K, Foreman RD, Hayek S, Kim P, Kinfe T, Kloth D, Kumar K, Rizvi S, Lad SP, Liem L, Linderoth B, Mackey S, McDowell G, McRoberts P, Poree L, Prager J, Raso L, Rauck R, Russo M, Simpson B, Slavin K, Staats P, Stanton-Hicks M, Verrills P, Wellington J, Williams K, North R, Neuromodulation Appropriateness Consensus Committee. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation 2014;17(6):515–50.

[4] Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W, Taylor R, Tronnier V, Truini A, Attal N. EAN guidelines on neurostimulation therapy in chronic pain conditions. Eur J Neurol 2016;23(10):1489–99.

[5] Duarte RV, McNicol E, Colloca L, Taylor RS, North RB, Eldabe S. Randomized placebo-/sham-controlled trials of spinal cord stimulation: a systematic review and methodological appraisal. Neuromodulation 2020;23(1):10–8.

[6] Oakley JC, Krames ES, Stamatos J, Foster AM. Successful long-term outcomes of spinal cord stimulation despite limited pain relief during temporary trialing. Neuromodulation 2008;11(1):66–73.

[7] North RB, Calodney A, Bolash R, Slavin KV, Creamer M, Rauck R, Vahedifar P, Fox I, Özaktay C, Panchal S, Vanquathem N. Redefining spinal cord stimulation "trials": a randomized controlled trial using single-stage wireless permanent implantable devices. Neuromodulation 2020;23(1):96–101.

[8] Sanchis-Lopez N, Romero-Garcia C, De Andres-Ibanez J, Martinez-Plumed R, Rodriguez-Gimillo P, Hernandez-Cadiz MJ, de Medrano VA. Medical device related pressure injury in the treatment of chronic pain: an early sign of explantation in suspected infection. Pain Physician 2018;21(3):E235–46.

[9] North R, Desai MJ, Vangeneugden J, et al. Postoperative infections associated with prolonged spinal cord stimulation trial duration (PROMISE RCT). Neuromodulation 2020;23:620–5.

[10] Osborne MD, Ghazi SM, Palmer SC, Boone KM, Sletten CD, Nottmeier EW. Spinal cord stimulator–trial lead migration study. Pain Med 2011 Feb;12(2):204–8.

[11] Eldabe S, Gulve A, Thomson S, Baranidharan G, Duarte R, Jowett S, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness? (TRIAL-STIM study): study protocol for a randomised controlled trial. Trials 2018;19(1):1–11.

[12] Eldabe S, Duarte RV, Gulve A, Thomson S, Baranidharan G, Houten R, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness (TRIAL-STIM)? A randomised controlled trial. Pain 2020;161(12):2820–9.

[13] Duarte RV, Thomson S. Trial versus No trial of spinal cord stimulation for chronic neuropathic pain: cost analysis in United Kingdom national health service. Neuromodulation 2019 Feb;22(2):208–14.

[14] Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007;132:179–88.

[15] Dones I, Levi V. Spinal cord stimulation for neuropathic pain: current trends and future applications. Brain Sci 2018 Jul 24;8(8):138.

[16] De Negri P, Paz-Solis JF, Rigoard Ph, Raoul S, Kallewaard JW, Gulve A, Thomson S, Canos-Verdecho MA, Love-Jones S, Williams A, Rascon-Ramírez FJ, Bayerl S, Llopis-Calatayud JE, Peña-Vergara I, Matis GK, Vesper J, Abejon D, Maino P, Papa A, Pei Y, Jain R. Real-world outcomes of single-stage spinal cord stimulation in chronic pain patients: a multicentre, European case series. Interventional Pain Medicine 2023;2:100263.

[17] Weinand ME, Madhusudan H, Davis B, Melgar M. Acute vs. Prolonged screening for spinal cord stimulation in chronic pain. Neuromodulation 2003 Jan;6(1):15–9.

[18] Colombo EV, Mandelli C, Mortini P, Messina G, De Marco N, Donati R, Irace C, Landi A, Lavano A, Mearini M, et al. Epidural spinal cord stimulation for neuropathic pain: a neurosurgical multicentric Italian data collection and analysis. Acta Neurochir 2015;157:711–20.

[19] Chadwick R, McNaughton R, Eldabe S, Baranidharan G, Bell J, Brookes M, Duarte RV, Earle J, Gulve A, Houten R, Jowett S, Kansal A, Rhodes S, Robinson J, Griffiths S, Taylor RS, Thomson S, Sandhu H. To trial or not to trial before spinal cord stimulation for chronic neuropathic pain: the patients' view from the TRIAL-STIM randomized controlled trial. Neuromodulation 2021 Apr;24(3):459–70.

[20] Palmer N, Guan Z, Chai NC. Spinal cord stimulation for failed back surgery syndrome. Patient selection considerations. Transl Perioper Pain Med 2019;6(3):81–90.

[21] Thomson S, Huygen F, Prangnell S, De Andrés J, Baranidharan G, Belaïd H, Berry N, Billet B, Cooil J, De Carolis G, Demartini L, Eldabe S, Gatzinsky K, Kallewaard JW, Meier K, Paroli M, Stark A, Winkelmüller M, Stoevelaar H. Appropriate referral and selection of patients with chronic pain for spinal cord stimulation: European consensus recommendations and e-health tool. Eur J Pain 2020 Jul;24(6):1169–81.

[22] Pahapill PA, Chen G, Arocho-Quinones EV, Nencka AS, Li SJ. Functional connectivity and structural analysis of trial spinal cord stimulation responders in failed back surgery syndrome. PLoS One 2020 Feb 19;15(2):e0228306.

[23] De Andres J, Ten-Esteve A, Harutyunyan A, Romero-Garcia CS, Fabregat-Cid G, Asensio-Samper JM, Alberich-Bayarri A, Marti-Bonmati L. Predictive clinical decision support system using machine learning and imaging biomarkers in patients with neurostimulation therapy: a pilot study. Pain Physician 2021 Dec;24(8): E1279–90.
[24] De Groote S, Goudman L, Van Schuerbeek P, Peeters R, Sunaert S, Linderoth B, De Andrés J, Rigoard P, De Jaeger M, Moens M. Effects of spinal cord stimulation on voxel-based brain morphometry in patients with failed back surgery syndrome. Clin Neurophysiol 2020 Nov;131(11):2578–87.
[25] Parker J, Karantonis D, Single P. Hypothesis for the mechanism of action of ECAP-controlled closed-loop systems for spinal cord stimulation. Healthc Technol Lett 2020 Jun 23;7(3):76–80.
[26] Levy R, Deer TR, Poree L, Rosen SM, Kapural L, Amirdelfan K, Soliday N, Leitner A, Mekhail N. Multicenter, randomized, double-blind study protocol using human spinal cord recording comparing safety, efficacy, and neurophysiological responses between patients being treated with evoked compound action potential-controlled closed-loop spinal cord stimulation or open-loop spinal cord stimulation (the evoke study). Neuromodulation 2019 Apr;22(3):317–26.
[27] Russo M, Cousins MJ, Brooker C, Taylor N, Boesel T, Sullivan R, Poree L, Shariati NH, Hanson E, Parker J. Effective relief of pain and associated symptoms with closed-loop spinal cord stimulation system: preliminary results of the avalon study. Neuromodulation 2018 Jan;21(1):38–47.
[28] Chakravarthy K, Bink H, Dinsmoor D. Sensing evoked compound action potentials from the spinal cord: novel preclinical and clinical considerations for the pain management researcher and clinician. J Pain Res 2020 Dec 4;13:3269–79.
[29] Mirza KB, Golden CT, Nikolic K, Toumazou C. Closed-loop implantable therapeutic neuromodulation systems based on neurochemical monitoring. Front Neurosci 2019 Aug 20;13:808.
[30] Lind AL, Emami Khoonsari P, Sjödin M, Katila L, Wetterhall M, Gordh T, Kultima K. Spinal cord stimulation alters protein levels in the cerebrospinal fluid of neuropathic pain patients: a proteomic mass spectrometric analysis. Neuromodulation 2016;19(6):549–62.
[31] McCarthy KF, Connor TJ, McCrory C. Cerebrospinal fluid levels of vascular endothelial growth factor correlate with reported pain and are reduced by spinal cord stimulation in patients with failed back surgery syndrome. Neuromodulation 2013;16(6):519–22.
[32] Kamieniak P, Bielewicz J, Kurzepa J, Daniluk B, Kocot J. Serum level of metalloproteinase-2 but not metalloproteinase-9 rises in patients with failed back surgery syndrome after spinal cord stimulation. Neuromodulation 2019;22(3): 262–8.
[33] De Andrés J, Navarrete-Rueda F, Fabregat G, García-Gutiérrez MS, Monsalve-Dolz V, Harutyunyan A, Mínguez-Martí A, Rodriguez-Lopez R, Manzanares J. Differences in gene expression of endogenous opioid peptide precursor. Cannabinoid 1 and 2 Receptors and Interleukin Beta in Peripheral Blood Mononuclear Cells of Patients With Refractory Failed Back Surgery Syndrome Treated With Spinal Cord Stimulation: Markers of Therapeutic Outcomes? Neuromodulation 2021 Jan; 24(1):49–60.
[34] Chakravarthy KV, Xing F, Bruno K, Kent AR, Raza A, Hurlemann R, Kinfe TM. A review of spinal and peripheral neuromodulation and neuroinflammation: lessons learned thus far and future prospects of biotype development. Neuromodulation 2019 Apr;22(3):235–43.
[35] De Andres J. Neurostimulation in the patient with chronic pain: forecasting the future with data from the present - data-driven analysis or just dreams?. rapm-2022-103962 Reg Anesth Pain Med 2022 Nov 17. https://doi.org/10.1136/rapm-2022-103962 [Epub ahead of print].

Jose De Andres*
Multidisciplinary Pain Management Department, General University Hospital, Valencia, Spain
Anesthesia Unit. Surgical Specialties Department, Medical School, University of Valencia, Valencia, Spain

* Multidisciplinary Pain Management Department, General University Hospital, Valencia, Spain.
E-mail address: deandres_jos@gva.es.