Brain Stimulation 12 (2019) 1617–1618

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Rapid onset and short washout periods of dorsal root ganglion stimulation facilitate multiphase crossover study designs

To the editor:

Crossover designs are useful in clinical trials where the disease population is limited, or the intervention is uncommon. Participants in a crossover design are exposed to each intervention (e.g. placebo and target drug), and outcomes are compared at the end of each period. This design facilitates the use of smaller sample sizes, as each participant acts as their own control and limits between-subject variability in statistical comparisons while increasing statistical power. A critical element in crossover designs is the implementation of an adequate washout period to prevent carryover effects between each intervention.

For pharmaceutical studies, washout periods are well-established and depend on the drug half-life in the participant's circulation. For clinical trials involving neuromodulation, however, washout periods have not been characterized or standardized with the same degree of rigour. Pre-clinical animal studies of dorsal root ganglion (DRG) stimulation suggest that neuronal activity diminishes within an order of minutes [1]. Additionally, clinical studies of electrical neuromodulation have reported both immediate (within minutes) [2] and long term (over months) effects [3] on symptom severity. We hypothesized that the majority of clinical effects on pain suppression occur immediately after onset and cessation of neurostimulation and report our evaluation of the wash-in and washout periods of acute DRG stimulation in chronic pain.

Methods

Ethical approval for this study was obtained from the South-Central Oxford Research Ethics Committee and conducted in accordance with the guidelines set out in the Declaration of Helsinki. Sixteen patients with diagnosed chronic pain syndromes and who had undergone permanent implantation of a DRG stimulator (DRGS) at the John Radcliffe Hospital were recruited for this study. Participants were assigned to begin the study in the OFF stimulation ($n = 8$) condition or the ON stimulation ($n = 8$) condition by block randomization. Each DRGS was then switched 'on' or 'off' respectively while pain scores were recorded every 30 seconds for 10 minutes.

Statistical analysis was conducted in GraphPad Prism software version 8.0 (La Jolla California USA, www.graphpad.com). We identified the mean increase (MI) and mean decrease (MD) for each condition and identified the time to achieve 75% (MI_{75}/MD_{75}) and 90% (MI_{90}/MD_{90}) of effect on pain scores. D'Agostino test was used to confirm that the data was normally distributed. Student's t-tests were used for pairwise comparisons and repeated measures ANOVA used to identify significant differences in pain scores between each timepoint. Tukey's posthoc test was applied to correct for multiple comparisons.

Results

The mean age of participants was 51 years ± 16.5 [mean ± SD] - ten (10) men, six [6] women. Mean baseline pain score before turning DRG stimulation 'on' was found to be 6.68 ± 2.75 and resulted in a statistically significant reduction in pain scores (Percentage suppression of pain = 40% ± 2.88, $t(7) = 3.503$, $p = 0.01$) over the 10-min period. Prior to turning 'off' DRG stimulation, the mean baseline pain score was found to be 4.37 ± 2.88 (mean ± SD) and upon cessation of stimulation resulted in a statistically significant increase in pain scores (Percentage increase in pain = 53% ± 1.180, $t(7) = 4.549$, $p = 0.0026$) [See Fig. 1].

The greatest variability in reported pain scores occurred within 60 s of turning OFF/ON the DRGS (range +2 to −2.5). Maximal improvement and worsening of pain scores occurred between 360 and 480 seconds of turning DRGS "on" and "off" respectively. Immediate effects on pain suppression occurred more quickly (MI_{75} reached within the first 30 seconds) compared to the carry-over effects upon cessation of stimulation (MD_{75} reached between 90 and 120 seconds). In contrast, 90% of the mean effect on pain

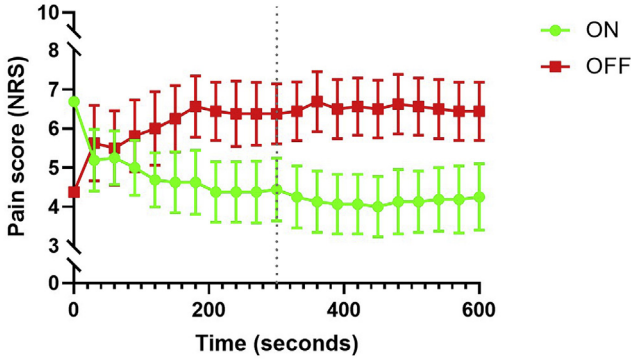

Fig. 1. Depicting change in pain scores (numerical rating scale) with time when turning Dorsal Root Ganglion stimulation 'on' (green) or 'off" (red). At 5 minutes (300s) (grey dotted line) after turning DRGS 'on' or 'off", there is no statistically significant change in reported pain scores (Mean ± SEM). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

https://doi.org/10.1016/j.brs.2019.08.015

from wash-in and washout (MI_{90} and MD_{90}) occurred between 180 and 240 seconds. Notably, after 300 seconds (5 minutes) of turning DRGS "on" or "off", there was no significant change in reported pain scores ($F(2, 18) = 4.32$, $p > 0.05$) from subsequent pain ratings [See Fig. 1].

Discussion

Our findings represent the first systematic approach to evaluate the acute effects of DRG stimulation and its washout period in chronic pain patients. Unfortunately, there is no consistency in the literature to methodologically quantify the acute effects of neurostimulation. Therefore, we employed a similar technique to that used for estimating the effects of deep brain stimulation (DBS) in alleviating the motor symptoms of Parkinson's disease, and the return of symptoms during DBS washout [4]. Our findings similarly reflect that 1) the majority of clinical improvement/worsening occurs within the first few minutes of onset/cessation of neurostimulation, 2) the rate of improvement occurs more rapidly during stimulation than the rate of symptom exacerbation during washout and 3) a plateau occurs, which has been identified to occur *5 minutes* after switching ON/OFF the DRGS.

While these acute effects of neurostimulation on chronic pain do not display significant variability after 5 minutes of turning the stimulator ON/OFF, it is possible that chronic DRG stimulation will produce additional long-term effects. Our findings of acute stimulation represent a 40% reduction in pain, while pain suppression during long-term evaluations of DRG stimulation tend to report improvements >50% [5]. This added effect on pain relief may reflect chronic neuroplastic changes, alterations in gene expression or cortical reorganization during long-term DRG stimulation.

Nevertheless, our estimate of acute DRG washout (10 minutes) resulted in pain exacerbation >50%. In concert with the minimal variability in pain scores during the latter half of this period, our evidence suggests that 10 minutes is a sufficient washout period for crossover studies investigating the acute effects of DRG stimulation. This evidence facilitates the ease of utilizing multi-phase crossover designs (N-of-1 trials) [6] in evaluating the effects of neuromodulation, and can decrease, or negate, the reliance on randomized controlled trials for surgical interventions.

Predominance of fast-decay effects or slow-decay effects during neurostimulation is seemingly dependent on the site of stimulation [7] and longevity of the disease [8]. Our methodology may be employed for different neurologic targets and disease cohorts to evaluate the temporal progression of clinical effects during electrical stimulation. Additionally, the incorporation of neurophysiologic recordings and/or neuroimaging during wash-in and washout evaluations would add substantially to our understanding of the acute and chronic effects of electrical stimulation on the human nervous system.

Conflict of interest declaration

The authors have no relevant conflicts of interest to disclose.

References

[1] Pawela CP, Kramer JM, Hogan QH. Dorsal root ganglion stimulation attenuates the BOLD signal response to noxious sensory input in specific brain regions: insights into a possible mechanism for analgesia. Neuroimage [Internet] [cited 2017 Oct 31]vol. 147. Academic Press Inc.; 2017 Feb 15. 10–8. Available from, http://linkinghub.elsevier.com/retrieve/pii/S1053811916306644.

[2] Barolat-Romana G, Myklebust JB, Hemmy DC, Myklebust B, Wenninger W. Immediate effects of spinal cord stimulation in spinal spasticity [cited 2019 Jul 21] J Neurosurg [Internet] 1985 Apr;62(4). 558–62. Available from, http://www.ncbi.nlm.nih.gov/pubmed/3871847.

[3] Deer TR, Levy RM, Kramer J, Poree L, Amirdelfan K, Grigsby E, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain [Internet] [cited 2019 May 17] Wolters Kluwer Health 2017;158(4):669–81. Available from, http://www.ncbi.nlm.nih.gov/pubmed/28030470.

[4] Temperli P, Ghika J, Villemure J-G, Burkhard PR, Bogousslavsky J, Vingerhoets FJG. How do parkinsonian signs return after discontinuation of subthalamic DBS? [cited 2019 Jul 21] Neurology [Internet] 2003 Jan 14;60(1): 78–81. Available from, http://www.ncbi.nlm.nih.gov/pubmed/12525722.

[5] Kallewaard JW, Edelbroek C, Terheggen M, Raza A, Geurts JW. A prospective study of dorsal root ganglion stimulation for non-operated discogenic low back pain. Neuromodulation Technol Neural Interface [Internet] 2019 Mar 1 [cited 2019 Jul 21]; ISSN: 10947159. Available from, http://www.ncbi.nlm.nih.gov/pubmed/30821901.

[6] Green AL, Shad A, Watson R, Nandi D, Yianni J, Aziz TZ. N-of-1 trials for assessing the efficacy of deep brain stimulation in neuropathic pain [cited 2019 Jul 24] Neuromodulation Technol Neural Interface [Internet] 2004 Apr;7(2):76–81. Available from, http://www.ncbi.nlm.nih.gov/pubmed/22151187.

[7] Cooper SE, Driesslein KG, Noecker AM, McIntyre CC, Machado AM, Butson CR. Anatomical targets associated with abrupt versus gradual washout of subthalamic deep brain stimulation effects on bradykinesia. In: Foffani G, editor. PLoS one [internet]. Public Library of Science; 2014 Aug 6 [cited 2019 Jul 24];9(8): e99663. Available from, http://dx.plos.org/10.1371/journal.pone.0099663.

[8] Cooper SE, McIntyre CC, Fernandez HH, Vitek JL. Association of deep brain stimulation washout effects with Parkinson disease duration, JAMA Neurol [Internet]. NIH Public Access; 2013 Jan [cited 2019 Jul 24]70, 1, 95-99, http://www.ncbi.nlm.nih.gov/pubmed/23070397. Available from.

Tariq Parker*
Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

Alex Green
Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

Tipu Aziz
Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

* Corresponding author. Linacre College, St. Cross Road, OX1 3JA, Oxford, UK.
E-mail addresses: tariq.parker@linacre.ox.ac.uk, tq.parker18@gmail.com (T. Parker).

21 August 2019
Available online 4 September 2019