Issues in design, conduct, and conclusions of JAMA's Hara et al.'s randomized clinical trial of spinal cord burst stimulation versus placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery

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Hara et al recently published a randomised controlled study comparing burst spinal cord stimulation (SCS) to sham.[1] The authors conclude that there was no difference between burst SCS and sham SCS in patients with chronic radicular pain after lumbar spine surgery. Having published methodological guidance for the conduct and reporting of sham-controlled neuromodulation trials, we applaud the author's for conducting this study.[2] However, importantly, our recent 3-arm sham controlled SCS study (sham vs four spike burst (BST) vs tonic sub-threshold stimulation at 500 Hz (T500)) had a different finding to those of Hara et al. Although there was no difference in mean pain reduction for BST versus sham (5%; 95% CI, −13% to 27%; p = 0.59), T500 had a greater pain reduction than both sham (25%; 95% CI, 8%–38%; p = 0.008) or BST (28%; 95% CI, 13%–41%; p = 0.002).[3]

In this editorial, we note several issues in design, conduct and conclusions of the Hara et al trial that make the authors conclusion of no effect of SCS compared to sham an unsafe one.

Concerns with study design

The choice of radicular pain as a target condition rather than the broader category of persistent spinal pain syndrome type 2 (PSPS-T2) is an interesting one and not justified by the authors. Indeed, we are told that participants were recruited if meeting the eligibility criterion of reported average pain intensity with a minimum of 5 on scale of 1 to 10 for leg pain using the Numeric Rating Scale (NRS). No information is given about eligibility criterion for low back pain (LBP) or what reported average pain intensity would be required for LBP to become an exclusion criterion.

The authors choice of the Oswestry Disability Index (ODI) as primary outcome measure, while not unusual in LBP studies is quite an unusual choice in SCS studies given that the therapy is a palliative one aiming at pain relief primarily, thus a choice of pain as the primary outcome measure is more logical. The authors did not provide a rationale for their choice of the ODI as a primary outcome.

The choice of the SCS waveform is unusual since the authors, according to their own protocol, intended to use a five-spike burst also known as BurstDR but eventually applied a four-spike burst without providing a rationale for this change from the protocol. This form of burst stimulation had already been tested and found to be equivalent to sham stimulation at 90% of the perception threshold,[3] yet the authors choose to retest the same mode at 50-70% of perception threshold. Having learned in 2021 that four spike burst SCS was equivalent to sham were the authors ethically justified in continuing their experiment?

Concerns with study conduct

The authors report conducting a 2-week SCS testing period with tonic stimulation using an external neurostimulator and implantation of those patients reporting a reduction of at least 2-points for leg pain using a NRS. In the protocol (supplement 2) a successful testing period was defined as ≥30% pain reduction.[1] A 2-point reduction in NRS does not correspond to ≥30% pain reduction, and both values deviate significantly from international guideline recommendations of a requirement of ≥50% pain reduction at trial to proceed to implant.[4] Furthermore, a lead positioned for optimal leg pain reduction is not the same for optimal LBP reduction.

During the 2-week SCS testing period, the participants were not evaluated for a response to the type of burst SCS or response to the stimulation below the 50% to 70% of the paraesthesia threshold level to be implemented. The mechanisms of action of SCS involves activation of spinal cord fibers to inhibit pain signalling in the dorsal horn of the spinal cord.[5]

The methods used to ensure the blinding of the sham arm and what the sham arm consisted of (e.g., device switched off) are not reported in the manuscript, protocol, or trial register (NCT03546738). It is therefore not possible to ascertain how the participants remained blind to the intervention being received. An assessment of effectiveness of blinding of patients or members of the research team was not conducted. Further, it is not clear what measures were in place in case the patients experienced sham sensations, or the patients needed to switch off the device in case of an emergency.

Concerns with the study conclusions

The type of burst SCS and stimulation at 50% to 70% of the paraesthesia perception threshold are not used in routine clinical practice and the manufacturer of the devices used in the study does not recommend the burst mode employed in the study since 2018. This limits the value of the findings from this study as these can only apply to a mode of burst that is not used or recommended by the manufacturer.

There are different modes of burst SCS with the most commonly used being a five-spike burst.[6] The findings from Hara et al are therefore not generalisable to other types of SCS or other types of burst SCS not evaluated in this study.

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