Peer Review File

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Reviewer A

Comment 1: After reviewing your manuscript, I have concerns about the literature search that was performed and the purported novelty of the topic.

The authors stated based the novelty and importance of this case report on this being: 1) the first care report of epidural hematoma following spinal cord stimulation resulting in paraplegia, and 2) published literature regarding complications and management is lagging.

Reply 1: *We want to highlight that we have made substantial revisions throughout the manuscript to better emphasize the novelty of our case report. Our study now places a greater focus on the distinctive medical comorbidities and addresses the underreported occurrence of permanent deficits associated with Spinal Cord Stimulation (SCS). Notably, our revised title, introduction, and discussion sections have undergone significant changes to more effectively convey the uniqueness of our findings. We believe these enhancements strengthen our contribution to broader discussions within the medical community, shedding light on the unprecedented nature of the documented case and encouraging further research into the underlying mechanisms of permanent paraplegia.*

Changes in the text:

Title changed to

> "Spinal Epidural Hematoma and Permanent Paraplegia Following Spinal Cord Stimulator Implantation: A Case Report"

Introduction –

> "As the popularity of SCS rises, the literature has raised questions about therapeutic benefits, leading to an increased focus on complications. The rates of complications are still quite debatable, but multiple large retrospective studies have consistently identified hardware-related issues as the most common postoperative complication. A recent study by Papadopoulos et al. highlighted lead migration or misplacement as the most frequent indication for reoperation (4). While serious adverse events are rare, they significantly impact SCS usage. A study by West et al. specifically examined hematoma incidence, revealing 0.81% overall and 0.32% neuraxial (5)."

Discussion-

> "The literature on hematomas associated with Spinal Cord Stimulation is limited. A retrospective analysis of 12,297 patients reported only 15 cases of hematomas within a 90-day period (15). A systematic review by West et al. found a hematoma incidence of less than 1%, with neuraxial hematomas occurring in less than 0.5% of cases (5). Notably, the study did not report any

instances of permanent paraplegia due to neuraxial hematomas; a single case reported paraplegia, but the patient recovered after debridement with no significant deficits (16).”

Comment 2: Later in the manuscript, the author acknowledges that this case report is similar to another with partial paraplegia despite initially stating this is the first one of its kind. The authors also failed to mention the research that has been published around complications and spinal cord stimulation in high-risk populations.

Reply 2: *We undertook a comprehensive examination and thorough analysis of complications outlined in the current literature. In order to elucidate the uniqueness of the topic, we incorporated extra references pertaining to general complications documented in the literature. In addition to these supplementary sources, we highlighted the unique factors that set apart this specific case from previous case report.*

Changes in the text:

Discussion

> “While extensively promoted as non-invasive and generally safe in various literature papers, SCS carry the potential for causing severe disability. Notably, there is a limited amount of reporting in the literature on permanent paraplegia arising from a SCS. To our knowledge, occurrences of hematoma in relation to SCS have been infrequently mentioned, and permanent paraplegia has never been discussed in the literature. Furthermore, a more thorough evaluation of the literature reveals that studies without financial interests show minimal therapeutic benefits.
>
> This case report highlights the serious consequences of spinal cord epidural hematomas, an extremely uncommon event. Remarkably, the deficits observed in this case did not show swift resolution after decompression, which is a rarity in itself. Another notable aspect of this report is the detailed exploration of the patient's medical history and the discussion surrounding their eligibility as a SCS candidate.
>
> The literature on hematomas associated with Spinal Cord Stimulation is limited. A retrospective analysis of 12,297 patients reported only 15 cases of hematomas within a 90-day period (15). A systematic review by West et al. found a hematoma incidence of less than 1%, with neuraxial hematomas occurring in less than 0.5% of cases (5). Notably, the study did not report any instances of permanent paraplegia due to neuraxial hematomas; a single case reported paraplegia, but the patient recovered after debridement with no significant deficits (16).
>
> In the absence of specific guidelines for spinal epidural hematomas post SCS placement, we can adopt the recommended approach for managing spontaneous spinal epidural hematomas to mitigate potential adverse outcomes. A multicenter study conducted by Fukui et al. underscored the significance of the time elapsed from onset to debridement as a critical prognostic factor. In their findings, surgery was typically conducted around 24 hours after the onset of symptoms (17).”

Comment 3: I would recommend the authors review the following publications:

1) Falowski SM, Tan H, Parks J, Abd-Elsayed A, Raslan A, Pope J. Anticipating and preventing complications in spinal cord stimulator implantation. Expert Rev Med Devices. 2023 May;20(5):365-372. doi: 10.1080/17434440.2023.2196399. Epub 2023 Apr 3. PMID: 36974624.

2) West T, Driver CN, D'Souza RS. Incidence of Neuraxial and Non-Neuraxial Hematoma Complications From Spinal Cord Stimulator Surgery: Systematic Review and Proportional Meta-Analysis. Neuromodulation. 2023 Oct;26(7):1328-1338. doi: 10.1016/j.neurom.2022.07.005. Epub 2022 Aug 17. PMID: 35985940.

3) Labaran L, Jain N, Puvanesarajah V, Jain A, Buchholz AL, Hassanzadeh H. A Retrospective Database Review of the Indications, Complications, and Incidence of Subsequent Spine Surgery in 12,297 Spinal Cord Stimulator Patients. Neuromodulation. 2020 Jul;23(5):634-638. doi: 10.1111/ner.12952. Epub 2019 Apr 22. PMID: 31009145.

4) Lee JM, Lee D, Christiansen S, Hagedorn JM, Chen Z, Deer T. Spinal Cord Stimulation in Special Populations: Best Practices from the American Society of Pain and Neuroscience to Improve Safety and Efficacy. J Pain Res. 2022 Oct 19;15:3263-3273. doi: 10.2147/JPR.S372921. PMID: 36304486; PMCID: PMC9594348.

Reply 3: *We thoroughly investigated the reported complications by conducting an exhaustive search, utilizing the comprehensive references provided. This inquiry encompassed a meticulous examination of seminal works by West et al., Labaran et al., and Lee et al., whose invaluable contributions significantly enhanced the depth and credibility of my investigation. By incorporating explicit citations from these publications into the revised paper, our goal was to not only enhance factual accuracy but also highlight the novelty of this case report.*

Changes in the text:

Introduction

> "As the popularity of SCS rises, the literature has raised questions about therapeutic benefits, leading to an increased focus on complications. The rates of complications are still quite debatable, but multiple large retrospective studies have consistently identified hardware-related issues as the most common postoperative complication. A recent study by Papadopoulos et al. highlighted lead migration or misplacement as the most frequent indication for reoperation (4). While serious adverse events are rare, they significantly impact SCS usage. A study by West et al. specifically examined hematoma incidence, revealing 0.81% overall and 0.32% neuraxial (5)."

Discussion

> "The literature on hematomas associated with Spinal Cord Stimulation is limited. A retrospective analysis of 12,297 patients reported only 15 cases of hematomas within a 90-day period (15). A systematic review by West et al. found a hematoma incidence of less than 1%, with neuraxial hematomas occurring in less than 0.5% of cases (5). Notably, the study did not report any instances of permanent paraplegia due to neuraxial hematomas; a single case reported paraplegia, but the patient recovered after debridement with no significant deficits (16)."

Reviewer B

The framework of the manuscript is intact and English writing is fluent. The study examines a rare case of epidural hematoma following insertion of a spinal cord stimulator in a patient with chronic back pain as well as co-morbid liver malignancy and transplant. The case itself highlights a rare complication of SCS and emphasizes that even with prompt debridement, the effects of spinal cord compression from the hematoma may be irreversible. The case properly emphasizes that clinicians should carry a high index of suspicion for hematomas following SCS implementation, given the severe and irreversible consequences that could result.

Comment 1: The paper would improve with some discussion in the introduction on the mechanism of SCS. It is true that it is not fully understood, but there are several papers that give great discussions on widely accepted mechanisms for SCS, and the historical theories on which SCS is based on- this may may impact your discussion on potential complications. Here are a few:

Melzack R, Wall PD. Pain mechanisms: a new theory. Science (80-). 1965;150(3699):971–979. doi: 10.1126/science.150.3699.971. ("gate control" pain theory)

Barolat G, Massaro F, He J, Zeme S, Ketcik B. Mapping of sensory responses to epidural stimulation of the intraspinal neural structures in man. J Neurosurg. 1993 Feb;78(2):233-9. doi: 10.3171/jns.1993.78.2.0233. PMID: 8421206. ("Barolat mapping")

Reply 1: *In the revamped introduction, we have incorporated valuable background information that traces the evolution and milestones in the development of SCS technology. This historical context not only provides a comprehensive foundation for our work but also enriches the reader's understanding of the significance of SCS in medical history.*

Moreover, we have dedicated substantial effort to exploring the current thoughts on the mechanism of action behind spinal cord stimulators. Understanding the intricacies of how SCS exerts its therapeutic effects is crucial for elucidating the potential benefits it offers. By delving into contemporary perspectives on its mechanism of action, we aim to present a well-rounded and informed discussion in our research.

Changes in the text:

Introduction

> “The exploration of targeting the spinal cord to modulate pain was initially introduced in a groundbreaking paper published by Science in 1965 (2). Over time, various treatments have emerged, including injection-based therapies and radiofrequency ablation, aiming at the spinal cord. While both treatment modalities may provide short-lived benefits, they often require frequent and ongoing procedures. In contrast, Spinal Cord Stimulation aims to overcome these limitations by offering longer-term pain relief with fewer necessary interventions.
>
> The placement of a SCS entails a subcutaneous implantable pulse generator connected to two electrodes, with leads extending into the epidural space posterior to the spinal cord dorsal columns. Although the exact mechanism underlying the pain-alleviating effects of SCS remains not fully understood, animal studies indicate the significance of the inhibitory neurotransmitter γ-amino butyric acid (GABA) in SCS analgesia (3).

Comment 2: Lines 77 to 86 involve a discussion on patient selection and alternative treatments to SCS. This deserves a more thorough discussion considering the case report is on an epidural hematoma in, a serious SCS complication. Your patient also had a malignancy, so it would be relevant to discuss how patients with malignancies or other co-morbid conditions may be more susceptible to SCS complications, including hematomas, lead migrations, infections, etc., and how this impacts the patient selection process.

Reply 2: *We have omitted the exploration of alternative treatments due to its extensive nature, recognizing its potential to be a standalone discussion. However, our attention has shifted significantly towards delving into the intricate medical complexities of the presented case and the associated recommended precautions.*

Our discussion now prominently centers around the critical aspect of patient selection criteria, with a heightened emphasis on the paramount importance of considering comorbid conditions within the context of this particular case. More specifically, our discussion meticulously outlines the patient's distinct comorbidities, conducting a comprehensive examination of how these conditions may impact the chosen treatment approach.

A noteworthy evolution in our discussion involves an in-depth analysis of existing literature and clinical studies, underscoring the significance of exercising due precautions before the placement of spinal cord stimulation (SCS), especially in high-risk populations with complex comorbidities.

Changes in the text:

Discussion

> "The American Society of Pain and Neuroscience (ASPN) acknowledges the need for clinical guidance in patients with chronic bleeding disorders. Lee et al. highlight the inadequacy of relying solely on common coagulation tests for pre-surgical assessment (18). The ASPN recommends detailed discussions and patient education, particularly in cases involving chronic bleeding disorders.
>
> The indications for the SCS trial were vague, with the patient managing chronic back pain with opiates and experiencing improvement with steroid injections. Minimal precautions were taken for severe medical comorbidities. The main precaution implemented involved the trial period of SCS. However, evaluating the effectiveness of the SCS trial encountered limitations due to its exceptionally short-term follow-up, potentially influenced by the placebo effect.
>
> Implications and actions needed: This Our case emphasizes the importance of impartially recognizing and assessing the risks associated with medical comorbidities when evaluating therapeutic benefits. In addition to preoperative discussions, it underscores the significance of promptly addressing neurological deficits following SCS placement to prevent severe consequences resulting from delayed diagnosis and treatment. To mitigate the risk of spinal epidural hematoma, particularly in patients with bleeding disorders, we concur with Traeger et al. in advocating for the restriction of SCS use to clinical trials until a proven therapeutic benefit is established (14)."

Comment 3: The case itself is extensively discussed with all important details mentioned. The image provides a good visual overview of the timeline of this case, but the timeline chart should be remodeled with a more professional font and layout, which would be more appropriate for this manuscript.

Reply 3: *We have remodeled the timeline chart for a more professional appearance.*

Changes in the text:

Comment 4: (Line 224) It would be more professional and appropriate to discuss this other case report without using only the first author's name, there are other authors involved as well who should be mentioned with "et al.". This differences between these two cases should also be discussed more in depth- why did the other case have a more favorable outcome? What other differences were there between the two cases in terms of patient co-morbidities, demographic, etc. Simply stating the outcome was more favorable is too vague.

Reply 4: *We have made sure the proper format when mentioning papers throughout the paper. As noted above in reply 2 for Reviewer A, a more thorough review of the literature regarding complications was undertaken to highlight the novelty of this case report. Additionally, the differences between the case report is discussed at length now.*

Changes in the text:

> "While extensively promoted as non-invasive and generally safe in various literature papers, SCS carry the potential for causing severe disability. Notably, there is a limited amount of reporting in the literature on permanent paraplegia arising from a SCS. To our knowledge, occurrences of hematoma in relation to SCS have been infrequently mentioned, and permanent paraplegia has never been discussed in the literature. Furthermore, a more thorough evaluation of the literature reveals that studies without financial interests show minimal therapeutic benefits.
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> This case report highlights the serious consequences of spinal cord epidural hematomas, an extremely uncommon event. Remarkably, the deficits observed in this case did not show swift resolution after decompression, which is a rarity in itself. Another notable aspect of this report is the detailed exploration of the patient's medical history and the discussion surrounding their eligibility as a SCS candidate.
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> The literature on hematomas associated with Spinal Cord Stimulation is limited. A retrospective analysis of 12,297 patients reported only 15 cases of hematomas within a 90-day period (15). A systematic review by West et al. found a hematoma incidence of less than 1%, with neuraxial hematomas occurring in less than 0.5% of cases (5). Notably, the study did not report any instances of permanent paraplegia due to neuraxial hematomas; a single case reported paraplegia, but the patient recovered after debridement with no significant deficits (16).
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> In the absence of specific guidelines for spinal epidural hematomas post SCS placement, we can adopt the recommended approach for managing spontaneous spinal epidural hematomas to mitigate potential adverse outcomes. A multicenter study conducted by Fukui et al. underscored the significance of the time elapsed from onset to debridement as a critical prognostic factor. In their findings, surgery was typically conducted around 24 hours after the onset of symptoms (17)."

Comment 5: There should also be more discussion on what changes have been adopted in the procedure to mitigate these complications and thus maximize the therapeutic effects of SCS. Simply stating that patients should be selected more carefully and that patients with multiple co-morbidities should be followed up more closely is too vague and doesn't add much to the current literature. Currently, there are several innovations in SCS aimed at reducing complication rates, including high frequency SCS, BURST SCS, and DRG stimulation. High frequency and BURST SCS have not been directly associated with bleeding complications, but DRG stimulation has been associated with decreased rates of lead migration and varying paresthesias with different body positions, and decreased lead migration may in turn reduce bleeding risk. It is pertinent to discuss such novel SCS techniques and whether they can potentially reduce the risk of hematoma formation following SCS implantation.

Reply 5: *Drawing upon an exhaustive analysis of existing literature, we meticulously dissected the advancements in spinal cord stimulation (SCS) techniques. Our introduction reflects a thorough exploration of high-frequency SCS, Burst SCS, and DRG stimulation, where each innovation was*

intricately examined for its potential impact on mitigating complications associated with traditional pain management methods.

Changes in the text:

Introduction

> "Several innovations in SCS focus on reducing complication rates. A widely accepted risk mitigation method involves a trial period for patient selection, where electrodes are temporarily placed in the epidural space, keeping the generator outside the body. In other innovative areas, the settings and electrical properties like high frequency and BURST SCS have been hypothesized to have an impact on complications (6). Additionally, dorsal root ganglion stimulation (DRG) has shown a decreased incidence of lead migration (7)."

Reviewer C

I would like to commend the authors for be transparent and sharing information about a serious and uncommon/unexpected complication. It is extremely important that serious adverse events following spinal cord stimulation such as this are presented. Still, I believe the manuscript can be improved by placing the treatment, SCS for back pain, in an evidence-based setting.

Comment 1: Abstract: The authors state that SCS is a valuable tool for managing chronic neuropathic pain. Although SCS is an increasingly used therapy, its efficacy has never been demonstrated. The abstract should be revised accordingly.

Reply 1: *We revised the paper, placing a stronger emphasis on the poorly demonstrated therapeutic benefits of Spinal Cord Stimulation (SCS). After a comprehensive review, we recognized the importance of highlighting this aspect throughout the abstract and, consequently, the entire paper.*

The revised abstract now delves deeper into the inadequacies surrounding the documentation of therapeutic outcomes in the context of SCS. By meticulously rephrasing key sections, we aimed to underscore the existing gaps in the literature and emphasize the need for further research to substantiate the therapeutic efficacy of SCS. This approach not only strengthens the overall argument but also positions our work as a valuable contribution to the ongoing discourse on this subject.

Throughout the paper, we have woven a narrative that consistently reinforces the notion of the poorly demonstrated therapeutic benefits of SCS. By revisiting each section and refining the language to align with this central theme, we believe we can better engage our audience and prompt them to critically examine the existing evidence. This, in turn, sets the stage for a more compelling and impactful discussion on the potential shortcomings and areas for improvement within the field.

Changes in the text:

Abstract

"Background: Spinal cord stimulators (SCS) have gained widespread popularity as an intriguing tool for managing chronic neurogenic pain. Despite the growing adoption of SCS as a therapeutic approach, there is a lack of demonstrated efficacy. The clinical utilization of SCS is on the rise, despite potential severe complications and the absence of clear evidence supporting its therapeutic benefits.

Case Description: We present a challenging case of acute spinal epidural hematoma secondary to SCS placement in a liver transplant recipient. The patient exhibited acute bilateral leg weakness, sensory deficits, and urinary dysfunction, two days after SCS placement. Urgent surgical decompression was performed three days after the permanent placement of the SCS. Even with multiple debridement procedures the patient did not regain any function and remained paraplegic. This case underscores the importance of vigilant monitoring post operatively and timely intervention when epidural hematomas develop.

The patient's intricate medical background, encompassing liver transplantation and chronic immunosuppression, contributed to the complexity of the case. Given these evident co-morbidities, the justification for SCS should have been unequivocal. However, what we observe is a vague clinical indication with minimal consideration for the associated risks.

Conclusions: This case highlights the need for cautious consideration of SCS due to its serious and lasting side effects in treating chronic back pain. Surgeons should reevaluate the widespread use of SCS, advocating for reserved usage in controlled trials until therapeutic benefits are firmly established. Despite potential pain relief, the risk of complications, including spinal epidural hematoma, should not be underestimated. Further research is urged to understand therapeutic benefits and assess short- and long-term complications comprehensively."

Comment 2: Key points: The authors state that the benefits of spinal cord stimulators outweigh the risks. This statement is unwarranted and should be removed. The efficacy of SCS beyond placebo has never been proven, whereas complications are well-documented.

Reply 2: *We have carefully revised the contents of the highlighted box, focusing on the removal of an unwarranted statement that previously suggested the benefits of SCS outweigh its risks without proper substantiation. In this revision, we have ensured the current most accurate literature.*

Changes in the text:

Highlight box

"Key Findings:

- Rare case report of SCS placement leading to spinal epidural hematoma with resulting permanent paraplegia.
- Even with decompression within 24 hours, the reversal of paraplegia may not be guaranteed.

What is known?

- Reoperation after SCS is common, often due to lead migration or misplacement; SCS have significant risks such as epidural hematoma, but permanent deficits are rarely reported.
- The benefits of SCS beyond placebo are unclear, with recent Cochrane reviews questioning previous literature, and a recent RCT showing no difference between SCS and placebo

What is the implication and what should change now?

- Restrict SCS use to controlled trials pending additional research on therapeutic benefits.
- Conduct short-term and long-term studies on SCS patients, particularly those with complex medical histories, to assess complications and long-term risks. Implement closer outpatient follow-up within 3 days of SCS placement to identify potential complications early."

Comment 3: The authors need to discuss and acknowledge the following issues concerning the patient history presented:

a. The indication for surgery was dubious

b. Should SCS be provided to patients with serious comorbidity (liver adenocarcinoma, cirrhosis, liver transplant, alcohol abuse etc.) and high risk of coagulopathy?

Reply 3: *After major revisions to the paper, we attribute the occurrence of this adverse event primarily to the patient's inadequate selection process and imprecise surgical indication. In our discussion, we now emphasize the significance of the patient's medical history, the ambiguity surrounding the surgical recommendation, and the presence of extensive medical co-morbidities. Furthermore, we have conducted a thorough literature search to identify recommendations tailored to this specific patient population.*

Changes in the text:

Discussion

> "The American Society of Pain and Neuroscience (ASPN) acknowledges the need for clinical guidance in patients with chronic bleeding disorders. Lee et al. highlight the inadequacy of relying solely on common coagulation tests for pre-surgical assessment (18). The ASPN recommends detailed discussions and patient education, particularly in cases involving chronic bleeding disorders.
>
> The indications for the SCS trial were vague, with the patient managing chronic back pain with opiates and experiencing improvement with steroid injections. Minimal precautions were taken for severe medical comorbidities. The main precaution implemented involved the trial period of SCS. However, evaluating the effectiveness of the SCS trial encountered limitations due to its exceptionally short-term follow-up, potentially influenced by the placebo effect.
>
> Our case emphasizes the importance of impartially recognizing and assessing the risks associated with medical comorbidities when evaluating therapeutic benefits. In addition to preoperative discussions, it underscores the significance of promptly addressing neurological deficits following SCS placement to prevent severe consequences resulting from delayed diagnosis and treatment. To mitigate the risk of spinal epidural hematoma, particularly in patients with bleeding disorders, we concur with Traeger et al. in advocating for the restriction of SCS use to clinical trials until a proven therapeutic benefit is established (14)."

Comment 4: Discussion: The authors need to discuss the use of SCS for back pain in light of the best available evidence.

a. The recent trial by Hara et al (1), published in JAMA, was the first placebo-controlled trial of SCS from a team without financial conflicts. It successfully blinded patients, surgeons, investigators, and the trial statistician. The trial found no benefit of SCS on pain, disability outcomes, and physical activity levels in

patients with persistent radicular pain following spine surgery. The improvement experienced by patients was just as large during placebo (i.e., no stimulation) and active stimulation. In this trial the stimulation settings were as recommended by the manufacturer. In the 6-month follow-up study (2), also published in JAMA, there was no benefit of allowing patients to control their own stimulation settings.

b. The most recent Cochrane review (Traeger el al, 2023) (3) and earlier reviews by O'Connell et al (4) and Knotkova et al (5) found evidence of no benefit on back pain. In a large real-world study (6), Dhruva et al found that SCS was not associated with a reduction in opioid use or nonpharmacologic pain interventions at 2 years. SCS was associated with higher costs, and SCS-related complications were common.

c. The authors also need to reflect on whether SCS should be provided outside well-designed placebo-controlled trials at all. (7) The efficacy of SCS beyond placebo has never been proven, whereas complications are well-documented. As it stands, SCS represents no- or low-value-care and this case report clearly demonstrates that serious unintended harm to patients is possible.

1. Hara S, Andresen H, Solheim O, et al. Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial. Jama 2022;328:1506-14.

2. Hara S, Andresen H, Solheim O, et al. Six-Month Follow-up of a Trial of Spinal Cord Burst Stimulation vs Placebo Stimulation and Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery. Jama 2023;329:1985-6.

3. Traeger AC, Gilbert SE, Harris IA, Maher CG. Spinal cord stimulation for low back pain. Cochrane Database Syst Rev 2023;3:Cd014789.

4. O'Connell NE, Ferraro MC, Gibson W, et al. Implanted spinal neuromodulation interventions for chronic pain in adults. Cochrane Database Syst Rev 2021;12:Cd013756.

5. Knotkova H, Hamani C, Sivanesan E, et al. Neuromodulation for chronic pain. Lancet 2021;397:2111-24.

6. Dhruva SS, Murillo J, Ameli O, et al. Long-term Outcomes in Use of Opioids, Nonpharmacologic Pain Interventions, and Total Costs of Spinal Cord Stimulators Compared With Conventional Medical Therapy for Chronic Pain. JAMA Neurol 2023;80:18-29.

7. Traeger AC, Bero LA. Corporate Influences on Science and Health-the Case of Spinal Cord Stimulation. JAMA Intern Med 2023.

Reply 4: *We have meticulously revised the content of the paper, resulting in significant enhancements in the abstract, discussion, and conclusion. Notably, we delved deeper into the current literature. Now, the discussion segment seamlessly integrating compelling evidence gleaned from recent trials, notably those conducted by Hara et al. The infusion of data from authoritative reviews, such as Traeger et al.,*

O'Connell et al., Knotkova et al., and Dhruva et al., has substantially augmented the depth and credibility of the discourse.

In particular, we have conscientiously addressed the imperative to circumscribe the application of Spinal Cord Stimulation (SCS) to clinical trials, emphasizing the pivotal necessity to establish a verifiable therapeutic benefit before widespread adoption. This stance is underscored by the comprehensive insights derived from Hara et al.'s trials and the nuanced analyses provided in the reviews by Traeger et al., O'Connell et al., Knotkova et al., and Dhruva et al.

The revised discussion section is now a formidable synthesis of empirical evidence and expert opinions, ensuring the paper not only aligns with the latest research but also advances a judicious and scientifically sound perspective. By acknowledging the prevailing uncertainties surrounding the therapeutic efficacy of SCS, the conclusion has been reframed to underscore the prudence of limiting its usage to controlled clinical settings. This nuanced approach positions the paper at the forefront of current discourse, contributing substantially to the ongoing dialogue on the appropriate use of SCS in the medical field.

Changes in the text:

Discussion

While the theoretical framework behind these devices appears highly promising, the data supporting their efficacy is less conclusive. The literature on SCS presents a distinct dichotomy, possibly attributed to the robust theoretical foundation coupled with compelling incentives for the companies involved.

The growing utilization of spinal cord stimulation can be linked to misleading assertions propagated by studies marked with significant bias and flawed methodologies (1). In a 2019 study by Lamer et al., spinal stimulation showed a higher responder rate and pain improvement, but 11 of the 12 studies were industry-sponsored. The only non-industry sponsored study found no difference in outcomes. The overall quality assessment using AMSTAR-2 rated it as moderate (8). Another study in 2020 by Duarte et al. reported a reduction in pain scoring with a greater effect than placebo. However, this review received a low to moderate AMSTAR-2 rating due to conflicts of interest among authors and poor methodology (9).

In 2021, Connell et al. published an intervention review with a robust methodology. In their study, they found all RCT results to have a high risk of bias (10). They also found poor quality and large inconsistencies in the reporting of adverse events. The authors' conclusions were:

> *"We found very low-certainty evidence that SCS may not provide clinically important benefits on pain intensity compared to placebo stimulation." (10)*

Following the insightful findings of Connell et al., a clear demand arose for unbiased randomized control trials. In response, Hara et al. conducted a placebo-controlled, crossover, randomized clinical trial published in JAMA in 2022. Involving 50 patients, the study revealed no significant difference in self-reported back pain change from baseline (11). Notably, Hara et al.'s study was the first to publish intermediate results of such a trial. At the 6-month follow-up, no significant difference in pain-related disability was observed among the 34 patients who completed post-trial follow-up (12).

Long-term outcomes were also assessed in the large retrospective comparative analysis by Dhruva et al. (13). In the propensity-matched population of 7560 patients, they found SCS placement was not associated with a reduction in opioid use or nonpharmacologic pain interventions at 2 years.

Expanding upon Connell et al.'s seminal systematic review, Traeger et al. conducted a comparable review. Like Connell's study, Traeger identified a significant prevalence of high detection and performance bias in the randomized control trials they examined, attributed to insufficient blinding and selective reporting (14). The authors drew similar conclusions from their findings:

> *"Data in this review do not support the use of SCS to manage low back pain outside a clinical trial. Current evidence suggests SCS probably does not have sustained clinical benefits that would outweigh the costs and risks of this surgical intervention." (14)*

Conclusion

"This case underscores the imperative for exercising heightened caution when considering the utilization of SCS. The gravity of the serious and enduring side effects necessitates thorough deliberation when opting for SCS over medical management in the treatment of chronic back pain. Our case report emphasizes the need for surgeons to reassess the widespread application of SCS, advocating for its reserved use in controlled trials until the therapeutic benefits are unequivocally established.

While SCS have the potential to offer pain relief, it is imperative not to underestimate the potential complications, such as spinal epidural hematoma. There is a call for further research to gain a deeper understanding of the genuine therapeutic benefits and to comprehensively evaluate the potential for serious complications in both the short and long term."