











Neuromodulation: a new approach for chronic pain relief in patients with sickle cell anemia

Teuromodulación: un nuevo enfoque para el alivio del dolor crónico en pacientes con anemia falciforme

Neuromodulação: uma nova abordagem para o alívio da dor crônica em pacientes com anemia falciforme

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ABSTRACT

The implementation of neuromodulators in the central nervous system aims to advance the treatment of chronic pain associated with sickle cell anemia. The progression of painful crises over time, combined with increased opioid use for pain control, highlights the urgent need for new therapeutic alternatives. These new options are essential to improve the quality of life for patients, who often face daily challenges related to pain management. Neuromodulation, by acting directly on the central nervous system, offers a promising approach with the potential to reduce opioid dependence and minimize its adverse effects, such as addiction and tolerance. By providing more lasting and effective relief, this strategy allows for continuous pain control, offering patients a safer alternative. The use of neuromodulators can transform how chronic pain is approached, promoting not only pain reduction but also an overall improvement in functionality and quality of life. Studies have shown that neuromodulation can be a viable and effective option for patients who do not respond adequately to traditional therapies. Furthermore, the long-term safety and efficacy of this technology are areas of growing interest in the medical community. This analysis is expected to highlight the benefits of this innovative approach, contributing to a greater understanding and dissemination of its use in chronic pain treatment, particularly in individuals suffering from sickle cell anemia, a debilitating condition that significantly affects their lives.

Keywords: neuromodulation; opioids; dependence; CNS; sickle cell anemia.

RESUMEN

La implementación de neuromoduladores en el sistema nervioso central tiene como objetivo promover avances en el tratamiento del dolor crónico asociado a la anemia falciforme. La progresión de las crisis dolorosas a lo largo del tiempo, junto con el aumento del uso de opioides para el control del dolor, pone de manifiesto la necesidad urgente de nuevas alternativas terapéuticas. Estas nuevas opciones son esenciales para mejorar la calidad de vida de los pacientes, quienes a menudo enfrentan desafíos diarios relacionados con el manejo del dolor. La neuromodulación, al actuar directamente sobre el sistema nervioso central, ofrece un enfoque prometedor con el potencial de reducir la dependencia de opioides y minimizar sus efectos adversos, como la adicción y la tolerancia. Al proporcionar un alivio más duradero y eficaz, esta estrategia permite un control continuo del dolor, ofreciendo a los pacientes una alternativa más segura. El uso de neuromoduladores puede transformar la manera en que se aborda el dolor crónico, promoviendo no solo la reducción del dolor, sino también una mejora general de la funcionalidad y de la calidad de vida. Los estudios han demostrado que la neuromodulación puede ser una opción viable y eficaz para los pacientes que no responden adecuadamente a las terapias convencionales. Además, la seguridad y la eficacia de esta tecnología a largo plazo constituyen áreas de creciente interés en la comunidad médica. Se espera que este análisis destaque los beneficios de este enfoque innovador, contribuyendo a una mayor comprensión y

difusión de su uso en el tratamiento del dolor crónico, especialmente en personas con anemia falciforme, una condición debilitante que afecta significativamente sus vidas.

Palabras clave: neuromodulación; opioides; dependencia; Sistema Nervoso Central (SNC); anemia falciforme.

RESUMO

A implementação de neuromoduladores no sistema nervoso central tem como objetivo promover avanços no tratamento da dor crônica associada à anemia falciforme. A progressão das crises dolorosas ao longo do tempo, aliada ao aumento do uso de opioides para o controle da dor, evidencia a necessidade urgente de novas alternativas terapêuticas. Essas novas opções são essenciais para melhorar a qualidade de vida dos pacientes, que frequentemente enfrentam desafios diários relacionados ao manejo da dor. A neuromodulação, ao atuar diretamente no sistema nervoso central, oferece uma abordagem promissora com potencial para reduzir a dependência de opioides e minimizar seus efeitos adversos, como dependência química e tolerância. Ao proporcionar um alívio mais duradouro e eficaz, essa estratégia permite um controle contínuo da dor, oferecendo aos pacientes uma alternativa mais segura. O uso de neuromoduladores pode transformar a forma como a dor crônica é tratada, promovendo não apenas a redução da dor, mas também uma melhora geral da funcionalidade e da qualidade de vida. Estudos demonstram que a neuromodulação pode ser uma opção viável e eficaz para pacientes que não respondem adequadamente às terapias convencionais. Além disso, a segurança e a eficácia dessa tecnologia em longo prazo constituem áreas de crescente interesse na comunidade médica. Espera-se que esta análise destaque os benefícios dessa abordagem inovadora, contribuindo para uma maior compreensão e disseminação de seu uso no tratamento da dor crônica, especialmente em indivíduos com anemia falciforme, uma condição debilitante que afeta significativamente suas vidas.

Palavras-chave: neuromodulação; opioides; dependência; Sistema Nervoso Central; anemia falciforme.

1. INTRODUCTION

Using neuromodular implants has emerged as a promising and effective approach for treating chronic pain, especially compared to the prolonged use of analgesic medications. These medications often lead to toxic effects and reduce patients' quality of life. Chronic pain, characterized by its persistence and resistance to conventional treatment, can result in a vicious cycle of excessive opioid and other medication use. This leads to complications like dependence, side effects, and decreased efficacy over time due to tolerance.

On the other hand, neuromodular implants are gaining prominence. These devices act directly on the central nervous system (CNS), modulating neuronal activity through electrical

stimuli. This technology offers a safer and more effective long-term alternative for pain treatment. The devices are typically implanted surgically in specific body areas and send electrical impulses to the nervous system, interfering with the transmission of pain signals to the brain. This allows for a significant reduction in pain without the adverse effects commonly associated with prolonged medication use.

Recent studies indicate that neuromodular implants can provide pain improvement in over 60% of cases, with benefits extending for years, offering continuous relief for patients suffering from conditions like chronic lower back pain, neuropathies, and pain related to disorders such as sickle cell anemia. This condition, in particular, is marked by recurrent painful crises and the frequent need for opioid analgesics. Neuromodulation offers a treatment option that can reduce dependence on these medications, thereby minimizing the risks of side effects like sedation, constipation, physical dependence, and even overdose.

Moreover, neuromodulation positively impacts patients' quality of life, allowing them to resume daily and social activities previously limited by chronic pain. By reducing the need for opioids and other CNS-affecting medications, patients also experience cognitive and emotional improvement. This is particularly relevant in cases of chronic pain, where the psychological impact can be devastating, leading to disorders like depression and anxiety. Another important aspect is that neuromodular implants are adjustable, allowing healthcare professionals to calibrate the intensity of electrical stimuli according to each patient's individual response. This flexibility is crucial to ensure that treatment remains effective as the patient's body adapts or the painful condition progresses. However, the success of neuromodulation treatment depends on appropriate patient selection, preliminary tests (such as temporary neuromodulation), and continuous follow-up by a multidisciplinary healthcare team.

Despite the numerous benefits, it's important to note that neuromodulation is not without risks. Like any invasive procedure, there is potential for complications such as infections, mechanical device failures, or adverse reactions to the implant. Therefore, a careful evaluation of the patient's profile is essential to ensure that neuromodulation is the best therapeutic option.

Neuromodulation has proven to be an effective and safe alternative to medication for chronic analgesia. With its ability to provide pain relief without the toxic effects of traditional analgesics, this technology offers a significant improvement in patients' quality of life. It's especially useful in cases of refractory pain and difficult-to-control conditions, such as sickle cell anemia and other chronic neuropathies. Continued research and technological advancements will undoubtedly further expand the possibilities of this treatment in the coming years.

2. COMPARISON BETWEEN NEUROMODULAR IMPLANTS AND PHARMACOLOGICAL TREATMENT FOR ANALGESIA: EFFICIENCY AND REDUCTION OF TOXIC EFFECTS

The use of neuromodular implants has shown great efficacy in treating chronic pain, offering an alternative to the prolonged management with analgesic medications, which often produce toxic pharmacological effects. While medications can cause dependence, tolerance, and other adverse effects over time, neuromodular implants act directly on the nervous system, modulating pain signals and providing continuous relief. Studies indicate a significant improvement in pain in over 60% of patients undergoing this type of therapy. In addition to reducing the need for opioids, this approach improves quality of life, allowing for greater pain control with fewer side effects and longer-lasting benefits (Walter *et al.*, 2010).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line treatment for chronic pain can provide temporary relief, but the prolonged use of these medications is associated with significant risks. Delirium, especially in the elderly, and the development of various morbidities are important clinical concerns. Furthermore, the continuous use of drugs like diclofenac sodium and ibuprofen has been widely correlated with an increased risk of cardiovascular diseases, such as heart attacks and hypertension, as well as gastrointestinal complications, including ulcers and hemorrhages. Thus, the inadequate management of these medications can worsen patients' health conditions instead of improving them (Olivênia *et al.*, 2018).

Chronic pain associated with sickle cell anemia (SCA), especially during crises, can reach almost unbearable levels, profoundly affecting patients' quality of life. In these situations, there's an escalation in medication use, often requiring more potent analgesics, antidepressants, and opioids. Although these treatments provide relief, prolonged opioid use increases the risk of dependence and respiratory depression, severe complications that can further compromise patient health. Additionally, this predisposition to addiction and the adverse effects of opioids reinforce the need for safer and more effective therapeutic alternatives in chronic pain management (Brasil, 2024).

Over the years, various research has been conducted on SCA, aiming to improve pain treatment and reduce red blood cell sickling. As a result of these advancements, the Clinical Protocol and Therapeutic Guidelines (PCDT) for SCA was updated to include hydroxyurea as a therapeutic option. Originally used as a chemotherapeutic agent for leukemia, hydroxyurea demonstrated significant efficacy in treating sickle cell anemia, helping to decrease the frequency of pain crises and complications associated with the disease. Its inclusion in the list of available medications represents an important advance for the clinical management of SCA, improving patients' quality of life (Rodrigues, 2023).

Prolonged use of hydroxyurea in treating sickle cell anemia, while effective in reducing crises, can be associated with hematological complications, such as polycythemia vera, a condition where there is an excessive production of blood cells. Although this condition

is treatable, clinical studies indicate that, in some patients, long-term hydroxyurea use can progress to leukemia, becoming a relevant risk for certain individuals. Therefore, despite the benefits in managing sickle cell anemia, regular patient monitoring is crucial to monitor for possible adverse effects and adjust treatment as needed (Araujo *et al.*, 2015).

Spinal cord stimulation (SCS), also known as pain neuromodulation, has emerged as an effective alternative in chronic pain control, especially in cases where prolonged opioid use causes significant damage to the body. This technique involves implanting electrodes in the spinal cord, which are connected to a generator implanted in the patient's body. The generator sends electrical impulses that interfere with pain signals sent to the brain, alleviating discomfort without the need for medication. Neuromodulation has been an increasingly used option to reduce the risks associated with prolonged opioid use and improve patients' quality of life (Andrade; Soares; Oliveira, 2022).

Before initiating the pain neuromodulation process, it's necessary to verify if the patient meets the clinical criteria for receiving the spinal implant. This treatment is indicated for conditions such as complex regional pain syndrome, post-laminectomy syndrome, neuropathic pain associated with vasculopathy, radiating pain, and other forms of difficult-to-manage chronic pain. After evaluation and approval for the procedure, the preparation phase for the trial begins. In this stage, the patient undergoes surgery where electrodes are implanted in the spinal cord, but the electrical impulse generator remains external to the body. This allows the doctor to adjust and regulate the electrical stimuli according to the patient's response to therapy, ensuring that pain control is optimized before the permanent installation of the internal generator. The trial typically lasts three to seven days, being crucial to ensure treatment efficacy before definitive surgery. Inclusion and exclusion criteria are established in Table 1 (Oliveira Júnior; Corrêa; Ferreira, 2016).

Table 1 - Inclusion and Exclusion Criteria for Sickle Cell Anemia Patients Who Are Candidates for Neuromodulation Treatment.

Inclusion Criteria	Exclusion Criteria
Patients with sickle cell anemia experiencing chronic pain refractory to conventional treatments, including opioids and anti-inflammatory drugs.	Patients with severe uncontrolled psychiatric disorders, such as severe depression or psychosis.
Presence of frequent painful crises, especially those that affect quality of life and do not respond to other treatments.	Patients with active infections, such as osteomyelitis, which may increase the risk of implant complications.
History of adverse response or adverse effects to prolonged opioid use.	Patients with allergy or intolerance to the materials of the electrodes or the neuromodulator generator.
Patient's ability to understand and adhere to post-operative follow-up, including neuromodulation adjustments.	Patients with severe coagulation disorders that may compromise the surgical process.

Indication of neuropathic or musculoskeletal pain of central origin associated with sickle cell anemia.	Patients with a contraindication to surgery or who cannot undergo the implant due to severe comorbidities.
Clinical stability and ability to tolerate test surgery and definitive implant.	Patients using anticoagulants without the possibility of temporary suspension for the surgical procedure.

Source: (Gallach-Solano; Morales Suárez-Varela, 2016).

In Table 1, you've listed the criteria that include or exclude patients as candidates for a spinal neurostimulator implant. These criteria are categorized by psychopathological profile, personality, comorbidity, social profile, cognitive dimension, and emotional dimension. Based on each sub-criterion, it's determined whether patients are suitable for spinal implant use (Gallach-Solano; Morales Suárez-Varela, 2016).

The context of using spinal neuromodulators in chronic pain treatment is crucial for understanding how the body reacts to painful stimuli. When a patient with severe neuropathy experiences pain, nerve endings in the limbs send signals to the spinal cord, which acts as a relay center. This spinal cord then carries the command to the brain, where the pain sensation is processed and interpreted. The brain, upon receiving these signals, informs the patient about the discomfort, allowing them to decide how to respond to the pain. This communication among nerve endings, the spinal cord, and the brain is fundamental for pain perception. Thus, neuromodulators have the potential to interrupt or alter this signal transmission, offering an effective alternative for chronic pain relief by reducing the intensity of signals reaching the brain and, therefore, improving patients' quality of life (Rodrigues, 2022).

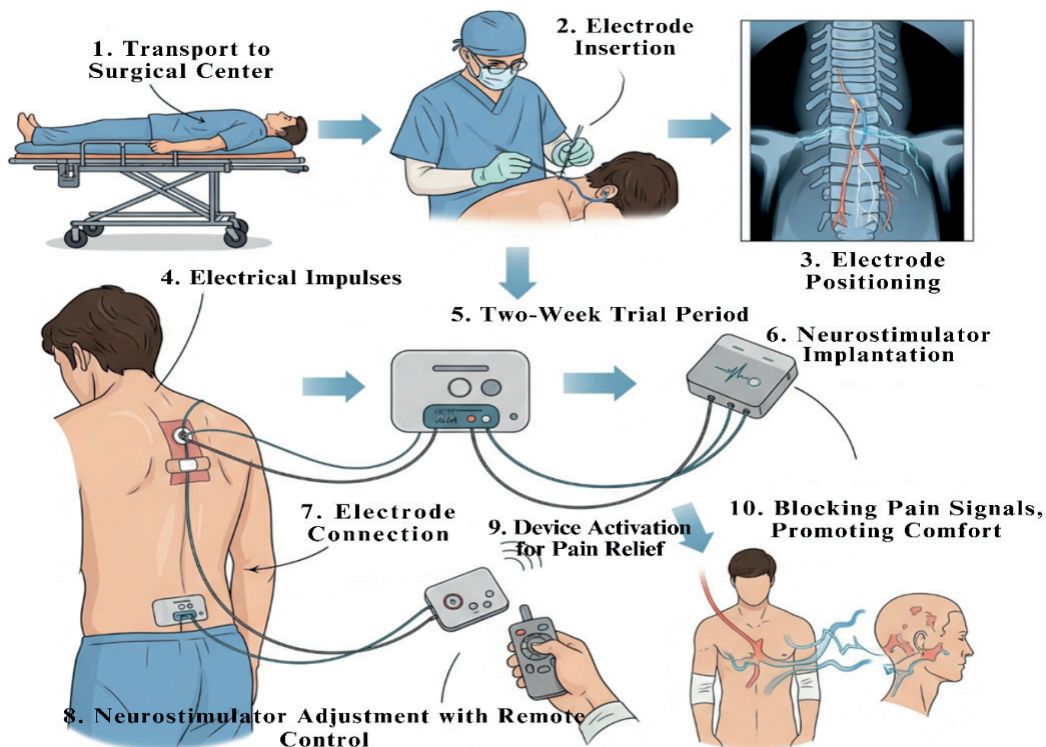
With the implantation of electrodes and the generator, a new mechanism for pain relief is established. When nerve endings send signals to communicate the presence of pain to the brain, these commands are intercepted by the electrodes installed in the spinal cord. This process prevents the brain from receiving severe pain information from the affected region. In this way, neuromodulation effectively blocks the transmission of painful signals, allowing the patient to experience a significant reduction in pain. This innovative technique not only improves quality of life but also enables an alternative approach to treating chronic conditions, minimizing reliance on opioids and other analgesics (Rodrigues, 2022).

Table 2 - Process of Neuromodulator Implantation.

Step	Description
1. Transport to Surgical Center	The patient is taken to the surgical center, where they will be prepared for the procedure.
2. Electrode Insertion	Through an incision, the electrodes are inserted into the spinal column.
3. Electrode Positioning	With the aid of X-rays, the electrodes are precisely positioned next to the spinal cord.
4. Electrical Impulses	Electrical impulses are sent through the electrodes to the spinal cord.
5. First Surgery (Trial)	The neuromodulator's generator is positioned externally for a two-week initial trial period.
6. Verification and Definitive Implant	After the trial period, if the patient responds well to the treatment, the generator is definitively implanted inside the body.
7. Electrode Connection	The implanted generator is connected to the electrodes, and the incision is closed.
8. Adjustments	Necessary configurations are made to the device with the aid of an external control.
9. Device Activation	When the patient feels pain, the device is activated, and the electrical impulses are adjusted to control the pain.
10. Blocking Pain Signals	The electrical impulses interrupt the pain signals sent from the affected limbs, providing comfort.

Source: (Adapted). Oliveira, 2023.

The neuromodulator implantation process involves surgery to place the electrodes and generator, a trial period to check treatment efficacy, and finally, device activation to control chronic pain, as seen in Image 1 (Chiote, 2021).

Image 1 - Spinal Neurostimulator Implantation for Chronic Pain Relief: A 10-Step Process

Source: (Adapted). Author, 2025

Subsequently, in the definitive surgery, the patient receives a device where they can control the intensity of the electrical impulses, turn it on or off, and choose pre-programmed stimulation settings determined by their attending physician. The generator is charged by induction, and only the external control and induction antenna can charge this generator. The external control, however, can be charged normally via a wall outlet, so it is always ready to power the generator and apply programming adjustments when needed. With the implementation of this technology for pain control, it has been verified that these devices are highly recommended for the treatment of chronic pain, based on patient reports regarding their practicality and responsiveness to treatment (Rodrigues *et al.*, 2022).

CONCLUSION

Neuromodulation has emerged as a promising alternative to long-term pharmacological treatment for chronic pain, especially when compared to opioids and analgesics, which carry significant risks of adverse effects. Given the high probability of toxicity associated with prolonged analgesic use and the risk of opioid dependence, the search for safer and more effective interventions is essential, particularly in patients with severe conditions like sickle cell anemia. However, the efficacy of spinal cord stimulation can vary among patients, requiring more research to identify those with the highest chance of a positive response, in addition to addressing the high costs of the procedure that limit access.

Despite the challenges, spinal cord stimulation emerges as an innovative solution to intercept pain signals before they reach the brain, offering considerable relief. The improvement in patients' quality of life, coupled with the reduction in medication dependence and side effects, is one of the main benefits of this approach. To ensure the viability of this technology for sickle cell anemia patients and for society, it is fundamental to improve patient selection criteria and increase accessibility and cost reduction. Furthermore, close post-operative follow-up should consider not only pain but also other aspects of quality of life, such as social and emotional well-being. Thus, neuromodulation can consolidate itself as an essential therapeutic tool in chronic pain management.

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