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Multimodal sedation guided by processed electroencephalography and autonomic nervous system monitoring for spinal cord stimulator implantation: retrospective identification of anesthetic drug doses

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Porto, 1 de junho de 2026

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Ao Dr. Francisco Lobo, um agradecimento especial pela oportunidade de realizar o estágio na Cleveland Clinic Abu Dhabi. A experiência proporcionada durante esse período constituiu um marco importante na minha formação médica, permitindo-me contactar com uma realidade clínica e científica inovadora, participar no meu primeiro projeto de investigação clínica e contribuir para um trabalho que viria a culminar na publicação do artigo que integra esta dissertação. O impacto desta experiência ultrapassou largamente o período do estágio, influenciando de forma significativa o meu percurso académico e pessoal.

À minha família, em especial à minha irmã Bia, aos meus pais e ao Tiago, as palavras não chegam para agradecer todo o apoio, compreensão e incentivo ao longo deste percurso. Obrigada por acreditarem sempre em mim e por estarem presentes em todos os momentos ao longo de toda a minha vida.

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“Tenho em mim todos os sonhos do mundo.”

— Fernando Pessoa

CONTEXTUALIZAÇÃO DO ESTÁGIO E ENQUADRAMENTO DA DISSERTAÇÃO

A presente dissertação tem como elemento central o artigo científico desenvolvido durante o estágio clínico que realizei na Cleveland Clinic Abu Dhabi (CCAD), no Anesthesiology Institute – Division of General Anesthesia entre 12 de fevereiro e 8 de março de 2024, sob a orientação do Dr. Francisco Lobo.

A oportunidade de realizar este estágio surgiu após a participação numa sessão promovida pelo ICBAS, dedicada a médicos portugueses que desenvolvem a sua atividade profissional no estrangeiro. Um dos oradores era o Dr. Francisco Lobo, naquele momento, anestesiologista na CCAD. O seu testemunho e o contacto com a realidade profissional e científica da CCAD despertaram o meu interesse, o que motivou o contacto com o Dr. Francisco e permitiu posteriormente a concretização desta oportunidade de formação.

A escolha da Anestesiologia prendeu-se com facto de ser uma das áreas médicas que mais desperta o meu interesse enquanto opção de futura especialidade, tornando particularmente relevante a possibilidade de contactar de forma próxima com a prática clínica e a investigação desenvolvidas num centro de referência mundial.

Durante o período de estágio, acompanhei a atividade clínica do Serviço de Anestesiologia no contexto de bloco operatório, observando diferentes técnicas anestésicas e participando na monitorização perioperatória dos doentes. Tive igualmente a oportunidade de assistir a alguns dos procedimentos de implantação de estimuladores medulares que deram origem ao estudo apresentado neste artigo. Paralelamente, participei na recolha, organização e tratamento dos dados clínicos utilizados na investigação. Após o regresso a Portugal, mantive colaboração com a equipa de investigação durante as diferentes fases de desenvolvimento do manuscrito científico, acompanhando o processo que culminou na sua publicação.

Este trabalho constituiu o meu primeiro contacto direto com a investigação clínica e permitiu-me compreender o processo de desenvolvimento de um projeto científico, desde o acompanhamento dos procedimentos cirúrgicos que deram origem ao estudo, até à publicação dos seus resultados.

O principal resultado académico deste estágio foi a publicação do artigo científico apresentado nesta dissertação, do qual sou coautora. O artigo foi publicado a 28 de agosto de 2025 na revista *Journal of Anesthesia, Analgesia and Critical Care* (IF 3.1). Atendendo ao facto de se tratar de um artigo científico já publicado e sujeito a revisão por pares, optou-se por incluir neste relatório a sua versão integral, preservando a estrutura e o formato originais da publicação.

RESUMO

Introdução

A estimulação medular (Spinal Cord Stimulation – SCS) é uma técnica validada para o tratamento da dor crónica refratária, habitualmente realizada em duas fases: uma fase inicial de teste, com colocação temporária do estimulador para avaliação da resposta clínica, seguida da implantação definitiva do dispositivo nos doentes que apresentam melhoria significativa da dor.

A colocação dos elétrodos requer habitualmente sedação e analgesia, sendo necessária uma fase de despertar intraoperatório para confirmar a posição ideal dos elétrodos através do feedback do doente.

Este trabalho descreve uma abordagem inovadora de sedação e analgesia multimodal baseadas em infusões alvo-controladas de propofol, remifentanil e dexmedetomidina, complementadas por bólus de cetamina, guiadas por monitorização eletroencefalográfica e do equilíbrio nociceção–antinociceção.

Métodos

Foi realizado um estudo de coorte retrospetivo, unicêntrico, incluindo todos os procedimentos de estimulação medular, tanto procedimentos de teste como implantes definitivos. Foi utilizado um protocolo anestésico padronizado, administrado por um único anestesiologista, baseado em infusões alvo-controladas de propofol, remifentanil e dexmedetomidina, complementadas com bólus de cetamina. O nível de sedação foi avaliado através da monitorização do eletroencefalograma processado e o balanço nocicepção-antinociceção através da actividade do Sistema Nervoso Autónomo usando o Índice de Analgesia Nocicepção (ANI). Foram recolhidos dados relativos às doses de cada fármaco administradas, concentrações *effect-site* dos fármacos, tempo até ao despertar intraoperatório, estabilidade hemodinâmica e necessidade de intervenção sobre a via aérea.

Resultados

Foram analisados um total de 25 procedimentos (11 testes e 14 implantes definitivos) realizados em 21 doentes, tendo 4 doentes sido submetidos a ambas as fases do procedimento. Todos os pacientes receberam o mesmo esquema farmacológico baseado em quatro fármacos. As concentrações *effect-site* medianas (intervalo interquartil) minimas e máximas do propofol necessárias para atingir um nível adequado de sedação (nível −4 da Escala de Agitação- Sedação de Richmond) foram de 1 (0,5) µg/mL e 1,5 (0,8) µg/mL, respetivamente. As concentrações *effect-site* medianas (intervalo interquartil)

mínimas e máximas de remifentanil necessárias para assegurar uma antinociceção adequada (Índice de Analgesia-Nocicepção entre 50 e 70) foram de 0,5 (0,3) ng/mL e 1,2 (0,4) ng/mL, respetivamente. As concentrações *effect-site* medianas (intervalo interquartil) mínimas e máximas de dexmedetomidina necessárias para assegurar uma antinociceção adequada foram de 0,3 (0,1) ng/mL e 0,5 (0,1) ng/mL, respetivamente. A dose mediana (intervalo interquartil) de cetamina foi de 25 (20) mg. A dose de cetamina utilizada durante os implantes definitivos foi significativamente superior à utilizada nos procedimentos de teste (30 [30] mg vs. 20 [10] mg), p = 0,006. O tempo médio até ao despertar intraoperatório foi de 114 ± 56 segundos, não se verificando diferenças significativas entre os grupos de teste e de implante.

Conclusões

Este estudo demonstra a viabilidade e segurança de um protocolo de sedação e analgesia multimodais para a implantação de sistemas de estimulação medular, combinando propofol, remifentanil, dexmedetomidina e cetamina, guiado por monitorização eletroencefalográfica e da monitorização da nociceção–antinociceção. A estratégia permitiu manter ventilação espontânea, estabilidade hemodinâmica e despertar intraoperatório rápido e previsível, fornecendo concentrações de referência potencialmente úteis para procedimentos semelhantes.

Palavras-chave

Sedação e analgesia multimodal; Eletroencefalograma; Antinocicepção; Estimulação medular;

ABSTRACT

Background

Spinal cord stimulation is a validated approach for managing chronic pain syndromes. The stimulator placement typically requires sedation, and an awake phase is needed to ensure optimal lead positioning. Usually performed in two stages: the first involves the temporary placement of the stimulator to evaluate its effect, followed by permanent implantation in cases where an improvement in pain is observed during the trial period.

We describe a novel multimodal sedation and analgesia approach using target-controlled infusions of propofol, remifentanil, and dexmedetomidine, combined with boluses of ketamine, guided by electroencephalography and nociception-antinociception balance monitoring.

Methods

This retrospective, single-center cohort study reviewed all spinal cord stimulator procedures, including both trials and permanent implants. A standardized anesthetic protocol, administered by a single anesthesiologist, included target-controlled infusions of propofol, remifentanil, and dexmedetomidine, with additional boluses of ketamine. Processed electroencephalogram guided sedation depth, and antinociception was assessed using the Analgesia Nociception Index. Data collected included drug doses, time to intraoperative awakening, hemodynamic stability, and airway management.

Results

A total of 25 procedures (11 trials, 14 permanent implants) were analyzed in 21 patients, with 4 patients undergoing both procedures. All patients received the same four-drug regimen. The median (interquartile range) minimum and maximum effect-site concentrations of propofol required to achieve an adequate level sedation (level−4 of the Richmond Agitation-Sedation Scale) were 1 (0.5) µg/mL and 1.5 (0.8) µg/mL, respectively. The median (interquartile range) minimum and maximum effect-site remifentanil concentrations needed to achieve sufficient antinociception (Analgesia Nociception Index between 50 and 70) were 0.5 (0.3) ng/mL and 1.2 (0.4) ng/mL, respectively. The median (interquartile range) minimum and maximum effect-site concentrations of dexmedetomidine required to achieve adequate antinociception were 0.3 (0.1) ng/mL and 0.5 (0.1) ng/mL, respectively. The median (interquartile range) dose of ketamine was 25 (20) mg. The ketamine dose used during the implant was significantly higher than during the trial procedure (30 (30) vs. 20 (10) mg), p=0.006.

The average time to intraoperative awakening was 114 ± 56 s, and there was no significant difference between the trial and implant groups.

Conclusions

This study demonstrates the feasibility and safety of a multimodal sedation protocol for the placement of a spinal cord stimulator, combining propofol, remifentanil, dexmedetomidine, and ketamine, guided by electroencephalogram and nociception-antinociception monitoring.

Keywords

Multimodal sedation and analgesia, Electroencephalogram, Antinociception, Spinal cord stimulation;

LIST OF ABREVIATIONS

CCAD - Cleveland Clinic Abu Dhabi

SCS - Spinal cord stimulation

EEG - Electroencephalogram

NANb - Nociception-antinociception balance

HRV - Heart rate variability

ES - Effect site

TCI - Target controlled infusion

ANI - Analgesia Nociception Index

PkPd - Pharmacokinetic/pharmacodynamic

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INTRODUCTION

Multimodal Sedation and Multimodal General Anesthesia: Pharmacological Profiles, Electroencephalographic Signatures, and Perioperative Nociception–Antinociception Balance Monitoring of Propofol, Dexmedetomidine, Remifentanil, and Ketamine.

Modern general anesthesia and sedation have evolved from approaches based on single agents to multimodal strategies, supported by the rational combination of drugs acting by different mechanisms in distinct neural pathways to achieve adequate hypnosis, effective antinociception, autonomic stability, and predictable recovery, while minimizing adverse effects associated with the use of unnecessary higher doses.[1-4]

No single drug is able to optimally meet all these requirements. Classical hypnotic agents, such as propofol, produce profound unconsciousness but lack significant analgesic properties and are associated with dose-dependent respiratory depression and hypotension.[5] Opioids, such as remifentanil, provide potent analgesia and effective suppression of nociceptive responses but carry a high risk of respiratory depression, opioid-induced hyperalgesia, and hemodynamic instability.[6,7]

Drugs such as dexmedetomidine and ketamine introduce distinct pharmacological profiles. Dexmedetomidine allows cooperative sedation and autonomic modulation with minimal respiratory depression, whereas ketamine offers robust analgesia, anti-hyperalgesic effects, and preservation of respiratory function through a dissociative mechanism.[8–11] These characteristics make these drugs particularly valuable in the construction of more balanced and physiologically sustainable sedation strategies and providing effective antinociception at lower doses.[3,4]

Multimodal sedation is based on similar principles, using different drugs, exploiting pharmacodynamic synergies and reducing excessive dependence on any individual agent. This approach allows finer titration, greater clinical predictability, and better adaptation to the specific demands of each procedure, including those requiring intraoperative awakening, neurological assessment, or maintenance of spontaneous ventilation.[1,4]

The increasing complexity of multimodal sedation strategies has been accompanied by the development of more precise drug delivery systems, particularly target-controlled infusion (TCI). Based on pharmacokinetic and pharmacodynamic models, TCI allows the clinician to target a desired effect-site or plasma concentration and adjust drug administration in a dynamic and predictable manner. This approach enables finer titration of anesthetic depth, facilitates rapid transitions between

levels of sedation, and improves interindividual reproducibility, making it particularly valuable in procedures requiring strict control over both hypnosis and analgesia, as well as rapid and controlled transitions between sedation and wakefulness.

In parallel, the development and application of electroencephalography (EEG) as a tool for monitoring anesthetic depth have introduced a new dimension to anesthetic practice. Different sedative and anesthetic agents produce characteristic electroencephalographic patterns, reflecting distinct neurophysiological mechanisms. Understanding these EEG signatures is essential for correctly interpreting depth-of-anesthesia indices and optimizing sedation strategies guided by neurophysiological objectives.[12–15]

Accordingly, the present chapter aims to analyze in an integrated manner the pharmacology of propofol, dexmedetomidine, remifentanil, and ketamine, addressing their mechanisms of action, pharmacokinetic and pharmacodynamic profiles, functional effects, and electroencephalographic manifestations. It further seeks to discuss the specific role of each of these agents in the context of multimodal sedation, highlighting how their combined use allows for safer, more predictable, and personalized anesthesia, grounded in solid pharmacological and neurophysiological principles.[1,4,12–15]

Propofol

Propofol is an intravenous hypnotic agent of the alkylphenol class, widely used for induction and maintenance of general anesthesia and in continuous sedation regimens. Its primary mechanism of action consists of potentiation of inhibitory neurotransmission mediated by GABA-A receptors, acting as a positive allosteric modulator and, at higher concentrations, as a direct agonist. This interaction increases chloride conductance, promotes neuronal hyperpolarization, and leads to global depression of cortical activity, resulting in dose-dependent loss of consciousness.[5,12]

From a pharmacokinetic perspective, propofol is characterized by high lipophilicity, which explains its rapid onset of action, typically between 30 and 45 seconds after intravenous administration. Following a bolus, rapid distribution from the central compartment to the central nervous system occurs, followed by redistribution to peripheral tissues, namely muscle and adipose tissue, a phenomenon responsible for the short duration of the hypnotic effect after single administrations. Its pharmacokinetic behavior is described by a multicompartmental model, with a rapid initial distribution phase, an intermediate redistribution phase, and a longer terminal phase associated with elimination.[5]

Propofol metabolism occurs predominantly in the liver through conjugation processes such as glucuronidation and sulfation, with relevant contributions from extrahepatic metabolism, particularly pulmonary and renal. Despite a relatively long terminal half-life, propofol exhibits high clearance, resulting in a relatively short context-sensitive half-time even after prolonged infusions, allowing predictable and rapid clinical recovery. These characteristics make it particularly suitable for titratable continuous sedation.[5]

Propofol is a potent hypnotic drug inducing impairment of consciousness. In addition to its hypnotic effects, propofol induces a reduction in sympathetic tone, peripheral vasodilation, and mild myocardial depression, explaining the hypotension frequently observed, particularly in hypovolemic patients, the elderly, or those with reduced cardiovascular reserve.[5] Recent experimental and clinical studies have shown that propofol has antinociceptive and anti-hyperalgesic properties.[16]

At the respiratory level, propofol exerts dose-dependent depression of the respiratory center, with reduced responsiveness to hypercapnia and hypoxemia, and may cause apnea after bolus administration or at high doses. This predictable respiratory depression constitutes an important limitation of its isolated use in contexts where preservation of spontaneous ventilation is desired.[5]

Dexmedetomidine

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist, widely used in intensive care sedation and in procedures requiring transient patient cooperation. It differs from other sedatives by its ability to induce sedation, anxiolysis, and an opioid-sparing effect, with significant preservation of respiratory function.[8,9]

From a pharmacokinetic standpoint, dexmedetomidine is administered intravenously and exhibits a rapid distribution phase followed by relatively predictable elimination. The drug distributes extensively into tissues and shows high plasma protein binding. Metabolism occurs predominantly in the liver through glucuronidation and cytochrome P450-mediated hydroxylation, producing inactive metabolites eliminated mainly via the kidneys.[8]

Pharmacodynamically, dexmedetomidine's primary mechanism of action consists of activation of central α_2-adrenergic receptors, particularly within the locus coeruleus, the main noradrenergic nucleus involved in the regulation of wakefulness. Activation of these receptors reduces norepinephrine release, promoting a sedative state that mimics physiological non-REM sleep. Unlike

GABAergic sedatives, this state allows the patient to remain easily arousable and cooperative when stimulated, a phenomenon often described as cooperative sedation.[9]

Beyond its sedative effect, dexmedetomidine also has peripheral antinociceptive properties. These effects result from modulation of descending inhibitory pain pathways and reduction of nociceptive transmission at the spinal level, contributing to decreased analgesic requirements in perioperative and intensive care settings. Although the analgesia associated with dexmedetomidine is not comparable to that of opioids, it assumes significant clinical relevance when integrated into multimodal regimens.[8,9]

From hemodynamic and respiratory perspectives, dexmedetomidine exhibits a profile distinct from that of classical sedatives. Reduction of central sympathetic tone frequently results in bradycardia and hypotension, particularly at higher doses or during loading doses. Transient peripheral vasoconstriction may also occur, related to activation of vascular α_2 receptors. In contrast to propofol and opioids, dexmedetomidine has minimal impact on the respiratory center, preserving ventilatory drive and airway reflexes, making it particularly useful in non-intubated patients or in clinical situations where respiratory safety is a priority.[8,9]

In contemporary anesthesia and sedation, dexmedetomidine plays a complementary role, allowing reduction of hypnotic and analgesic doses, improving autonomic stability, and facilitating smooth transitions between sedation and wakefulness. Its pharmacological predictability and cooperative sedation profile make it especially suitable for integration into multimodal strategies, in association with other agents with distinct mechanisms of action.[1-4,8,9]

Remifentanil

Remifentanil is a selective μ-opioid receptor agonist, primarily used for intraoperative analgesia in contexts requiring precise, intense, and short-duration control of the nociceptive response. It differs from other opioids by its extremely rapid onset of action, high pharmacokinetic predictability, and cessation of effect independent of infusion duration, characteristics that make it particularly suitable for procedures requiring rapid recovery.[6]

From a pharmacokinetic perspective, remifentanil presents a unique profile resulting from its rapid hydrolysis by nonspecific esterases in blood and tissues. This metabolism is independent of hepatic and renal function, ensuring predictable duration of action even in patients with impairment of these organs. After intravenous administration, it rapidly distributes to central compartments, establishing

quick equilibrium between plasma and the central nervous system, allowing a close relationship between administered dose and observed clinical effect.[6]

One of its most relevant characteristics is its extremely short context-sensitive half-time, which remains virtually constant even after prolonged infusions. Thus, interruption of administration leads to a rapid decrease in plasma concentration and predictable clinical recovery within minutes, allowing fine, real-time adjustment of analgesic depth throughout the surgical procedure.[6]

Pharmacodynamically, remifentanil acts through activation of μ-opioid receptors, producing potent analgesia and marked attenuation of autonomic and somatic responses to surgical stimulation, with only modest sedative effect. It lacks sufficient hypnotic properties to induce unconsciousness when used alone and is therefore administered in association with hypnotic agents in anesthetic contexts.[6]

At the hemodynamic and respiratory levels, remifentanil may cause bradycardia, hypotension, and dose-dependent ventilatory depression, particularly when administered as a bolus or in association with other depressant drugs. These effects require careful monitoring of ventilation and cardiovascular stability during its use.[6–7]

A clinically relevant aspect is the risk of opioid-induced hyperalgesia and acute tolerance, particularly with high doses or prolonged infusions. This phenomenon may translate into increased pain and analgesic requirements in the immediate postoperative period, reinforcing the importance of integrating remifentanil into multimodal analgesic strategies.[7]

In contemporary anesthesia and sedation, remifentanil primarily plays the role of a short-acting analgesic component, allowing strict control of the nociceptive response without compromising predictability of emergence. Its association with hypnotic agents and autonomic modulators enables reduction of individual doses, optimization of intraoperative stability, and facilitation of rapid and controlled recovery.[1-4,6–7]

Ketamine

Ketamine is a phencyclidine derivative that acts predominantly as a non-competitive NMDA receptor antagonist, producing a dissociative anesthetic state characterized by profound analgesia, alterations in perception and consciousness, and relative preservation of airway reflexes and spontaneous ventilation. Introduced into clinical practice in the 1970s, ketamine exhibits a unique pharmacological profile that distinguishes it from other sedative and hypnotic agents used in anesthesia.[10,11]

From a pharmacokinetic standpoint, ketamine is highly lipophilic, with rapid onset of action after intravenous administration, generally within less than one minute. It rapidly distributes to the central nervous system, where it exerts its main clinical effect, with initial termination of action largely explained by redistribution to peripheral tissues. Metabolism occurs predominantly in the liver through N-demethylation, producing norketamine, an active metabolite with lower anesthetic potency that contributes to the overall duration of the analgesic effect. Elimination is mainly renal, in the form of metabolites.[10,11]

Pharmacodynamically, ketamine's primary mechanism of action consists of blockade of NMDA receptors, which play a central role in excitatory neurotransmission, pain modulation, and central sensitization phenomena. By inhibiting these receptors, ketamine reduces glutamatergic transmission and interferes with sensory and cognitive integration, resulting in a dissociative state in which pain perception is profoundly attenuated, even in the presence of intense nociceptive stimuli. Unlike GABAergic agents, ketamine does not induce global suppression of cerebral activity but rather a functional dissociation between different neuronal networks.[10,11]

In addition to NMDA antagonism, ketamine interacts with multiple neurotransmitter systems, including opioid and monoaminergic receptors and ion channels, contributing to its analgesic, sympathomimetic, and psychomimetic effects. This multimodal action explains its efficacy in reducing central sensitization and preventing opioid-induced hyperalgesia, conferring a relevant opioid-sparing role.[11]

At the hemodynamic level, ketamine generally exerts a stimulatory effect, with increases in heart rate, blood pressure, and cardiac output, mediated by inhibition of catecholamine reuptake and sympathetic activation. These characteristics make it particularly useful in hypovolemic or hemodynamically unstable patients, although caution is required in those with significant cardiac disease. From a respiratory perspective, ketamine is distinguished by preservation of spontaneous ventilation and airway reflexes and is also a potent bronchodilator.[10,11]

Among adverse effects, psychomimetic reactions such as vivid dreams, hallucinations, and dysphoria are noteworthy, particularly during the emergence phase. These effects are dose-dependent and may be attenuated through slow administration, dose reduction, or association with other sedative drugs.[10]

In modern anesthesia, ketamine assumes an essential role as an analgesic and anti-hyperalgesic agent, offering a unique combination of potent analgesia, hemodynamic stability, and respiratory

preservation. Its use requires careful integration with other drugs, allowing maximization of benefits and minimization of undesirable effects.[1-4,10,11]

Electroencephalographic Signatures

Different sedative and anesthetic agents modulate cerebral activity in distinct ways, which is reflected in specific electroencephalographic patterns. These signatures are not merely technical markers but represent different neurophysiological mechanisms of sedation, analgesia, and alteration of consciousness.[12–15]

Propofol induces predominance of well-organized frontal alpha waves, associated with delta waves as the dose increases. This pattern reflects strong thalamocortical synchronization mediated by potentiation of GABAergic neurotransmission, leading to functional disconnection between frontal and posterior cortical regions. Progressive increase in delta activity accompanies loss of consciousness and suppression of responsiveness and is typical of deep, predictable anesthetic states.[12]

Dexmedetomidine produces a distinct electroencephalographic pattern, closer to physiological non-REM sleep. There is predominance of slow and delta waves, often associated with spindle-like activity, with partial preservation of cortical organization. This pattern reflects inhibition of the locus coeruleus and reduction of noradrenergic tone, allowing cooperative sedation in which the patient can be easily aroused. Unlike propofol, dexmedetomidine does not induce abrupt cortical disconnection but rather a gradual transition to a reduced vigilance state.[13]

Remifentanil, as a pure opioid, does not produce a specific hypnotic EEG signature. When used alone and in high doses, it may be associated with a slight increase in delta activity and reduction of faster frequencies, but its primary effect is modulation of nociceptive and autonomic responses. When combined with hypnotic agents, remifentanil significantly alters electroencephalographic patterns, reducing beta activity and modifying spectral parameters used in depth-of-anesthesia monitors. These changes reflect interference with EEG interpretation rather than a direct cortical sedative effect.[6,7]

Ketamine presents a unique electroencephalographic signature, profoundly distinct from other agents. It is characterized by increased theta and gamma activity, often accompanied by reduced alpha activity and intermittent gamma oscillation patterns (“gamma bursts”) at higher doses. This pattern reflects functional dissociation induced by NMDA receptor blockade, with preservation or even activation of specific cortical circuits despite loss of behavioral responsiveness. Unlike propofol

and dexmedetomidine, ketamine does not globally suppress cortical activity but reorganizes it in a fragmented and dissociative manner.[12,14]

Identification of low doses of ketamine and dexmedetomidine that provide antinociception mediated by peripheral mechanisms is only possible with the use of EEG, as these effects should not cause any changes in the cortical and sub-cortical neural pathways. Therefore, when ketamine and dexmedetomidine are used solely for analgesia in combination with propofol, the observed EEG changes are expected to primarily reflect the effects of propofol.[15] The appearance of typical 12-Hz, short-duration spindles and K complexes translates an unnecessarily high dose of dexmedetomidine while the decrease in the alpha power induced by propofol or the appearance of fast beta or gamma oscillations are signs of hypnotic doses of ketamine.[15]

Perioperative Nociception–Antinociception balance monitoring

Perioperative nociception–antinociception balance (NANb) monitoring aims to provide an objective assessment of the relationship between surgical nociceptive stimuli and the patient's analgesic state during anesthesia. Traditional indicators such as heart rate, blood pressure, lacrimation, or movement are indirect and often unreliable because they may be influenced by factors such as hypovolemia, vasoactive drugs, anesthetic depth, or autonomic dysfunction. Consequently, several dedicated nociception monitors have been developed to optimize intraoperative analgesia, reduce opioid consumption, and improve postoperative pain outcomes.

Currently available technologies include the Surgical Pleth Index (SPI), which analyzes pulse-wave amplitude and heartbeat intervals; the Nociception Level Index (NOL), a multiparametric monitor that integrates photoplethysmography, skin conductance, and temperature; pupillometry, based on pupillary reflex dilation; qNOX, derived from electroencephalographic signals; and the Analgesia Nociception Index (ANI).[17-20]

The ANI monitor assesses autonomic nervous system activity by analyzing heart rate variability, focusing on the high-frequency component associated with respiratory sinus arrhythmia and parasympathetic tone. The monitor produces a numerical index from 0 to 100, with higher values indicating predominant parasympathetic activity and adequate antinociception, whereas lower values suggest sympathetic predominance and insufficient analgesia. In clinical practice, ANI values above approximately 50–60 are generally considered indicative of adequate intraoperative analgesia.[21,22]

The ANI system is non-invasive and uses standard ECG electrodes placed on the chest. It provides both an instantaneous ANI (ANIi) and a moving average ANI (ANIm), allowing continuous real-time monitoring of nociception–antinociception balance during surgery. ANI-guided anesthesia has been associated in some studies with reduced intraoperative opioid administration and improved postoperative pain prediction.[23-24]

Despite its promise, ANI monitoring has limitations. Because it depends on autonomic nervous system activity, measurements may be affected by arrhythmias, beta-blockers, anticholinergic drugs, vasoactive medications, emotional stress, and altered autonomic function.[25] Furthermore, evidence regarding its impact on major clinical outcomes remains heterogeneous, and ANI should therefore be interpreted as an adjunct rather than a replacement for clinical judgment. Unfortunately, ANI has been unavailable on the market since 2024.

Multimodal Sedation and Analgesia

Integrated analysis of the effects of propofol, dexmedetomidine, remifentanil, and ketamine demonstrates that these drugs do not induce a homogeneous sedative state nor act on the same neurobiological mechanisms. Instead, each agent intervenes in distinct dimensions of regulation of consciousness, nociception, and autonomic response, supporting contemporary approaches to sedation based on pharmacological complementarity.[1-4]

In this context, multimodal sedation allows distribution of sedative effects across different functional axes—hypnosis, analgesia, autonomic modulation, and sensory dissociation—avoiding excessive reliance on a single drug and reducing the need for high doses. This strategy translates into greater clinical predictability, improved hemodynamic and respiratory stability, and enhanced capacity for fine adjustment of patient state, particularly relevant in environments requiring rigorous titration of sedation.[1-4]

Thus, multimodal sedation should be understood not merely as the association of multiple agents but as a functional integration of distinct pharmacodynamic mechanisms aimed at optimizing clinical efficacy and safety. This perspective frames the combined use of different sedatives as a rational and well-grounded option, consistent with current principles of anesthesiology and intensive care medicine.[1,4]

These principles become particularly relevant in clinical scenarios where conventional anesthetic strategies are insufficient to meet procedural demands.

In procedures such as spinal cord stimulator implantation, anesthetic management presents a unique challenge that goes beyond conventional sedation or general anesthesia. Optimal lead positioning requires intraoperative neurological feedback, making it necessary to alternate between adequate sedation and a controlled awake state. This imposes the need for a technique that ensures patient comfort and immobility during painful stages, while allowing rapid, predictable, and cooperative awakening for functional testing.[1-4]

In this context, strategies based on deep sedation or single-agent techniques are often insufficient, as they either compromise respiratory function, delay recovery, or limit the precision of intraoperative neurological assessment. The anesthetic approach must therefore be highly titratable, preserve spontaneous ventilation, and allow fine control over the balance between hypnosis and analgesia.[1-4,15]

These requirements make spinal cord stimulator implantation an ideal model for the application of multimodal sedation strategies, particularly when combined with neurophysiological monitoring such as electroencephalography, enabling individualized and dynamic adjustment of anesthetic depth. This clinical scenario provides a compelling framework to explore multimodal, EEG-guided sedation approaches, as described in the following study.[12–15]

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RESEARCH

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Multimodal sedation guided by processed electroencephalography and autonomic nervous system monitoring for spinal cord stimulator implantation: retrospective identification of anesthetic drug doses

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Abstract

Background Spinal cord stimulation is a validated approach for managing chronic pain syndromes. The stimulator placement typically requires sedation, and an awake phase is needed to ensure optimal lead positioning. We describe a novel multimodal sedation approach using target-controlled infusions of propofol, remifentanil, and dexmedetomidine, combined with boluses of ketamine, guided by electroencephalography and nociception-antinociception balance monitoring.

Methods This retrospective, single-center cohort study reviewed all spinal cord stimulator procedures, including both trials and permanent implants. A standardized anesthetic protocol, administered by a single anesthesiologist, included target controlled infusions of propofol, remifentanil, and dexmedetomidine, with additional boluses of ketamine. Processed electroencephalogram guided sedation depth, and antinociception was assessed using the Analgesia Nociception Index. Data collected included drug doses, time to intraoperative awakening, hemodynamic stability, and airway management.

Results A total of 25 procedures (11 trials, 14 permanent implants) were analyzed in 21 patients, with 4 patients undergoing both procedures. All patients received the same four-drug regimen. The median (interquartile range) minimum and maximum effect-site concentrations of propofol required to achieve an adequate level sedation (level −4 of the Richmond Agitation-Sedation Scale) were 1 (0.5) µg/mL and 1.5 (0.8) µg/mL, respectively. The median (interquartile range) minimum and maximum effect-site remifentanil concentrations needed to achieve sufficient antinociception (Analgesia Nociception Index between 50 and 70) were 0.5 (0.3) ng/mL and 1.2 (0.4) ng/mL, respectively. The median (interquartile range) minimum and maximum effect-site concentrations of dexmedetomidine required to achieve adequate antinociception were 0.3 (0.1) ng/mL and 0.5 (0.1) ng/mL, respectively. The median (interquartile range) dose of ketamine was 25 (20) mg. The ketamine dose used during the implant was significantly higher than during the trial procedure (30 (30) vs. 20 (10) mg), $p = 0.006$. The average time to intraoperative awakening was 114 ± 56 s, and there was no significant difference between the trial and implant groups.

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Conclusions This study demonstrates the feasibility and safety of a multimodal sedation protocol for the placement of a spinal cord stimulator, combining propofol, remifentanil, dexmedetomidine, and ketamine, guided by electroencephalogram and nociception-antinociception monitoring.

Keywords Multimodal sedation, Electroencephalogram, Spinal cord stimulation

Background

Spinal cord stimulation (SCS) was introduced into clinical practice in 1967 [1] and today has an important role in the treatment of chronic pain [2]. SCS devices send electrical signals through electrodes placed in the epidural space to targeted areas of the spinal cord, such as the dorsal column or the dorsal root ganglion [3]. SCS is indicated for various painful conditions such as failed back surgery syndrome, peripheral neuropathy, intractable radiculopathy, complex regional pain syndrome, peripheral vascular disease, and refractory angina pectoris when conservative measures fail to provide adequate analgesia. Additional off-label indications have been described, including chronic pelvic pain, chronic abdominal pain, and central neuropathic pain [4].

The procedure consists of two steps: an initial temporary trial to determine the patient's response to the therapy and a second procedure to percutaneously implant the stimulator device if the patient shows significant clinical improvement.

Various anesthetic techniques for this procedure have been described, including sedation, general anesthesia, and epidural anesthesia, using different combinations of hypnotic and analgesic drugs [5–7]. SCS placement under sedation to minimize pain and discomfort is commonly employed [7, 8] with an intraoperative awake phase for spinal cord mapping and optimal electrode placement. General anesthesia has been recommended for patients with morbid obesity, sleep apnea, and anxiety [9].

We aimed to describe and validate a new multimodal sedation approach that combines propofol, dexmedetomidine, remifentanil, and ketamine with dosing guided by electroencephalogram (EEG) and nociception-antinociception balance (NANb) monitoring using heart rate variability (HRV).

Methodology

Study design and objectives

This retrospective study aimed to determine the doses of anesthetic drugs in patients undergoing SCS procedures.

The study was conducted in accordance with the Declaration of Helsinki, and the Institutional Research Ethics Committee approved this study (REC CCAD A-2025–012), waiving the requirement for informed consent.

Population

All cases of SCS-related procedures, including trials and implantations, performed between October 2021 and March 2023 used the same multimodal anesthetic approach guided by processed EEG and NANb monitoring and performed by the same anesthesiologist.

Data collection

The following data were extracted from electronic medical records (EPIC, Epic Systems Corporation, Verona, WI, USA).

Procedural details are as follows:

- Performance of SCS
- Whether the procedure was a trial or a permanent implant

Data from the anesthetic technique is as follows:

- Propofol (minimum and maximum effect-site (ES) concentrations, µg/ml)
- Remifentanil (minimum and maximum ES concentrations, ng/ml)
- Dexmedetomidine (minimum and maximum ES concentrations, ng/ml)
- Ketamine (total dose, mg)
- Time for intraoperative awakening
- Need of vasopressor drugs
- Need of airways rescue

Statistical analysis

Data were analyzed using descriptive statistics. The Shapiro–Wilk normality test was performed to assess the normal distribution of continuous variables. Continuous variables are presented as median (interquartile range) or average ± standard deviation, as appropriate. The independent samples Mann–Whitney *U* nonparametric test was used to compare variables between groups. The online statistical software Prism, available at https://www.graphpad.com/features, and the IBM SPSS® Statistics version 30, were used for the data analysis. A p-value < 0.05 was considered statistically significant.

Anesthetic management

All patients had the same anesthetic protocol after a preprocedural assessment conducted by the same anesthesiologist or by the Center of Perioperative Medicine.

Monitoring

All patients received standard monitoring, including electrocardiography, noninvasive blood pressure measurements taken every 3 min, pulse oximetry, and capnography.

Root® platform (Masimo Corporation, Irvine, CA, USA) was used to monitor the electroencephalogram using SedLine® (Masimo Corporation, Irvine, CA, USA). The SedLine® monitor uses a frontal montage in positions F7, F8, Fp1, and Fp2 as specified in the international 10–20 system.

ANI® (M'Doloris Medical Systems, Lille, France) incorporated in the Root® platform was used to assess the NANb. The ANI® is a dimensionless number that ranges from 0 to 100, with values above 70 indicating increased parasympathetic activity and reduced nociception; values below 50 correspond to a dominant sympathetic tone and poor antinociception [10].

,Anesthetic technique

Sedation was conducted using target controlled infusions (TCI) of propofol, employing the modified Marsh model [11] in ES mode, and remifentanil, utilizing the Minto model [12, 13]. The infusion of dexmedetomidine was managed by TivatrainerX® (Gutta BV, Aerdenhout, the Netherlands, available at https://www.tivatrainer.com) in Assist Mode, using the Hannivoort-Colin model [14, 15] in ES mode (Fig. 1).

The changes in the doses of propofol, ketamine, and dexmedetomidine were based on the dynamic changes in their specific electroencephalographic signatures assessed on the raw EEG and on the spectrogram (Fig. 2A), while the doses of remifentanil were based on the ANI.

Propofol TCI started at 1.5 µg/mL in stepwise increments until typical 10-Hz spindles superimposed on delta waves with the peak-max phase-coupling pattern appeared [16], which coincides with a level − 4 of the Richmond Agitation-Sedation Scale [17].

Simultaneously, TCI of remifentanil at 0.5 ng/mL effect site was started with further titration based on the level of nociceptive stimulation and aiming for ANI values between 50 and 70.

After achieving a steady-state concentration of propofol and remifentanil, the infusion of dexmedetomidine was started at a low-nociceptive ES concentration of 0.15 ng/mL, followed by slight increases until the appearance of the typical 12-Hz, short-duration spindles and K complexes generated by dexmedetomidine [18–20]. If such electroencephalographic grapho-elements appear, translating into an unnecessarily high dose of dexmedetomidine, the ES concentration was decreased until the reappearance of the spindles generated by propofol.

Small boluses of 5 mg of ketamine were administered after achieving the steady-state concentration of dexmedetomidine, avoiding decreased alpha power or appearance of faster oscillations [21].

During the induction, paracetamol (1 g IV), parecoxib (40 mg IV), and ondansetron (4 mg IV) were administered.

Concentrations of propofol, remifentanil, and dexmedetomidine were titrated closely to the moment of intra-procedural awakening. Subsequently, the infusions of dexmedetomidine and propofol were interrupted following the proceduralist's indication regarding the timing for placing the leads and the readiness for neurological testing. TCI of remifentanil was kept during the awake phase.

For the trial procedure, where no more painful events occurred after testing and the SCS generator was placed over the skin, only remifentanil was kept until the end (Fig. 1A).

For the definitive subcutaneous placement of the SCS after testing, the EEG-guided infusions of propofol and dexmedetomidine were resumed and stopped at the end of closure with additional boluses of ketamine and supplementary skin infiltration with local anesthetic drug (Fig. 1B).

The time for intraoperative awakening was defined as the period from when the proceduralist requested the patient to be awake until the patient followed commands and was recorded for each patient using the stopwatch available on the anesthesia monitor.

Results

Data were retrieved from 25 procedures (11 involved only the placement of the SCS for trial, and 14 had the placement for the definitive implant); 4 patients experienced both procedures, for a total of 21 patients (12 males, 9 females; average age 49 ± 18 years).

All patients received a combination of propofol, dexmedetomidine, ketamine, and remifentanil as part of the multimodal sedation approach described in the methodology.

Spontaneous ventilation was maintained in all patients, with no cases requiring face mask ventilation or any other advanced airway support. No vasopressors were needed to keep the mean arterial pressure above 20% of the baseline values.

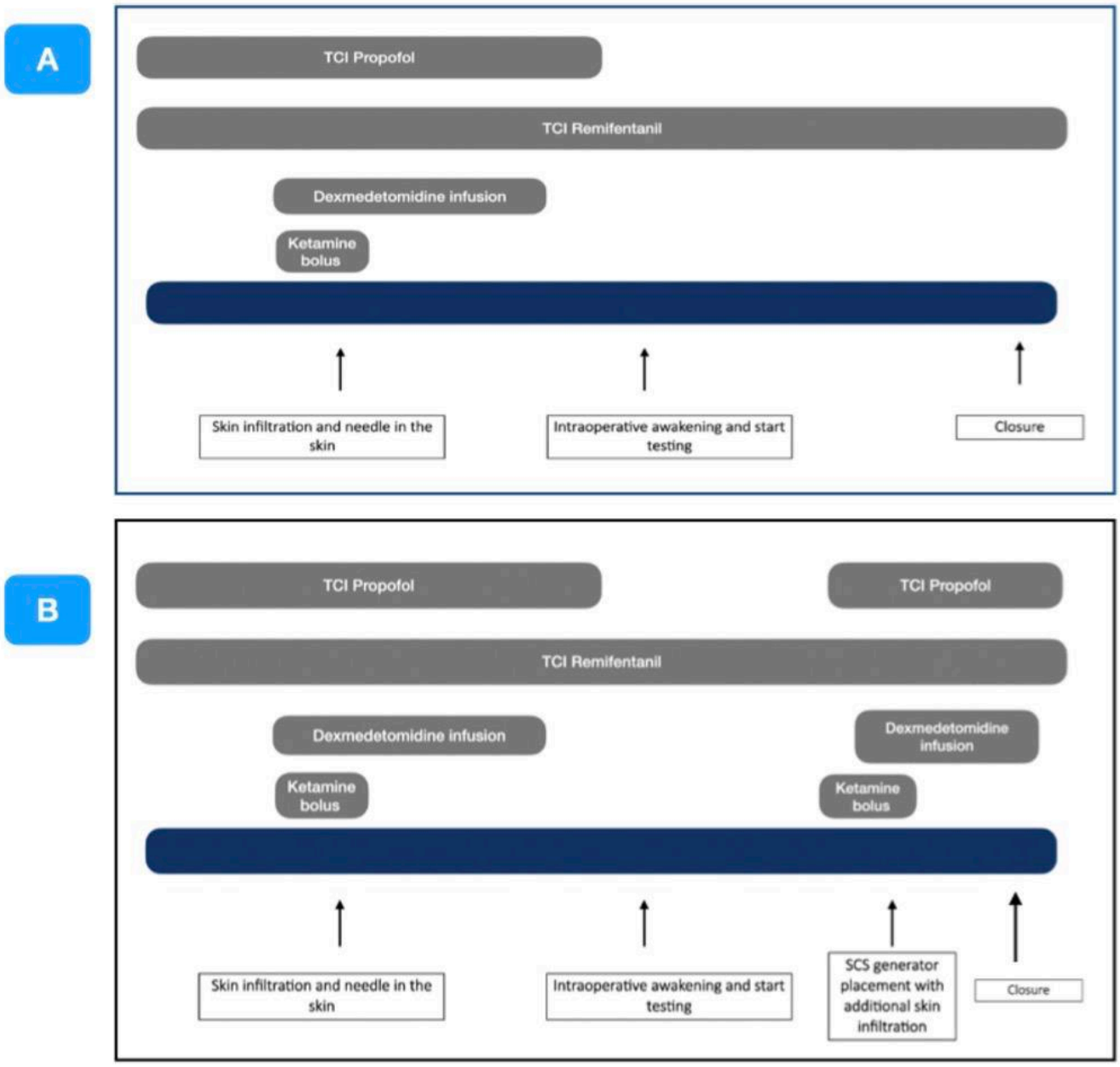

Fig. 1 Anesthesia approach timeline. **A** The timeline for anesthetic management for spinal cord stimulator placement (trial procedure). **B** The timeline for anesthetic management for spinal cord stimulator placement (definitive implant procedure)

(See figure on next page.)

Fig. 2 Screenshots of the root monitor displaying examples of EEG and ANI changes during various intraoperative events. **A** The EEG displays a typical pattern of sedation induced by propofol, characterized by alpha rhythms (light blue box) and spindles (red boxes), along with some slow oscillations (green box). The average (orange line) and instantaneous (yellow line) ANI trends indicate oscillations over time corresponding to different NANb levels. **B** Intraoperative awakening displaying a gradual transition from the alpha-delta pattern (blue box) to fast frequencies (pink box)

The time for intraoperative awakening was 96 (53) s. No significant difference was found between the time for intraoperative awakening during trial seconds and

Fig. 2 (See legend on previous page.)

Table 1 Effect-site concentrations of propofol, remifentanil, and dexmedetomidine, doses of ketamine, and time for intraoperative awakening

		Total	Trials	Implants	*p*-value
Propofol effect-site concentration (μg/mL)	Min	1 (0.5)	0.6 (0.6)	1 (0.4)	0.609
	Max	1.5 (0.8)	1.5 (1.2)	1.6 (0.7)	0.687
Remifentanil effect-site concentration (ηg/mL)	Min	0.5 (0.3)	0.5 (0.3)	0.6 (0.3)	> 0.999
	Max	1.2 (0.4)	1.2 (0.5)	1.3 (0.3)	0.344
Dexmedetomidine effect-site concentration (ηg/mL)	Min	0.3 (0.1)	0.3 (0.2)	0.3 (0.1)	0.767
	Max	0.5 (0.1)	0.5 (0.2)	0.6 (0.1)	0.075
Ketamine dose	Dose	25 (20)	**20 (10)**	**30 (30)**	**0.006**
Time for intraoperative awakening (s)		96 (53)	96 (57)	106 (52)	0.936

Values as median (interquartile range). Statistically different ($p < 0.05$, Mann–Whitney *U*-test) are marked in bold

definitive implant second procedures, respectively (96 (57) s vs 106 (52) s with $p = 0.936$) (Table 1).

Anesthetic drug doses

The median minimum and maximum ES concentrations of propofol required to achieve an adequate sedative level were 1 (0.5) μg/mL and 1.5 (0.8) μg/mL, respectively. No significant difference was found between minimum and maximum ES concentrations during trials and definitive implant procedures (Table 1).

The median minimum and maximum ES concentrations of remifentanil, calculated by the Minto model, required to achieve an adequate level of antinociception were 0.5 (0.3) ng/mL and 1.2 (0.4) ng/mL, respectively. No significant difference was found between minimum and maximum ES concentrations during trials and definitive implant procedures (Table 1).

The median minimum and maximum ES concentrations of dexmedetomidine, calculated by the Hannivoort model, required to achieve an adequate level of antinociception were 0.3 (0.1) ng/mL and 0.5 (0.1) ng/mL. No significant difference was found between minimum and maximum ES concentrations during trial and definitive implant procedures (Table 1).

The median dose of ketamine was 25 (20) mg. The dose of ketamine used in the definitive implant was significantly higher than the dose used during the trial procedure (30 (30) vs 20 (10) mg) (Table 1).

Discussion

This study describes a multimodal sedation approach for SCS placement that utilizes TCI of propofol, remifentanil, and dexmedetomidine, supplemented by ketamine boluses, with dosing guidance from frontal EEG and HRV monitoring. The rationale for multimodal sedation is based on the interactions between antinociceptive and hypnotic drugs, which act in different neural pathways through distinct mechanisms. This interaction requires lower doses of the multiple drugs used, resulting in fewer undesirable side effects [22].

Choosing anesthetic drugs with favorable pharmacokinetic/pharmacodynamic (PkPd) profiles and administering them using TCI with adequate models targeting the effect site are crucial for achieving smooth and rapid intraoperative awakening and facilitating faster dose changes compared to those using weight-time-based schemes [23, 24].

Recognizing the specific electroencephalographic signatures of anesthetic drugs enables the titration of the dose to achieve the desired effect and individualize the required dose [25, 26].

A stepwise increase in propofol ES concentration until the appearance of the delta-alpha pattern with peak-max phase coupling [16, 27] was accompanied by impaired arousal and responsiveness. The ES concentration at that moment can serve as the reference target for further anesthetic management.

The initial ES target concentration of 0.5 ng/mL for remifentanil was chosen based on previous data showing the effectiveness of low doses to blunt low-intensity nociceptive stimuli without respiratory depression [28–30] and our preference to use opioid-sparing anesthesia [31–33]. Further titration of remifentanil dosing was based on the ANI. ANI computes signals of heart rate variability, assessing the balance between the sympathetic and parasympathetic activity [10, 34], and has been shown to be helpful as part of a multimodal monitoring in cases of sedation and in conscious patients [35, 36].

Dexmedetomidine has antinociceptive properties by activating inhibitory interneurons located in the dorsal horn of the spinal cord [22, 37, 38] at doses that do not affect the level of arousal, thereby not inducing changes in the EEG but sufficient to be detected by the ANI monitor [35]. Inspecting spindles' morphology avoids unnecessarily high doses of dexmedetomidine with a high probability of hemodynamic changes [39, 40] and

delayed emergence. Spindles generated by dexmedetomidine resemble the sleep spindles that appear during the N2 stage of physiological sleep with maximum power at 13 Hz in frontal regions, while those associated with propofol have an asymmetrical shape with a baseline shift or, alternatively, are superimposed on a slow wave and with two or three waxing and waning oscillations separated by a "breaking point" with a higher frequency component at twice the dominant frequency of the spindle [41, 42].

Dexmedetomidine has been preferred over propofol for SCS placement [8, 43, 44], but no single study has investigated the effectiveness of combining both drugs. Ter Bruggen and colleagues [45] compared the long-term effects of sedation with dexmedetomidine to sedation with propofol during the implantation of SCS and found no statistical difference in long-term outcomes like global perceived effect, pain course, and functional status. However, there was a trend towards greater satisfaction among patients who had sedation with dexmedetomidine.

Combining dexmedetomidine with propofol may significantly decrease the blood pressure and the heart rate [46]. Still, the individualized dosing achieved using TCI with EEG and NANb monitoring may decrease these undesirable side effects.

Ketamine has known peripheral antinociceptive effects [47–50] exerted at low doses which can be determined using a similar approach, based on the absence of changes in the EEG, particularly the appearance of fast beta or gamma oscillations, or, at a lower dose, only a decrease in the power of the alpha frequencies induced by propofol [21]. Due to the significant PkPd variability of ketamine, especially when used with propofol [51], its boluses must be minimal and have an adequate interval between each dose. The higher dose found in the procedure for definitive implant of the SCS reflects the need to supplement antinociception in the last step of the procedure, with the tunnelization of the wires and placing the stimulator subcutaneously.

The fast intraoperative awakening within approximately 2 min, likely due to EEG and NANb monitoring and the PkPd modeling of the IV drugs, enabled us to initiate reliable neurologic testing. We should highlight the smooth intraoperative awakening without agitation or confusion, possibly due to the use of dexmedetomidine [52–54] and the use of the combined use of EEG and ANI [55, 56]; despite a subjective impression, this was the primary advantage noted by the two proceduralists involved in the study, who compared it to their previous experiences with propofol infusion supplemented with fentanyl boluses.

Limitations

This study has several limitations that must be acknowledged. It is a retrospective cohort study involving a small sample of patients from a single center and under the care of one anesthesiologist, which may introduce sampling bias. However, we have no reason to suspect that our population differs from patients requiring treatment with SCS.

Another limitation of our approach was the inability to use TCI of dexmedetomidine because the institution lacked pumps incorporating PkPd models for dexmedetomidine. However, the use of pharmacokinetic simulation with Tivatrainer® has been described in cases involving intraoperative awakening [29].

Finally, our patient population is relatively young; therefore, we may expect to find lower doses of the anesthetic drugs in older patients [57].

Conclusions

In summary, we describe a multimodal sedation strategy for placing SCS using propofol, dexmedetomidine, remifentanil, and ketamine, optimized through TCI infusions guided by EEG and NANb monitoring. This study provides average concentrations of these drugs that may serve as a reference in similar clinical cases.

Abbreviations

SCS	Spinal cord stimulation
EEG	Electroencephalogram
NANb	Nociception-antinociception balance
HRV	Heart rate variability
ES	Effect site
TCI	Target controlled infusion
ANI	Analgesia Nociception Index
PkPd	Pharmacokinetic/pharmacodynamic

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Authors' contributions

AS, ARA, MA, FAL: collected and curated data. RT and EF performed the surgeries. FAL was the anesthesiologist in charge of all the procedures. AS, MA, RT, EF and FAL wrote the manuscript. All the authors approved the final version of the manuscript.

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Data availability

- Anonymized data will be provided upon a valid request.

Declarations

Ethics approval and consent to participate

The Institutional Research Ethics Committee approved this study (REC CCAD A-2025–012).

Competing interests
The authors declare no competing interests.

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