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ORIGINAL ARTICLE

A Double-Blind Comparative Study of burstDR Versus Tonic Epidural Motor Cortex Stimulation for the Treatment of Intractable Neuropathic Pain

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ABSTRACT

Background: Preliminary studies on epidural motor cortex stimulation (eMCS) for the treatment of drug-resistant neuropathic pain have supported the extension to novel stimulation waveforms, in particular burstDR. However, only a low level of evidence is available. The aim of this retrospective observational study was to compare the analgesic efficacy of burstDR versus tonic eMCS.

Methods: Patients suffering from unilateral, drug-resistant neuropathic pain were selected for eMCS. During the trial phase, burstDR and tonic waveforms were successively applied for three consecutive months in a double-blinded fashion and in a random order. The primary outcome criterion was the percentage of pain relief (%PR) at 3 and 6 months. The secondary outcome criterion was the proportion of patients reporting a superior %PR with the burstDR waveform.

Results: Thirteen patients were included. The averaged %PR was $75.4\% \pm 18.6\%$ after burstDR eMCS and $61.1\% \pm 28.6\%$ after tonic eMCS ($p = 0.21$). Nine patients preferred the burstDR waveform for chronic eMCS ($p = 0.16$), and six of them were able to decrease or withdraw their analgesic drug intake. No adverse side effect was encountered in relation to burstDR eMCS.

Conclusions: BurstDR eMCS seems at least as effective as tonic eMCS for the treatment of drug-resistant neuropathic pain and shows a similar safety profile. Although the precise mechanisms of action remain to be fully elucidated, adequate matching between the oscillatory rhythm in the motor cortex and that of the burstDR waveform may increase synaptic efficacy, thus enhancing the functional connectivity of the motor cortex with remote brain networks involved in pain modulation.

Significance Statement: In the present paper, we provide for the first time a double-blinded study comparing burstDR versus tonic eMCS for the treatment of intractable, drug-resistant neuropathic pain. Our results show that burstDR eMCS is a promising option in a population of patients especially difficult to treat, and support the ongoing move toward new stimulation waveforms able to more efficiently activate the brain networks involved in pain modulation.

1 | Introduction

Epidural (primary) motor cortex stimulation (eMCS), first introduced by Tsubokawa et al. in the early 1990s (Tsubokawa

et al. 1991, 1993), is an established, last-resort option for the management of intractable neuropathic pain resistant to pharmacological and behavioural therapies. Its efficacy has been confirmed in randomised, double-blinded, sham-controlled

crossover trials (Lefaucheur et al. 2009; Nguyen et al. 2008; Velasco et al. 2008; Hamani et al. 2021). Main indications are represented by post-stroke pain, trigeminal pain, (and less frequently) phantom limb pain, and pain secondary to brachial plexus injury (Ramos-Fresnedo et al. 2022). The rate of pain relief tends to vary across cohorts (Ramos-Fresnedo et al. 2022), but outcomes could be dramatically improved by selecting the best candidates for eMCS according to their preoperative analgesic response to several sessions of high-frequency (5–20 Hz) repetitive transcranial magnetic stimulation (rTMS) targeting the motor cortex contralateral to pain (Lefaucheur, Keravel, and Nguyen 2011; André-Obadia et al. 2014; Pommier et al. 2018).

Pain relief induced by eMCS is achieved through one or two epidural electrodes sutured to the dura mater and positioned over the area of the motor cortex corresponding to the painful territory (i.e., homotopic eMCS; Nguyen et al. 1999). By analogy with the original paresthetic waveform that has been used for many years in spinal cord stimulation (SCS), the current conventional paradigm of eMCS corresponds to a tonic pattern at low frequency (typically 25–130 Hz; Ramos-Fresnedo et al. 2022). However, during the past decade, a novel SCS paradigm called burstDR has been introduced by De Ridder et al. (2010), consisting of a 40 Hz burst mode with five spikes at 500 Hz per burst. BurstDR stimulation waveform is unique in the sense that it mimics the natural firing pattern of the central nervous system, in particular the oscillatory rhythm of the medial thalamus–anterior cingulate cortex circuit, which drives the emotional dimension of pain processing (Jahnsen and Llinás 1984; Swadlow and Gusev 2001). Importantly, compared to tonic SCS, burstDR SCS modulates both the medial (emotional) and lateral (sensory-discriminative) pain pathways and demonstrated superior pain relief and a similar safety profile in a large randomised controlled trial (Deer et al. 2018). Additionally, it has been shown that burstDR auditory cortex stimulation better suppresses noise-like tinnitus than tonic stimulation (De Ridder et al. 2011), thus underlining the importance of further investigating new stimulation designs also at the cortical level.

However, to date, very limited evidence supports the analgesic efficacy of burstDR eMCS, with only preliminary data derived from two small-size studies (Sokal et al. 2019, 2020; Nüssel et al. 2021). Herein, our objective was therefore to compare, in a double-blinded and crossover fashion, the capability of burstDR and tonic eMCS to alleviate intractable, drug-resistant neuropathic pain in a cohort of thirteen consecutive patients.

2 | Methods

2.1 | Study Design

This retrospective observational study, which was conducted in a single tertiary academic medical center with 25 years' experience in eMCS, compared the analgesic efficacy of burstDR versus tonic eMCS with a double-blinded design. Data were collected prospectively according to a specific clinical protocol and were retrospectively analysed. Approval was obtained from the research ethics committee (IRBN872022/CHUSTE) in accordance with the declaration of Helsinki, and all patients gave their written informed consent for participation in the study.

2.2 | Patients

Inclusion criteria comprised adult patients (≥ 18 years-old) suffering from unilateral, intractable, drug-resistant neuropathic pain with severe intensity (numerical rating scale [NRS] $\geq 7/10$) for at least 1 year. Exclusion criteria comprised ferromagnetic components and implanted microprocessors (e.g., direct acoustic cochlear stimulator), drug-resistant or active epilepsy, pacemaker, pregnancy, and severe depression with catastrophising and/or personality disorders, as assessed in a multidisciplinary Pain Centre including psychiatric examination. The Hospital Anxiety Depression (HAD) score was systematically collected as an independent marker of anxiety or mood disorder.

Pharmacoresistance was considered when drugs proven to be efficacious in neuropathic pain, alone or in combination, fail to induce useful pain relief from the patient/physician point of view after an appropriate duration of treatment with adequate dosage, or if intolerable side effects occur (Hansson et al. 2009). Various drugs were used as first-line (serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, gabapentin) and second-line (pregabalin, tramadol) treatments, according to the French guidelines for the management of neuropathic pain, updated in 2021 (Moisset et al. 2020).

Patients were considered eligible for eMCS after having exhibited a reliable (pain relief $\geq 30\%$) and reproducible analgesic response following at least four preoperative sessions of navigated (Visor2, ANT, Hengelo, Netherlands), robot-guided (Smartmove, ANT), high-frequency (20 Hz) rTMS (MagPro stimulator with a figure-eight coil, Magventure Tonika Electronic, Farum, Denmark) targeting the motor cortex (hand knob area) contralateral to pain. At the end of the rTMS trial, all patients were back to their baseline pain scores prior to the performance of eMCS.

For each patient, we systematically collected: (1) demographic data (age, gender); (2) clinical characteristics of pain (aetiology, topography, semiology, duration); and (3) electrophysiological recordings (laser-evoked potentials [LEPs] and somatosensory evoked potentials [SSEPs], classified as normal, impaired, or abolished), if available.

2.3 | Operative Technique for eMCS

The operative technique for eMCS has been reported in more detail elsewhere (Nuti et al. 2005). Briefly, under general anaesthesia, two paddle-shaped, 4-contacts electrodes (Lamitrode, Abbott, Chicago, IL, USA) were sutured to the dura mater over the motor contact, through a craniotomy delineating the central sulcus of Rolando. The motor cortex was localised thanks to multimodal mapping. Reconstructed 3D brain images with overlying functional magnetic resonance imaging (MRI) data were incorporated into a navigation system (Kolibri, Brainlab, Feldkirchen, Germany), and the exact location of the central sulcus/motor cortex was then confirmed online with electrophysiological mapping (SSEPs phase reversal technique, motor evoked potentials [MEPs] recording). The positioning of the electrodes was adjusted according to the topography of the painful territory, as previously described (Pommier et al. 2018; Figure 1). During

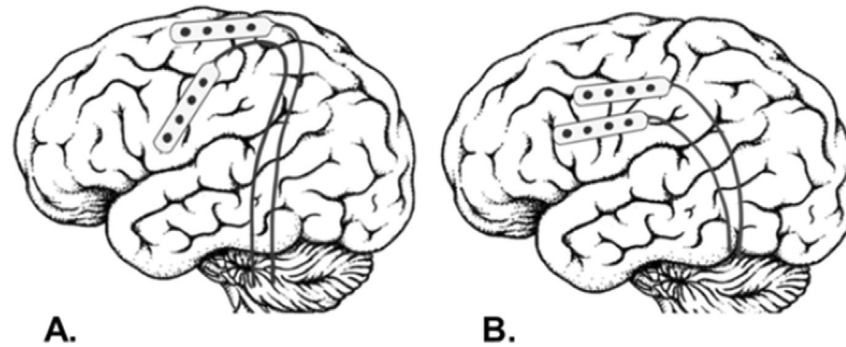


FIGURE 1 | Schematic drawing of the positioning of the electrodes according to pain topography. (A) Pain covering the whole hemi-body. (B) Pain covering the upper limb and face.

the same operative stage, the electrodes were connected to a dual-channel stimulator (Proclaim, Abbott) capable of delivering both burstDR and tonic waveforms, implanted within a subcutaneous pocket just above the pectoral fascia. On postoperative day one, a computed tomography (CT) scan was systematically performed and co-registered (mutual information algorithm) to the preoperative MRI to assess the accurate placement of the electrodes.

2.4 | Stimulation Protocol

During the first postoperative 6 months (trial phase), all patients successively received both stimulation waveforms in a double-blinded fashion and in a random order, i.e., three consecutive months of burstDR eMCS and then three consecutive months of tonic eMCS, or vice versa, without a washout interval. To ensure a homotopic eMCS with respect to the painful territory, the activated contacts (bipolar configuration) were chosen according to their anatomo-functional locations, as assessed by intraoperative electrophysiological findings and on postoperative CT scan images co-registered to preoperative MR images. BurstDR waveform was administered applying the same specific parameters as currently described for SCS (Vesper et al. 2019; Deer et al. 2022): trains of five spikes with a pulse width of 1 ms and an internal frequency of 500 Hz, a burst rate of 40 Hz, cyclisation of 30 s “on”/90 s “off”. Amplitude was set to 1.0–1.5 mA, i.e., in a range consistent with the settings reported in preliminary burstDR eMCS studies (Sokal et al. 2019, 2020; Nüssel et al. 2021). The tonic waveform used the following parameters, as classically described for conventional eMCS: frequency = 40 Hz, pulse width = 250 μ s, amplitude = 80% of motor threshold, cyclisation = 30 min. “on”/30 min. “off”. Polarities of electrodes remained unchanged between burstDR and tonic eMCS.

2.5 | Outcomes Assessment After eMCS

The primary outcome criterion was the percentage of pain relief (%PR) declared by the patient. %PR is a subjective pain improvement score corresponding to a continuous 0%–100% scale based on the appraisal of pain intensity change, which has been previously validated for long-term evaluation of eMCS efficacy (Nuti et al. 2005). %PR was systematically recorded at 3 and 6 months by a pain physician (not involved in eMCS programming) who

was blinded to the ongoing stimulation waveform. Patients were asked to quantify their level of pain relief from 0% (absence of pain relief) to 100% (complete pain relief), considering their baseline pain level prior to surgery. The secondary outcome criterion was the proportion of patients reporting a superior %PR with the burstDR waveform (compared to the tonic waveform) at the end of the trial phase.

After completion of the 6-month trial phase, the patient had to choose the most valuable stimulation waveform (i.e., burstDR or tonic) to retain for chronic eMCS, depending on two criteria, in this order of importance: (1) the efficacy in reducing pain; (2) in the case of equivalence for criteria (1), the estimated longevity of the stimulator’s battery, by selecting the paradigm offering the lower energy consumption. During this open-label phase, further variables were collected: possible change in the level of analgesic drug intake (three conditions: unchanged, decreased, withdrawn); the yes/no response to the question of whether the patient, assuming a similar level of eMCS efficacy, would agree to undergo surgery again; and the treatment modality she/he preferred between multiple rTMS sessions and eMCS (three conditions: equivalence, rTMS, eMCS).

2.6 | Statistical Analysis

R software (version 4.1.3) was used for statistical analysis. Qualitative variables were expressed as the percentage of occurrence in the cohort. Quantitative variables were expressed as the mean \pm SD. A comparison between burstDR and tonic eMCS was performed by using a generalised linear model with a random effect, with %PR as the dependent variable and treatment sequence (i.e., burstDR–tonic or tonic–burstDR) as a fixed effect. A χ^2 test was used to compare the proportion of patients who preferred the burstDR waveform or the tonic waveform at the end of the trial phase. Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Patients

Thirteen patients (twelve women, mean age = 48.4 \pm 11.7 years, range = 30–68 years) suffering from unilateral neuropathic pain of various aetiologies underwent eMCS between January

2019 and April 2023. Mean postoperative follow-up was 27.2 ± 13.0 months (range = 10–53 months). Clinical characteristics are summarised in Table 1. Before eMCS, all patients had been previously treated according to recommendations for neuropathic pain management (Moisset et al. 2020; Table 2). They were considered eligible for eMCS because of an intractable, drug-resistant pain condition and because they previously exhibited a reliable ($\geq 30\%$) and reproducible %PR (on average, for the overall patient population = $67.7\% \pm 22.4\%$, range = 30%–100%) after at least four sessions of 20-Hz rTMS (Pommier et al. 2018). In the entire cohort, the HAD score was 12.5 ± 4.2 for anxiety and 9.0 ± 3.3 for depression.

3.2 | Comparison Between burstDR and Tonic eMCS

Outcomes in terms of %PR are summarised in Table 3 and Figure 2. In the overall patient population, the averaged %PR was $75.4\% \pm 18.6\%$ after burstDR eMCS and $61.1\% \pm 28.6\%$ after tonic eMCS ($p = 0.21$). There was no “sequence effect”, i.e., the order of treatments (burstDR–tonic or tonic–burstDR) did not influence the outcomes.

By the end of the trial phase, the burstDR waveform was the preferred paradigm retained for chronic eMCS in 9/13 patients, given a superior pain relief over tonic eMCS. Conversely, the tonic waveform was chosen as the more effective paradigm by 4/13 patients ($p = 0.16$).

3.3 | Outcomes at Last Follow-Up

All patients declared a preference for eMCS in comparison to multiple sessions of rTMS, which could be linked either to a superior and more stable pain relief over time or to the advantage of being delivered from iterative admissions at the hospital every 15–20 days to perform rTMS maintenance treatment. Furthermore, all patients also declared that they would agree to undergo surgery again assuming a similar level of eMCS efficacy.

At the last follow-up visit, we did not observe any diminution in the magnitude of pain relief. Analgesic drug intake was decreased or withdrawn in 10/13 patients (6/9 patients in the group treated with burstDR eMCS and 4/4 patients in the group treated with tonic eMCS).

3.4 | eMCS Adverse Side Effects

During the trial phase with the tonic waveform, one patient (No. 1) presented two episodes of focal seizures with transient language suspension (full recovery in < 1 min) and a normal CT scan at postoperative day 10. There was no seizure recurrence after a slight decrease in the amplitude of stimulation (from 3.0 to 2.5 mA). No antiepileptic drug was introduced.

No adverse side effect (e.g., seizures, abnormal headaches) was reported in relation to the burstDR waveform in the short and long term.

We did not regret any wound dehiscence, hardware infection, or neurological complication.

4 | Discussion

The strength of the present study is to provide for the first time a double-blind, crossover comparison of burstDR versus tonic eMCS for the management of chronic neuropathic pain refractory to the best pharmacological treatment. eMCS is particularly well suited for a comparative study of different waveforms in a blinded fashion since it does not evoke any sensation, leading the patient (and the observer) totally unaware regarding the nature of the ongoing stimulation paradigm.

Our results showed that the burstDR waveform is at least as effective as the (conventional) tonic waveform in relieving pain. Nine out of 13 patients preferred burstDR over tonic waveform due to the subjective impression of superior pain relief. At the group level, a superior pain relief was obtained with burstDR eMCS compared to tonic eMCS ($75.4\% \pm 18.6\%$ vs. $61.1\% \pm 28.6\%$), although the difference did not reach statistical significance, possibly because of the small sample size of the study. At the individual level, one patient (No. 2) reported a dramatic gain in terms of %PR after burstDR compared to tonic eMCS, whereas another (No. 4) reported the opposite. Such observations underline the importance of testing different stimulation waveforms in chronic neuropathic pain patients submitted to eMCS, with the goal of an optimised, personalised treatment. There was no washout interval during the trial phase, but the second stimulation period (randomly assigned to burstDR or tonic waveform in nearly equal proportion) was likely long enough (3 months) to be devoid of prolonged effect related to the first paradigm tested. As currently described for SCS, we administered a burstDR waveform with intermittent cycling (30 s “on”/90 s “off”) and at low amplitude, allowing us to decrease energy consumption and to preserve the battery of the stimulator without compromising clinical efficiency (Vesper et al. 2019; Deer et al. 2022). Applying the burstDR waveform over the motor cortex appeared safe, without any adverse side effects reported.

In our experience, although burstDR eMCS showed promising results in patients selected according to a good responsiveness to multiple preoperative sessions of high-frequency rTMS, it should not be proposed as a rescue option in subjects previously habituated to tonic eMCS for a long time and in whom surgery failed to improve pain. Among our cohort of eMCS patients, two patients (non-included in this study, unpublished data) operated on in the early 2000s before appropriate preoperative rTMS screening was regularly done in our Centre, demanded a (second) re-implantation of the stimulator when the battery had been depleted, although they reported only a slight (%PR $\leq 10\%$) or even absent pain relief. This gave us the opportunity to replace the depleted stimulator delivering only the tonic waveform with a new-generation stimulator capable of delivering both tonic and burstDR waveforms. Unfortunately, no additional improvement in pain relief was observed after activation of the burstDR stimulation paradigm, underlining the prime importance of rTMS screening as the most valuable tool to accurately select the best candidates for eMCS.

TABLE 1 | Clinical characteristics of patient population.

Case no.	Gender	Age (years)	Pain characteristics							Lesion type	SSEPs	LEPs
			Continuous	Paroxysytic	Allodynia	Hyperpathia	Pain topography	Hyperpathia	Lesion type			
1	F	40	No	No	No	No	No	Lower limb	Ischemic stroke (insula)	Normal	Impaired	
2	F	43	No	No	Yes	No	No	Upper limb	Hemorrhagic stroke (internal capsule, lenticular nucleus)	Normal	NA	
3	M	53	Yes	Yes	Yes	No	No	Hemibody	Cervical spondylotic myelopathy	Normal	NA	
4	F	44	Yes	Yes	Yes	Yes	Yes	Hemibody	Multiple Sclerosis	Normal	NA	
5	F	30	No	No	Yes	Yes	Yes	Lower Limb	Multiple Sclerosis	Normal	NA	
6	F	68	Yes	Yes	Yes	No	No	Face	Trigeminal pain	Normal	NA	
7	F	68	Yes	No	Yes	No	No	Hemibody	Ischemic stroke (insula)	Normal	NA	
8	F	35	No	No	Yes	Yes	Yes	Hemibody	Ischemic stroke (insula)	Normal	NA	
9	F	53	Yes	No	Yes	Yes	Yes	Hemibody	Unknown	Normal	Normal	
10	F	46	Yes	Yes	Yes	No	No	Lower and upper limb	Spinal cord lesion of unknown origin	Normal	Impaired	
11	F	47	Yes	No	No	Yes	Yes	Hemibody	Hemorrhagic stroke	Normal	NA	
12	F	59	Yes	No	Yes	Yes	Yes	Hemibody	Ischemic stroke	Normal	NA	
13	F	44	Yes	Yes	Yes	Yes	Yes	Lower limb	Post traumatic cervical myelopathy	Normal	Impaired	

Abbreviation: NA, not available.

TABLE 2 | Medications used before eMCS.

Case no.	SSRI or SNRI antidepressants	Tricyclic antidepressants	Antiepileptics	Benzodiazepines	Ketamine	Level 2 and 3 analgesics
1	No	No	Gabapentin, Pregabalin	No	No	No
2	Duloxetine	Amitriptyline	Gabapentin, Pregabalin	Clonazepam	No	Yes
3	No	No	Gabapentin, Pregabalin	No	No	Yes
4	Venlafaxine	Amitriptyline	Gabapentin, Pregabalin	Clonazepam	No	No
5	Venlafaxine	Amitriptyline, Clomipramine	Gabapentin, Pregabalin	Clonazepam	Yes	Yes
6	No	No	Gabapentin, Pregabalin, Carbamazepine, Lamotrigine	No	No	No
7	No	No	Pregabalin	Clonazepam	No	No
8	Venlafaxine	Amitriptyline	Gabapentin	No	No	Yes
9	Venlafaxine	Clomipramine	Gabapentin, Pregabalin	Clonazepam	No	Yes
10	Duloxetine	No	Carbamazepine	Clonazepam	Yes	Yes
11	No	No	Pregabalin	No	No	Yes
12	Duloxetine	No	Gabapentin	Clonazepam	No	Yes
13	Duloxetine	Amitriptyline	Gabapentin, Pregabalin	No	No	Yes

Abbreviations: SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

To our knowledge, there were only two recent studies that previously investigated the analgesic effects of burstDR eMCS for the management of intractable neuropathic pain. In 2019, Sokal et al. (2019, 2020) undertook an unblinded study comparing burstDR versus tonic eMCS in six patients suffering from post-stroke ($n = 3$) or trigeminal ($n = 3$) neuropathic pain. During the postoperative period, patients could change the stimulation paradigm between burstDR and tonic as early as 5–7 days by using their own remote controller, and outcomes were evaluated after 4 weeks during an outpatient visit, based on the personal choice of patients who were selecting the most frequently applied paradigm, inducing the most efficient pain relief. Five out of six patients found burstDR eMCS more effective than tonic eMCS. The mean baseline NRS was 95 mm, decreasing on average to 72 and 53 mm with tonic and burstDR waveforms, respectively ($p = 0.003$). The authors concluded that burstDR eMCS is a promising modality in patients previously habituated to tonic eMCS. However, the study design included potential confounding factors. Indeed, eMCS usually takes several days or weeks to produce maximum analgesia, and its clinical efficiency may be long-lasting even after eMCS discontinuation (Croft et al. 2002). Therefore, the possibility for the patients to early and repetitively alternate between burstDR and tonic waveforms during the testing phase may have introduced bias, the pain relief rated at a given moment being not necessarily the result of the ongoing

stimulation paradigm but possibly the consequence of the previous one. In 2020, Nüssel et al. (2021) reported the case of a single patient suffering from post-stroke neuropathic pain, in which burstDR eMCS provided a significant (decrease in NRS pain level from 9/10 [preoperative period] to 2/10 [postoperative period]) and prolonged (extended follow-up of 5 years) pain relief.

The concept of burstDR has been developed by De Ridder et al. (2010) on the basis of a biomimetic stimulation waveform resembling the natural firing pattern of the central nervous system, in particular the pain network (Jahnsen and Llinás 1984; Swadlow and Gusev 2001). The role of gamma oscillations (often at 40 Hz) in the subjective experience of pain has been demonstrated (Croft et al. 2002). Furthermore, a burst-discharge pattern is frequently observed within the sensory relay nuclei of the thalamus in patients suffering from neuropathic pain (Brown and Barbaro 2003), which may evoke short- and long-term plasticity in connected brain networks involved in pain processing. The transition from acute to chronic pain is believed to be the result of an altered oscillation rhythm within the medial thalamus–anterior cingulate cortex circuit (thalamocortical dysrhythmia model) responsible for the emotional appraisal of pain (Bliss et al. 2016). To date, burstDR waveform has been applied mainly for SCS to treat chronic neuropathic pain of peripheral origin. A large randomised controlled trial with level 1 evidence

TABLE 3 | Outcomes after eMCS.

Case no.	%PR with rTMS	First stimulation paradigm	%PR after Burst ECMS	%PR after tonic ECMS	Stimulation paradigm retained for chronic eMCS	Preference (rTMS versus eMCS)	Yes/No response	Changes in level of analgesic drugs intake
1	90%	Tonic	90%	80%	Burst	eMCS	Yes	Withdrawn
2	70%	Burst	90%	10%	Burst	eMCS	Yes	Unchanged
3	50%	Tonic	80%	70%	Burst	eMCS	Yes	Decreased
4	80%	Tonic	40%	80%	Tonic	eMCS	Yes	Decreased
5	80%	Tonic	70%	90%	Tonic	eMCS	Yes	Decreased
6	50%	Burst	70%	50%	Burst	eMCS	Yes	Unchanged
7	100%	Burst	100%	100%	Burst	eMCS	Yes	Withdrawn
8	30%	Burst	50%	20%	Burst	eMCS	Yes	Decreased
9	70%	Tonic	65%	70%	Tonic	eMCS	Yes	Withdrawn
10	40%	Burst	60%	40%	Burst	eMCS	Yes	Unchanged
11	100%	Burst	100%	40%	Burst	eMCS	Yes	Decreased
12	70%	Burst	90%	95%	Tonic	eMCS	Yes	Decreased
13	50%	Burst	75%	50%	Burst	eMCS	Yes	Decreased

Abbreviation: NA, not applicable.

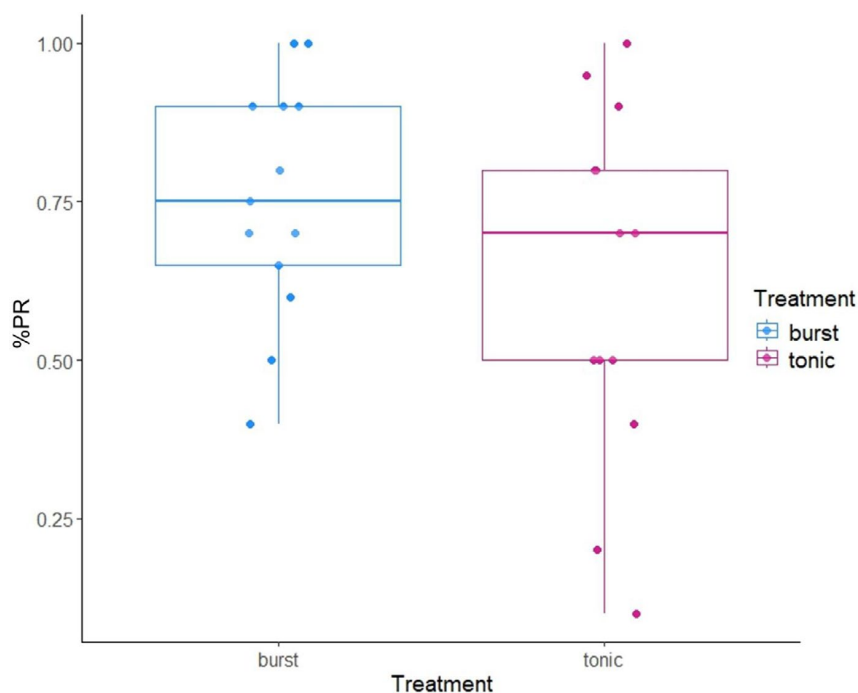


FIGURE 2 | Pain relief after BurstDR and Tonic eMCS. %PR, percentage of pain relief.

has demonstrated superior pain relief with burstDR SCS compared to tonic SCS in patients with chronic intractable pain of the trunk and/or limbs (Deer et al. 2018). Bocci et al. (2018) observed that burstDR SCS dampened the brain LEPs significantly more than tonic SCS (Bocci et al. 2018). Interestingly, burstDR

SCS influenced both the short-latency N1 (which source is localised in the secondary somatosensory cortex) and late-latency P2 (anterior cingulate cortex) waves, which represent the sensory-discriminative and emotional dimensions of pain, respectively. Furthermore, by using EEG recordings, De Ridder, Perera, and

Vanneste (2017) found that burstDR SCS (but not tonic or placebo SCS) produced synchronised activity in the anterior cingulate cortex. Taken together, these data suggest that burstDR SCS may modulate both the lateral and medial pain pathways.

Although the precise mechanisms of action of tonic eMCS remain to be fully elucidated, some experimental studies in humans have provided valuable insights using positron emission tomography and electrophysiological recordings (García-Larrea et al. 1997). Current hypotheses suggest that tonic eMCS may influence the ascending and descending networks relevant to pain transmission and processing. Bottom-up activation of the medial thalamus–anterior cingulate cortex circuit may modulate the emotional appraisal of pain, while top-down activation of the periaqueductal grey matter may lead to descending inhibition of pain transmission toward the spinal cord (García-Larrea and Peyron 2007). Additionally, increasing evidence indicates that tonic eMCS triggers a release of endogenous opioids (Maarrawi et al. 2007). We are not aware of eMCS studies focused specifically on pain relief mechanisms induced by the burstDR waveform. A recent study conducted in three patients demonstrated that burst eMCS is associated with an improvement not only in subjective pain scores but also in objectifiable parameters of autonomic cardiovascular modulation (Borutta et al. 2023). Animal studies demonstrated that burst firing is more powerful to activate the cerebral cortex (Swadlow and Gusev 2001; Sherman 2001). This may be due to the fact that burst firing requires less temporal integration to reach the depolarisation threshold of a neurone, and therefore burstDR stimulation may activate neurones that are not activated by tonic stimulation. Furthermore, burstDR stimulation delivers significantly higher electrical charge per second than tonic stimulation, which could lead to a more powerful biological effect (Miller et al. 2016). Finally, it is noteworthy that brain oscillation rhythms are a critical phenomenon implied in physiological, pathological, and even therapeutic (neuromodulation) processes. One hypothesis is that burstDR eMCS is best suited to interfere with the proposed thalamocortical dysrhythmia model. Furthermore, synchronous gamma oscillations, often at 40 Hz, have been demonstrated throughout the brain, including the motor cortex and thalamus (Funk and Epstein 2004; Khanna and Carmena 2017). Therefore, adequate matching between the oscillatory rhythm in the motor cortex and that of the burstDR waveform may increase synaptic efficacy, thus enhancing the functional connectivity of the motor cortex with remote brain networks involved in pain modulation.

5 | Conclusions

Although previous SCS randomised control trials have demonstrated the superiority of the burstDR waveform over the tonic waveform, the present study—the first to compare burstDR eMCS versus tonic eMCS in a double-blinded fashion—found no statistically significant difference in terms of the magnitude of pain relief between the two paradigms. However, burstDR eMCS proved to be safe, and a greater number of patients preferred this stimulation waveform. Future studies with larger cohorts are needed to further investigate the analgesic effects of burstDR eMCS in intractable, drug-resistant neuropathic pain.

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Conflicts of Interest

The authors declare no conflicts of interest.

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