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A Pilot Double-Blind Randomised Sham-Controlled Trial of Paraesthesia-Free Burst Waveform Spinal Cord Stimulation in a Small Case Series of Patients with Chronic Spinal or Limb Pain

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Abstract

The aim of this study was to identify methodological issues that might influence comparison of burst versus sham spinal cord stimulation for treating chronic pain. Six patients with an implanted BurstDR spinal cord stimulator were assessed double-blind during eight 3-to-4-day ON or OFF cycles over a 28-day period. The stimulator was switched off during two randomly selected cycles. Pain intensity was the primary outcome, and secondary outcomes included analgesic consumption, activity estimation and sleep quality. To minimise stimulation wash-in and wash-out effects, ratings during the first two days of each cycle, or where rescue medication was taken, were discarded. Mean ratings during ON versus OFF cycles were compared using Wilcoxon's signed-ranks test. Pain ratings averaged 4.1 ± 2.0 during OFF cycles and 3.9 ± 2.5 during ON cycles (difference not significant). However, ratings were one or more points higher during OFF than ON cycles in two patients with recent stimulator implants who correctly identified the stimulator status during most cycles. Patients were more refreshed on waking during ON than OFF cycles but burst stimulation did not influence ratings

of pain interference, mood, sensitivity to mechanical stimulation or consumption of rescue medication. The findings in our case series point to the importance of investigating individual differences in response to burst spinal cord stimulation. To establish whether this treatment is effective for managing chronic pain, selecting patients with short wash-in and wash-out times, or including lengthy periods of wash-in and wash-out in the study protocol, is crucial. Selection criteria should also include pain ratings at entry of 3 or less on a 0-10 scale; stable physical and psychological functioning with little disability; minimal rescue medication; and patients who take less than 50 morphine equivalents per day.

Keywords
Trial design; spinal cord stimulation; methodology; chronic pain; burst stimulation; sleep quality

1. Introduction

High-quality double-blind placebo or sham controlled studies of spinal cord stimulation treatment effects are sparse [1-4] but are increasingly demanded by authorities surveying the cost effectiveness of spinal cord stimulation treatment. In an appraisal of studies published up to January 2019 [3], methods of placebo/sham control and blinding were found to be poorly reported or introduced potential biases in most studies. Studies published since then have encountered similar methodological challenges (Table 1).

Table 1 Placebo-controlled double blind crossover trials of paraesthesia-free burst spinal cord stimulation published since 2020.

Authors	Participants	Methods	Findings
Sokal et al. [2]	18 patients with failed back surgery syndrome and/or complex regional pain syndrome entered the crossover trial and another 5 patients were excluded from analysis	Patients were randomized to receive 14-day sequences of conventional supra-threshold low frequency (40-60 Hz) stimulation; sub-threshold 1 kHz stimulation; clustered tonic (burst) stimulation; and sham (no stimulation). Thirteen patients underwent a 2-week trial of low frequency stimulation to check the coverage of pain area with paraesthesia. Electrical stimuli were delivered by a non-rechargeable (17 cases) or rechargeable (1 case) implantable pulse generator. This patient recharged the battery for half an hour once per week despite the battery status (and thus was	Pain intensity scores were significantly lower during each treatment period than before the stimulator was implanted. All forms of treatment were equivalent to each other and to sham.

		potentially unblinded). There were no washout periods between treatments.	
Eldabe et al. [1]	19 patients with chronic back and leg pain who had obtained stable pain relief from conventional spinal cord stimulation	Patients were randomized to receive 14-day sequences of sub-threshold burst stimulation; tonic sub-threshold stimulation at 500 Hz (T500); and sham spinal cord stimulation. Electrical stimuli were delivered by an implantable pulse generator which was recharged daily for 2 hours and which adjusted the voltage output to be 10% below the paraesthesia threshold in any body posture. Data were assessed during the last 5 days of each condition. A current leak was included in the sham condition to balance charging times in the three conditions.	Pain intensity scores were significantly lower in the T500 condition than in the burst and sham conditions, which were equivalent to each other.
Hara et al. [4]	50 patients with radicular pain after surgery for degenerative lumbar spine disorders	All patients underwent a 2-week trial of supra-threshold stimulation to check the coverage of pain area with paraesthesia and that pain decreased by at least 2 points on a 0-10 numeric rating scale. Eligible patients were randomized to receive two 3-month blocks of paraethesia-free burst stimulation and two 3-month blocks of sham stimulation. Electrical stimuli were delivered by a non-rechargeable implantable pulse generator. The clinical trial nurse who adjusted settings on the stimulator (and thus was not blinded to the treatment allocation) also collected data from the trial participants.	Oswestry Disability and pain intensity scores were equivalent in the burst and sham conditions

Devices that deliver burst waveforms are routinely programmed to be entirely paraesthesia-free and to cycle with more off time than on time. As these devices have primary cell batteries which require no interaction with the patient such as charging, the patient can be entirely unaware of the on-off status of their stimulation treatment. Hence, employing these devices in double-blind placebo or sham controlled studies of spinal cord stimulation may overcome some of the limitations of prior research. Despite early promise [5, 6], findings in double-blind sham controlled studies of burst spinal cord stimulation are mixed [1, 2, 4, 7], possibly because of methodological complexities in studies conducted to date [3].

The aim of this study was to identify methodological issues in a small series of patients that might affect comparison of burst versus sham stimulation. The pain intensity score was the primary outcome, and secondary outcomes included analgesic consumption, activity estimation and sleep quality.

2. Materials and Methods

2.1 Participants

All patients with an implanted BurstDR spinal cord stimulator who attended a small private pain management practice were reviewed for suitability to participate in this study. To identify approximate wash-in and washout times, patients were asked to identify when pain increased after they switched their stimulator off (the wash-out interval) and when pain decreased when the stimulator was reactivated (the wash-in interval). Inclusion criteria included significant pain relief without any accompanying sensation from electrical stimulation, and self-reported wash-in and wash-out intervals of less than 2 days. Patients were excluded if they did not fulfil the inclusion criteria but there were no additional exclusion criteria.

The target for the sample was 10 patients. Of the 25 patients assessed for eligibility, six patients who met the inclusion criteria agreed to participate in the double-blind component of the study during the study period (September 2020 to June 2023) (Figure 1). Each patient had a history of chronic injury-induced back, neck or limb pain associated with neuropathic symptoms and neural sensitization (Table 2). Five patients were implanted with a non-rechargeable device. The other patient (Case 5 in Table 2) was implanted with a device that required recharging every six weeks. In this case, the device was recharged prior to the study and the remote control was locked to prevent notification of charge depletion. In each case, stimulation amplitude was always at least 40% below the perception threshold to avoid any sensation associated with stimulation.

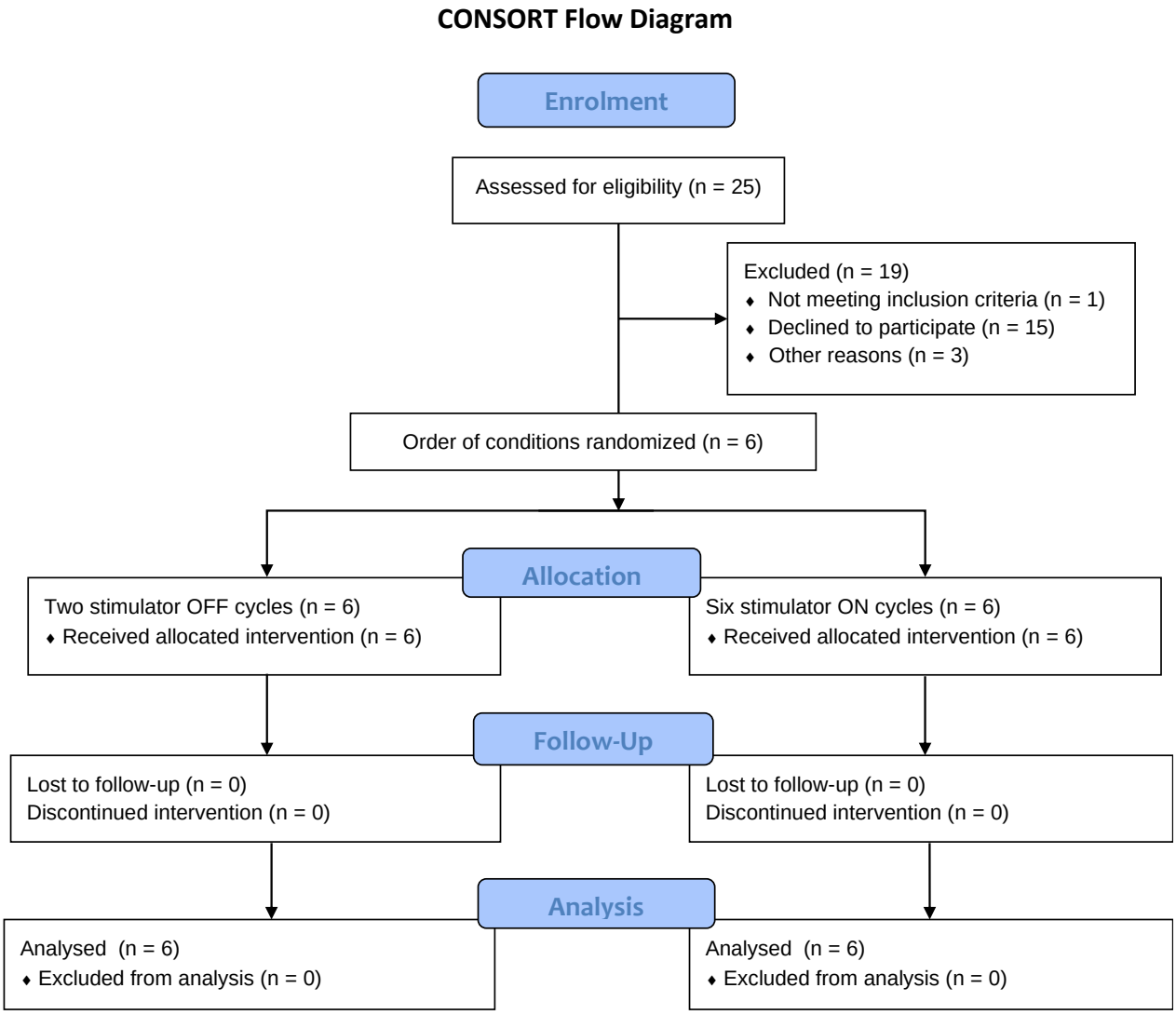

Figure 1 Flow diagram of participant recruitment and withdrawal. Of the 25 patients assessed for eligibility, one was excluded because pain failed to stabilise after the stimulator was implanted. Fifteen patients who met the inclusion criteria declined to participate for various reasons (reluctant for the stimulator to be switched off; work obligations; commuting difficulties; pending surgery; or moving house). Three other patients decided not to participate after the wash-out assessment: one because of difficulty coping with pain when the stimulator was switched off; another because relatives were concerned that participation would disrupt pain control; and the third because of concerns about muscle weakness and falling when the stimulator was switched off. The six patients who entered the double-blind part of the study completed every assessment in all eight 3-to-4-day cycles (two with the stimulator OFF and six with the stimulator ON).

Table 2 Clinical details.

Case number, age, sex	Pain history	Current medications	Pain at baseline (0-10) [a]	Lead position	Programming
1. 55, F [b]	Chronic injury-induced L5 and S1 low back pain associated with neuropathic sciatic nerve symptoms and neural sensitization for 8 years. Stimulator implanted 15 months ago.	Tapentadol; Amitriptyline; Pregabalin; Rivaroxaban; Propranolol; Pantoprazole; Desvenlafaxine; NSAIDS (rescue medication)	3	Octrodes at T8 and T9	BurstDR: 0.4 mA cycling program 30 s ON/90 s OFF
2. 28, M	Chronic cervical pain associated with neuropathic symptoms and neural sensitization after a traction injury to the right arm 3 years ago. Stimulator implanted 16 months ago.	Buprenorphine; Tapentadol; Pregabalin; Duloxetine; Nortriptyline; Oxycodone (rescue medication)	3	Octrodes at C2 and C7	BurstDR: 0.2 mA cycling program 30 s ON/180 s OFF
3. 60, M [b]	Whiplash injury resulting in 13-year history of neck, arm and head pain following a motor vehicle accident. Stimulator implanted 14 months ago.	Tapentadol; Pregabalin; NSAIDS; Saxagliptin; Simvastatin; (no rescue medication taken)	4	Octrodes at C4 and C5	BurstDR: 0.3 mA cycling program 30 s ON/180 s OFF
4. 64, F	Neuropathic pain associated with 11-year history of patella dislocation followed by multiple surgeries. Stimulator implanted 12 months ago.	Gabapentin; Clonidine; Lignocaine; Buprenorphine (rescue medication)	6	Octrode at T10	BurstDR: 0.2 mA cycling program 30 s ON/180 s OFF
5. 57, M [c]	Neuropathic and nociplastic symptoms associated with chronic low back pain for 3 years after a work injury. Stimulator implanted 5 months ago.	None; (no rescue medication taken)	1	Octrodes at T8 and T9	BurstDR: 0.3 mA cycling program 30 s ON/90 s OFF

6. 59, F [c]	Chronic injury-induced cervical and low back pain for >40 years treated with multiple surgeries resulting in postsurgical sciatica. Stimulator implanted 2 months ago.	NSAIDS; Gabapentin; Tramadol (rescue medication); Estradiol; Irbesartan; Tapentadol (rescue medication)	0	Octrodes at T8 and T9	BurstDR: 0.6 mA cycling program 30 s ON/90 s OFF

[a] Average pain over the past 24 hours (unblinded, stimulator ON). [b] Employed part-time. [c] Employed full-time.

2.2 Clinical Trial Registration

The trial protocol was registered prospectively with the Australian and New Zealand Clinical Trials Registry (registration number ACTRN12620000720910).

2.3 Procedures

A stimulator technician switched the stimulator off for two of eight 3-to-4-day cycles over a 28-day period. The 'OFF' periods were not consecutive and were determined by a computer randomisation program. Neither the patient nor a nurse assessor who collected data knew whether the stimulator was ON or OFF. Patients retained their remote control but it was locked to prevent access to stimulator status and program details. Patients were advised to contact the stimulator technician to receive the code to unlock the controller and restore their preferred program if they were in distress. However, none took up this option.

Patients filled out a pain diary three times/day (on waking, 8 hours later, and before going to bed) for 28 consecutive days, noted how long they were able to walk and sit comfortably, and recorded details of any rescue medication consumed (Figure 2). Pain was rated on a 0-10 scale, where 0 corresponded to “no pain” and 10 to “intense pain”. Minimum periods of walking and sitting were later recoded as “a minute or less” (0), “up to 10 minutes” (1), “up to 1 hour” (2) and “longer than 1 hour” (3). In addition, sleep parameters (time going to bed, number of awakenings, time getting out of bed, approximate sleep time, quality of sleep) were recorded in a standard sleep diary. At baseline and at the end of each cycle, patients completed the Brief Pain Inventory (relating to the past 24 hours) [8], the Pain Catastrophising Scale (relating to the present moment) [9], and the Depression, Anxiety and Stress Scale (where ratings related to the patient’s experience during the previous week [at baseline] or 3- or 4-day cycle) [10]. Behavioural signs of pain during standard timed tasks (repeated trunk flexion, repeated sit-to-stand, timed up and go, loaded reach and 50-foot walk) [11] were assessed by the nurse assessor. In addition, the pressure-pain threshold and sharpness ratings to five 1-second applications of a spring-loaded pin (40 g, Neuro-pen, Owen Mumford, Woodstock, Oxfordshire, UK), with rests of 1 s between each application, were assessed at a reference site (mid-forehead). Sharpness was rated verbally between 0 (not sharp) to 10 (extremely sharp). To assess “wind-up”, patients rated sharpness to the first and final application of the pin. Mean scores at trial baseline are listed in Table 3.

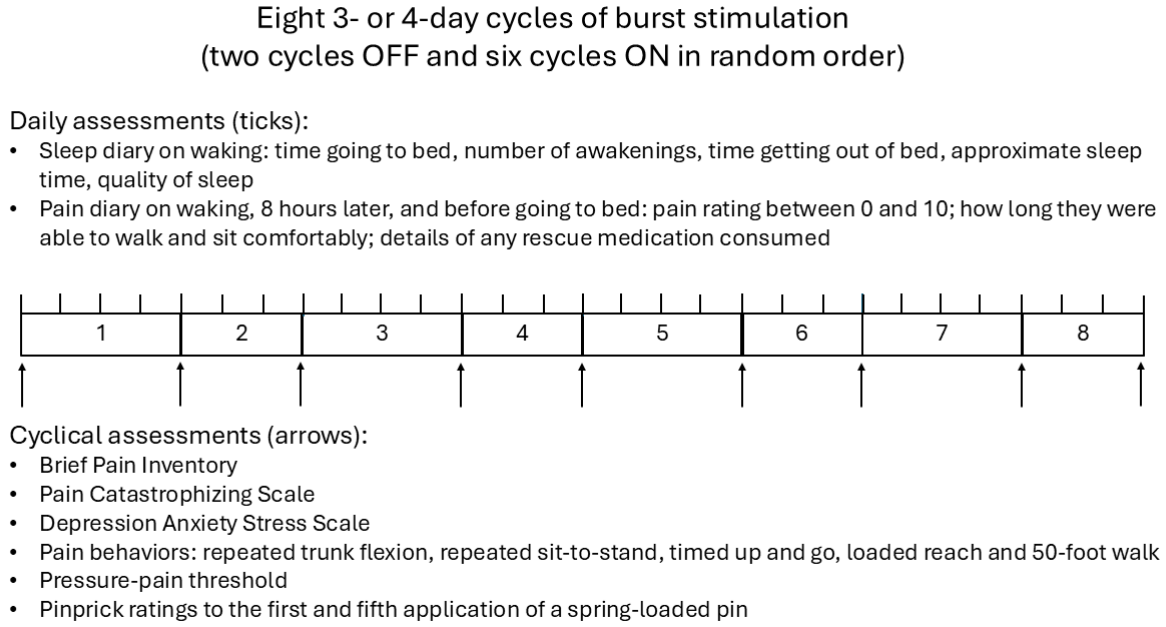

Figure 2 Timing of assessments. Patients filled out a diary each day for 28 consecutive days (ticks). In addition, assessments were carried out by the nurse assessor on Day 1 (Trial baseline) and thereafter on the last day of each 3- or 4-day cycle (arrows).

Table 3 Secondary outcomes at baseline and during the trial in the six patients enrolled in the study.

	Mean ± standard deviation		
	Baseline	OFF cycles	ON cycles
Rescue medication (% of days/cycle)		16.7 ± 30.3	22.2 ± 20.9
Minimum periods of walking [a]		1.8 ± 1.2	1.5 ± 1.1
Minimum periods of sitting [a]		1.3 ± .9	1.2 ± 1.0
Time in bed (hours)		7.2 ± 1.9	7.5 ± 1.8
Difficulty falling asleep [b]		0.9 ± 0.9	0.7 ± 0.7
Number of awakenings		2.9 ± 2.8	3.0 ± 2.5
Approximate sleep time (hours)		6.1 ± 1.2	6.2 ± 1.8
Refreshed on waking [c]		**0.5 ± 0.6** *	**0.8 ± 0.7**
Behavioral signs of pain			
Repeated trunk flexion (s)	**34.6 ± 10.8** #	28.7 ± 7.0	**31.1 ± 9.1**
Repeated trunk flexion (pain behaviours) [d]	0.7 ± 0.5	0.5 ± 0.5	0.6 ± 0.4
Repeated sit-to-stand (s)	24.4 ± 12.3	21.9 ± 10.3	21.2 ± 10.6
Repeated sit-to-stand (pain behaviours) [d]	0.7 ± 0.8	0.4 ± 0.5	0.6 ± 0.4
Timed up and go (s)	2.2 ± 1.3	2.0 ± 1.1	2.2 ± 1.2
Timed up and go (pain behaviours) [d]	0.3 ± 0.8	**0.2 ± 0.3** *	**0.5 ± 0.5**
Loaded reach (cm)	32.7 ± 17.3	23.2 ± 8.6	23.0 ± 9.0
Loaded reach (pain behaviours) [d]	0 ± 0	0.1 ± 0.2	0.1 ± 0.1
50 foot walk (s)	15.3 ± 3.7	15.2 ± 4.2	14.9 ± 4.6

50 foot walk (pain behaviours) [d]	0 ± 0	0.3 ± 0.4	0.1 ± 0.2
Brief Pain Inventory (0-10 ratings)			
Worst pain in past 24 hours	**4.0 ± 2.8** #	5.5 ± 2.5	**5.2 ± 2.7**
Least pain in past 24 hours	1.7 ± 1.6	2.7 ± 1.9	2.7 ± 1.7
Average pain in past 24 hours	2.8 ± 2.1	4.1 ± 1.2	4.0 ± 2.3
Pain interferes with general activity	5.2 ± 4.4	4.6 ± 2.4	5.0 ± 3.0
Pain interferes with mood	5.0 ± 4.0	4.3 ± 3.8	4.2 ± 3.7
Pain interferes with walking ability	5.2 ± 4.2	4.8 ± 3.2	4.9 ± 3.5
Pain interferes with normal work	5.3 ± 4.3	5.8 ± 3.6	5.2 ± 3.5
Pain interferes with relations with other people	4.0 ± 4.4	3.2 ± 3.4	3.3 ± 3.6
Pain interferes with sleep	4.8 ± 3.9	4.8 ± 3.8	4.6 ± 2.4
Pain interferes with enjoyment of life	4.7 ± 4.3	4.4 ± 2.8	4.6 ± 3.3
Mood			
Depression (0-21)	4.7 ± 4.1	3.0 ± 5.3	3.4 ± 5.7
Anxiety (0-21)	4.7 ± 3.7	3.3 ± 4.0	3.6 ± 5.6
Stress (0-21)	7.2 ± 4.8	5.4 ± 5.3	5.8 ± 6.3
Pain catastrophizing (0-52)	8.3 ± 10.9	6.3 ± 8.9	8.3 ± 13.7
Sensitivity to mechanical stimulation			
Pressure-pain threshold (kg)	2.0 ± 1.2	1.6 ± 1.0	1.7 ± 1.1
Sharpness to pinprick (one application) (0-10)	0.8 ± 0.4	1.0 ± 0.5	0.9 ± 0.3
Sharpness to pinprick (five applications) (0-10)	1.0 ± 0.6	1.1 ± 0.2	1.1 ± 0.3

[a] A minute or less = 0; up to 10 minutes = 1; up to 1 hour = 2; longer than 1 hour = 3.

[b] Easily = 0; after some time = 1; with difficulty = 2.

[c] Fatigued = 0; somewhat refreshed = 1; refreshed = 2.

[d] None = 0; 1 = mild; 2 = moderate; 3 = severe.

* Significant difference between ON and OFF cycles ($p < 0.05$, Wilcoxon's test).

Significant difference between Baseline and ON cycles ($p < 0.05$, Wilcoxon's test).

2.4 Statistical Approach

Exploratory statistical analyses were carried out using version 28 of SPSS for Statistics. The primary analysis was a comparison of mean pain ratings during double-blind periods of stimulation (ON versus OFF) using Wilcoxon's signed ranks test. To minimise wash-in and wash-out effects after the stimulator was switched off or on, ratings during the first two days of each cycle were discarded. Ratings on days where rescue medication was taken were also excluded. Secondary outcomes (consumption of rescue medication; sleep parameters) were investigated using a similar approach. Additional secondary outcomes recorded during clinical assessments (pressure-pain thresholds; sharpness ratings; behavioural signs of pain; and scores on the Brief Pain Inventory, Pain Catastrophizing Scale and Depression, Anxiety and Stress Scale) were compared between Stimulation ON versus OFF cycles using Wilcoxon's test. Sharpness ratings to single and repeated applications of the calibrated pin were investigated in a Stimulation (ON versus OFF) × Applications (one versus five) repeated measures analysis of variance. In addition, to assess practice and expectancy effects, secondary outcomes recorded during the first baseline visit (when the

stimulator was ON) were compared with ratings during double blinded ON cycles using a similar approach.

No patient was lost to follow-up and no data were excluded from the final analysis. The criterion of statistical significance was $p < 0.05$. The alpha level was not adjusted to reduce Type 1 errors as this was an exploratory pilot study. Results are reported as the mean ± standard deviation.

2.5 Ethics Statement

Patients provided written informed consent for the procedures, which were approved by Murdoch University's Human Research Ethics Committee (permit number 2020/044, approved 1st May, 2020). The Information Letter and Consent Form are included in Supplementary materials.

3. Results

The sample consisted of three men and three women aged between 28 and 64 years with longstanding pain. The burst DR spinal cord stimulator had been implanted 2-16 months before entry into the trial (mean ± standard deviation 10.7 ± 5.8 months, Table 2). Before the stimulator was implanted, pain ratings ranged between 5 and 9 on a 0-10 scale of pain intensity (mean ± standard deviation 6.8 ± 1.2) compared with a range between 1 and 4 (mean rating 2.4 ± 1.1) 10 days to two months after the implant.

3.1 Differences between Baseline and ON Cycles

Patients completed the "Repeated trunk flexion" task more quickly during ON cycles than at baseline ($p = 0.028$), possibly reflecting a practice effect (Table 3). However, other behavioural measures of pain did not change.

Patients rated their worst pain in the past 24 hours to be greater during blinded ON cycles (mean worst pain rating 5.2 ± 2.7) than during unblinded stimulation at baseline (mean worst pain rating 4.0 ± 2.8) ($p = 0.043$), but other measures of pain and mood did not change (Table 3).

3.2 Primary Outcome for Differences between OFF and ON Cycles

Pain ratings averaged 4.1 ± 2.0 during OFF cycles and 3.9 ± 2.5 during ON cycles ($p = 0.600$). In two of six patients, pain ratings were one or more points higher during OFF than ON cycles and, in another two cases, were slightly higher during OFF than ON cycles (Table 4). In the other two patients, pain ratings were higher during ON than OFF cycles. Notably, pain ratings were higher during OFF than ON cycles in patients whose stimulator had been implanted most recently (Spearman's $\rho = 0.94$, $p = 0.005$) (Table 4).

Table 4 Effect of burst stimulation on pain.

Case number	Stimulator implanted	Pain with stimulator OFF (0-10)	Pain with stimulator ON (0-10)	% change in pain with stimulation	Stimulator status judged correctly		
					OFF (2 cycles)	ON (6 cycles)	P [a]
1	15 months ago	5.5	6.7	22% ↑	0 (0%)	1 (17%)	0.7500
2	16 months ago	3.9	4.6	19% ↑	1 (50%)	1 (17%)	0.1875
3	14 months ago	6.7	6.5	2% ↓	1 (50%)	2 (33%)	0.1406
4	12 months ago	4.5	3.3	27% ↓	1 (50%)	5 (83%)	0.0593
5	5 months ago	3.0	2.0	35% ↓	1 (50%)	4 (67%)	0.0791
6	2 months ago	1.0	0.4	57% ↓	2 (100%)	2 (33%)	0.0352

[a] Probability of guesses during all eight cycles being correct at greater than chance frequency.

Only one of six patients correctly guessed whether the stimulator was ON or OFF at greater than chance levels although the trend approached statistical significance in two other cases (Table 4). None of the patients reported that they experienced paraesthesiae or other electrically-induced sensations during ON cycles. However, pain ratings were higher during OFF than ON cycles in patients who correctly guessed the stimulator status during most cycles (Spearman's $\rho = 1.00$, $p < 0.001$) (Table 4), suggesting that these patients used pain intensity as a cue to judge whether the stimulator was ON or OFF.

Examination of pain ratings during blinded wash-out and wash-in periods indicated that pain ratings increased after the stimulator was switched off in Cases 3-6 (i.e., those patients who most accurately judged whether the stimulator was OFF or ON) and returned toward baseline once the stimulator was switched back on in Cases 3-5 (Figure 3).

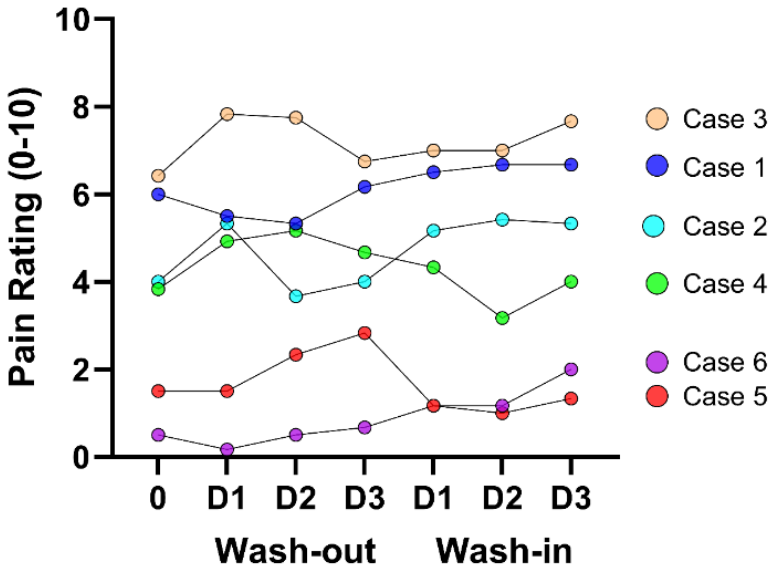

Figure 3 Changes in pain during double-blind cycles after the stimulator was switched OFF (wash-out) and back ON (wash-in). "0" refers to the 24 hours before the stimulator was switched OFF and "D1-D3" refers to Days 1-3 after the stimulator was switched OFF or ON.

3.3 Secondary Outcomes

In each of the four patients who took rescue medication (Table 2), pain ratings were 1.6 to 2.6 points higher on a 0-10 scale of pain intensity on days where rescue medication was taken (mean pain ratings 5.6 ± 2.0) than on medication-free days (mean pain ratings 3.5 ± 2.1). During the six ON periods, rescue medication was taken on 22.2 ± 20.9% of days/cycle whereas rescue medication was taken on 16.7 ± 30.3% of days/cycle during OFF periods (not significant).

Minimum periods of walking and sitting were similar during OFF and ON cycles (Table 3). Patients were less refreshed on waking during OFF cycles than ON cycles ($p = 0.042$) but electrical stimulation did not alter other sleep parameters. Likewise, most secondary outcomes recorded during clinical assessments were similar following OFF and ON cycles (Table 3). The only exception was the severity of pain behaviours (sighing; breath-hold; grimace; guarding; rubbing; and antalgic gait), which were greater during the "Timed up and go" test following ON than OFF cycles ($p = 0.039$). There was no evidence of "wind-up" after repeated application of a pin to the forehead either after OFF or ON cycles.

3.4 Adverse Events

No adverse effects of electrical stimulation were reported during the trial.

3.5 Case Reports

Case 1 was a 55-year-old female with persistent pain in the right lumbar region extending into the right lateral thigh and lateral calf after injuring her back at work 8 years previously. Pain was associated with mood and sleep disturbances. Fifteen months before the study, a burst waveform dorsal spinal cord stimulator was implanted. One month later, back pain had resolved and leg pain was reduced by 60%. However, she subsequently developed constant burning and shooting pain bilaterally in the lumbar and thoracic regions, being worse on the right, which decreased somewhat after physiotherapy treatment. At trial baseline, she scored in the moderate range for anxiety on the DASS. During the double-blind phase of the trial, stress ratings were mildly elevated when the stimulator was ON and just below this level when the stimulator was OFF. She was not able to detect when the stimulator was ON rather than OFF, and pain ratings were higher when the stimulator was ON than OFF. Pain did not change consistently during the 3-day cycle after the stimulator was switched OFF, and did not decrease during the 3-day cycle after the stimulator was switched back ON (Figure 3).

Case 2 was a 28-year-old male with persistent right sided neuropathic pain in his neck, head and arm after a traction injury to the right arm 3 year ago, associated with mood and sleep disturbances. Sixteen months before the study, a burst waveform cervical and upper dorsal spinal cord stimulator was implanted. Six weeks later, neck and head pain had decreased and arm pain had resolved. At trial baseline, he scored in the severe range on the DASS for depression and stress and in the extremely severe range for anxiety. These mood disturbances persisted throughout the trial both when the stimulator was ON and OFF. During the double-blind phase of the trial, he was unable to detect whether the stimulator was ON or OFF at greater than a chance level, and pain ratings were higher when the stimulator was ON than OFF. Pain increased within 24 hours after the stimulator was switched OFF but then returned toward previous levels. Pain did not decrease during the 3-day cycle after the stimulator was switched back ON (Figure 3).

Case 3 was a 60-year-old male with a 13-year history of predominantly left-sided neck, head and arm pain following a rear end motor vehicle collision. His mood was generally positive but pain interfered with sleep. Pain decreased and function improved after implantation of a cervical spinal cord stimulator 8 years after the accident. Fourteen months before the study, the tonic waveform battery was revised to a burst waveform battery with marked analgesic benefit. At trial baseline, he scored in the mild range on the DASS for depression, the moderate range for anxiety and the normal range for stress. Apart from mild anxiety when the stimulator was OFF, mood disturbances subsided during the trial. He was unable to detect whether the stimulator was ON or OFF at greater than a chance level, and pain ratings were similar when the stimulator was ON and OFF. Specifically, pain increased within 24 hours after the stimulator was turned OFF but returned toward previous levels during the third day of the cycle. Pain did not decrease during the 3-day cycle after the stimulator was switched back ON (Figure 3).

Case 4 was a 64-year-old female with an 11-year history of neuropathic pain in the left anterolateral knee region after a patella dislocation, followed by multiple surgeries on the patella culminating in patellectomy. Pain was associated with sleep disturbances and was aggravated by walking and standing. Twelve months before the study, a burst waveform spinal cord stimulator was implanted. Two months later, knee pain had decreased more than 50% and she was able to sit comfortably and walk further than before. At trial baseline, she scored in the moderate range on

the DASS for depression and in the normal range for anxiety and stress. All scores were within the normal range throughout the trial both when the stimulator was ON and OFF. She was able to detect when the stimulator was ON in 5 of 6 ON cycles, and pain ratings were lower when the stimulator was ON than OFF. Notably, pain increased within 24 hours after the stimulator was turned OFF and decreased within 24 hours after the stimulator was switched back on (Figure 3).

Case 5 was a 57-year-old male with a 3-year history of persistent disabling lumbar region pain triggered by a work injury. His pain was aggravated by prolonged sitting or walking and disturbed his sleep. Five months before the study, a burst waveform dorsal spinal cord stimulator was implanted. Eight days later, he reported an 80% reduction in back pain and had ceased taking regular analgesics. At trial baseline and throughout the rest of the trial, he scored in the normal range on the DASS for depression, anxiety and stress. During the double-blind phase of the trial, he was able to detect when the stimulator was ON in 4 of 6 ON cycles, and pain ratings were lower when the stimulator was ON than OFF. Pain increased within 48 hours after the stimulator was turned OFF and decreased within 24 hours after the stimulator was switched back on (Figure 3).

Case 6 was a 59-year-old female with a history of persistent lumbar and leg pain since her teens. Previous lumbar spinal surgeries were followed by neuropathic pain typical of post-surgery syndromes. Her mood was generally positive but sleep was often disturbed by pain. A burst waveform spinal cord stimulator was implanted two months before the study. One month later, she reported a sustained reduction in back and leg pain of about 90%. At trial baseline, she scored in the mild range on the DASS for stress and the normal range for depression and anxiety. All scores were within the normal range throughout the rest of the trial both when the stimulator was ON and OFF. During the double-blind phase of the trial, she was able to detect when the stimulator was ON in 2 of 6 ON cycles and when the stimulator was off in both OFF cycles. Pain ratings were lower when the stimulator was ON than OFF. Further inspection of scores indicated that pain was absent during and after one OFF cycle. Pain began within 24 hours during the second OFF cycle but failed to resolve within three days after the stimulator was switched back ON (Figure 3).

4. Discussion

In recent placebo-controlled double-blind crossover trials of paraesthesia-free spinal cord burst stimulation, pain intensity was equivalent during periods of burst and sham stimulation [1, 2, 4]. Similarly, on a group basis, pain intensity was equivalent during burst and sham stimulation in the present case series. Moreover, burst stimulation did not influence ratings of pain interference, mood, sensitivity to mechanical stimulation or consumption of rescue medication. However, when examined individually, a clinically meaningful reduction in pain intensity (a decrease of 30% or more) [12] was identified during burst stimulation in 2 of 6 patients. These two patients correctly identified the stimulator status during most of the cycles, suggesting that stimulation inhibited pain directly or that pain decreased as a placebo effect of stimulation when the patient thought that the stimulator was ON. In addition, stimulation completely inhibited pain during most cycles in a third patient. Notably, wash-out and wash-in effects were stronger and the stimulator had been implanted more recently in these three patients than in three others who benefited less from burst stimulation during the blinded part of the trial.

Patients were more refreshed on waking during ON than OFF cycles, but stimulation did not affect other sleep parameters. Benefits of burst stimulation on sleep outcomes have been reported

in case series of patients with chronic pain [13, 14] but, to our knowledge, this has yet to be confirmed in a fully-powered placebo-controlled double-blind study. Given our preliminary findings, further such studies seem warranted.

Contrary to expectations, the severity of pain behaviours was greater during the "Timed up and go" test following ON than OFF cycles. The reason for this is unclear but one possibility is that burst stimulation inhibited lower but not higher levels of pain. Alternatively, this might have been a chance finding as we did not correct for multiple comparisons in this exploratory study.

4.1 Limitations

The strengths of our study include the double-blind protocol as neither the participant nor the assessor received incidental cues that might have unblinded the stimulation condition. In particular, the pulse generator did not require recharging and stimulation was delivered below the sensory threshold. We assessed multiple secondary outcomes including effects of stimulation on sleep and mood; behavioural signs of pain during standard physical tasks; and sensitivity to mechanical stimulation. Thus, we are confident that most anticipated benefits of stimulation on the patients' day-to-day lives were assessed.

Despite these strengths, our study has several limitations. Most importantly, the small sample size in this case series precludes firm conclusions about effects of burst stimulation on pain or its correlates. We aimed to recruit patients who reported stable pain reduction on low levels of medication with relatively good mood and function and with wash-in and wash-out periods of less than two days. However, it proved difficult to identify patients who fulfilled these criteria and who were willing to enter the study, as it involved considerable travelling and disrupted their stimulation treatment and daily activities.

Although all six patients met the inclusion criterion of significant pain relief after the stimulator was implanted, pain had returned to mild or moderate levels at trial onset in four patients despite ongoing stimulation (Table 2). Hence, ceiling effects might have limited further increases in pain during OFF cycles. Burst stimulation appeared to be most effective in patients whose stimulator had been implanted recently. Reasons for a reduction in benefit of stimulation over the course of time might include physiological adaptation to stimulation, the emergence of a new source of pain, or technical issues such as lead migration that compromised optimal pulse delivery. Such issues need to be examined systematically in larger trials.

Expectancy effects might have influenced wash-in and wash-out times during the selection process as patients identified when pain increased after they switched their stimulator off and when pain decreased when the stimulator was reactivated. This could be addressed in future studies by including false-positive and false-negative assessments (e.g., by informing patients that the stimulator was on when it was off and vice versa) or by carrying out this assessment double-blind.

Understandably, our patients were concerned about how they would manage their pain during OFF cycles but were reassured that they could access breakthrough medication and that the OFF periods would be infrequent and would last less than five days. Nevertheless, it was apparent that some of the patients were hypervigilant toward pain throughout the trial, as shown by higher ratings for "Worst pain in past 24 hours" during stimulation ON periods than at baseline. As this might have influenced consumption of breakthrough analgesic medication and, in turn, masked effects of electrical stimulation, more stringent criteria for using rescue medication should be considered in

future trials. A related issue was the presence of mood disturbances in some of our patients, which might have influenced their experience of pain and/or consumption of rescue medication.

Finally, effects of stimulation might not have peaked during the 3-to-4-day cycles of stimulation or may have persisted beyond the 2-day period reserved for washing out these effects. Specifically, as burst stimulation was delivered during 6 of the 8 cycles, failure of carryover effects to dissipate completely during OFF cycles might have masked differences between ON and OFF periods of stimulation. This might have been particularly problematic for mood ratings as depression, anxiety and stress were rated at the end of each cycle in relation to the entire 3-to-4-day cycle.

4.2 Conclusions and Recommendations

Our findings reinforce the need for fully powered placebo-controlled double-blind trials of spinal cord burst stimulation for treating chronic spinal pain, as this treatment may be effective for only a subgroup of patients or benefits might decline over time. In addition to assessing effects on pain intensity, outcomes should include effects on sleep as this appeared to hold some promise in our case series.

Our findings also highlight several methodological issues that might influence comparison of versus sham stimulation. A major consideration is to select patients with short wash-in and wash-out times (e.g., less than 24 hours) or to include lengthy periods of wash-in and wash-out in the study protocol. For example, effects of stimulation may be easier to identify during ON/OFF cycles of 5 to 7 days than during the 3-to-4-day cycles used here. In addition, consumption of breakthrough pain medication should be monitored to identify any resultant confounding of pain reports or other outcome measures.

Finally, to determine whether burst electrical stimulation is effective for at least a subgroup of patients, we suggest that selection criteria include: pain ratings at entry of 3 or less on a 0-10 scale; stable physical and psychological functioning with mild or no disability; and patients who take less than 50 morphine equivalents per day and who do not take daily breakthrough analgesic medication. We hope that these guidelines will assist in establishing whether spinal cord burst stimulation is effective for managing chronic spinal pain.

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Author Contributions

John Salmon: Conceptualization, methodology, writing - review and editing. Peter Drummond: Conceptualization, methodology, writing - original draft, formal analysis, writing - review and editing.

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Competing Interests

John Salmon holds Nevro stock and received payments from Nevro and Abbott for lectures and presentations, participating in advisory board meetings, attending conferences and participating in company multicentre and investigator-initiated studies. He also received payments from Nalu and ShiraTronics for attending conferences and participating in their studies. Peter Drummond declares that no competing interests exist.

Data Availability Statement

Data is available upon reasonable request to the corresponding author.

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