Analgesic efficacy of "burst" and tonic (500Hz) spinal cord stimulation patterns: a randomised placebo-controlled crossover study

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ABSTRACT

Objectives

The aim of this study was to compare the efficacy in reducing pain intensity in adult subjects suffering from chronic back and leg pain of burst (BST) and tonic sub-threshold stimulation at 500Hz (T500) versus sham stimulation delivered by a spinal cord stimulation (SCS) device capable of automated postural adjustment of current intensity.

Materials and Methods

A multicentre randomised double-blind, 3-period, 3-treatment, crossover study was undertaken at two centres in United Kingdom. Patients who had achieved stable pain relief with a conventional SCS capable of automated postural adjustment of current intensity were randomised to sequences of BST, T500 and sham SCS with treatment order balanced across the 6 possible sequences. A current leakage was programmed into the implantable pulse generator (IPG) in the sham period. The primary outcome was patient reported pain intensity using a visual analogue scale (VAS).

Results

Nineteen patients were enrolled and randomised. The mean reduction in pain with T500 was statistically significantly greater than that observed with either sham (25%; 95% CI, 8% to 38%; P=0.008) or BST (28%; 95% CI, 13% to 41%; P=0.002). There were no statistically significant differences in pain VAS for BST versus Sham (5%; 95% CI, -13% to 27%; P=0.59). Exploratory sub-group analyses by study site and sex were also conducted for the T500 versus sham and BST versus sham comparisons.

Conclusions

The findings suggest a superior outcome versus sham from T500 stimulation over BST stimulation and a practical equivalence between BST and sham in a group of subjects with leg and back pain habituated to tonic SCS and having achieved a stable status with stimulation.

Key words: spinal cord stimulation; randomised double-blind crossover trial; burst stimulation; tonic sub-threshold stimulation; sham stimulation

INTRODUCTION

Spinal cord stimulation (SCS) is a recognised treatment of chronic neuropathic and vascular pain. The practice of SCS was, until recently, based on adequate electrode placement in the epidural space in order to elicit paraesthesia that covers the entire pain area. A recent change of paradigm in SCS is the development of stimulation modes that provide pain relief without paraesthesia such as subthreshold, burst and high frequency SCS.

Effectiveness reported across different studies varies; randomised controlled trials (RCTs) have shown superiority of high frequency (1) and burst stimulation (2) in obtaining pain reduction when compared to paraesthesia-inducing SCS. Both of these studies were open-label (i.e. participants or outcome assessors were not blinded). Data from parallel and crossover RCTs have reported no differences in effectiveness between different paraesthesia-free frequencies,(3) between high frequency (10kHz) and paraesthesia inducing stimulation,(4) high frequency (5kHz) and placebo,(5) and between burst and different frequencies (i.e. 40, 500, 1200Hz).(6) These studies were single (i.e. outcome assessors only) or double-blind (i.e. outcome assessors and participants). In a double-blind crossover RCT burst stimulation was found to be superior to 500Hz tonic SCS and placebo.(7) Methods to elicit placebo or sham stimulation have been found to differ considerably in trials of SCS (8) potentially affecting the interpretation of effectiveness of SCS.(9)

Some neurons in the central nervous system including the spinal cord fire in groups of action potentials followed by periods of quiescence (bursts), whereas others, in the same stage of sensory processing, fire in a tonic continuous manner. It is believed that both bursting and tonic firing neurons transmit information and might occur in parallel with sensory systems.(10, 11) Preclinical studies suggest that burst firing is more efficient than tonic firing in activating the cerebral cortex.(12-14) This may be due to the ability of presynaptic terminals to detect burst firing patterns and selectively transmit it to postsynaptic neurones. The data argue for a neural code in which synchronised bursts are the optimal input.(12)

The aim of this study was to compare sham (i.e. no stimulation) to the analgesic efficacy of 2 modes (patterns) of active SCS at sub-threshold current intensity (i.e. burst [BST] and 500Hz [T500]) in a double-blind, three-period three-treatment crossover multicentre RCT.

METHODS

Study design and participants

The current study was a multicentre, double-blind, three-period three-treatment crossover RCT. Two different modes of active stimulation (BST and T500) were compared to sham (i.e. no stimulation).

Patients treated with SCS were recruited from two sites in the United Kingdom: South Tees Hospitals NHS Foundation Trust (The James Cook University Hospital) JCUH and Newcastle-upon-Tyne NHS Trust (Royal Victoria Infirmary) NuTH. Inclusion criteria were adults (≥18 years) with leg and back pain (whether unilateral or bilateral), who achieved stable pain relief with conventional SCS (i.e. paraesthesia inducing stimulation with frequency <150Hz) using the Medtronic's rechargeable spinal cord stimulator RestoreSensor® and with either 1 or 2 epidural leads, had not requested reprogramming in the three months prior to study participation, confirmed they received pain relief from the device and reported constant ≥70% paraesthesia coverage. Exclusion criteria were: patients with an SCS device other than the one aforementioned, not capable of using or understanding how to handle the equipment or not capable to complete the study measures. The study was approved by the UK Health Research Authority North East – York Research Ethics Committee (14/NE/1043). All patients provided written informed consent prior to randomisation. The trial is reported in accordance with the CONSORT extension to randomised crossover trials (15) and recommendations for reporting of placebo/ sham RCTs of SCS.(8)

Randomisation and masking

Patients were randomised to receive one of the 6 combinations of burst stimulation, tonic stimulation at 500 Hz or sham (Figure 1). Patients were introduced to the study and consented by blinded clinicians who then handed over the patients' care to nursing staff. Nursing staff were split into two groups with no cross over allowed between the groups. Group one was blinded outcome assessors and group two consisted of unblinded nurse programmers. Unblinded nurse programmers were trained by the sponsor in the use the experimental programmer. Unblinded nurse programmers were trained to provide an identical programming sequence in all periods. Eligible patients were randomly assigned to treatment sequence by means of a central randomisation service using text message randomisation via a non-blinded investigator. Patients and outcome assessors were blind to treatment assignment (order). The non-blinded nurse programmers were responsible for providing clinical care for the patients in the study but did not take part in any study data collection.

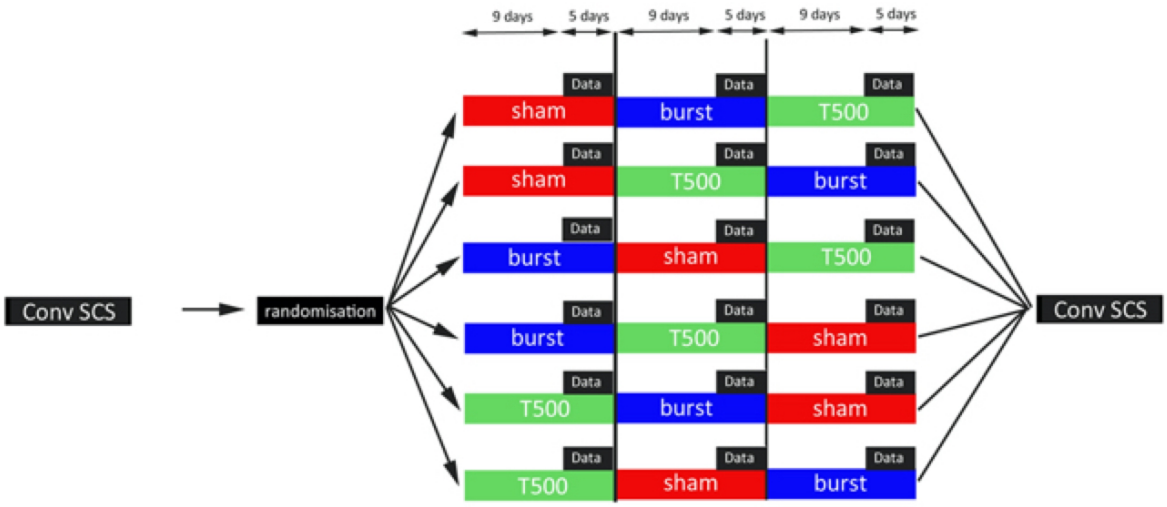

Figure 1. Study crossover design

To ensure blinding of participants, a current leak was programmed during sham phases so that the charging time (and the possible skin heating) were similar regardless whether BST, T500 or sham was delivered. For BST, a 4 spiked burst was used with passive charge balanced at the end of the 4 spiked burst (Figure 2).
Patients were not provided with a handheld patient programmer, but all had access to a modified recharging unit for the duration of the study. The "study unit" had a disabled screen and alarms and no information about the battery charge was available. Patients in all study phases were asked to recharge their device daily for 2 hours.

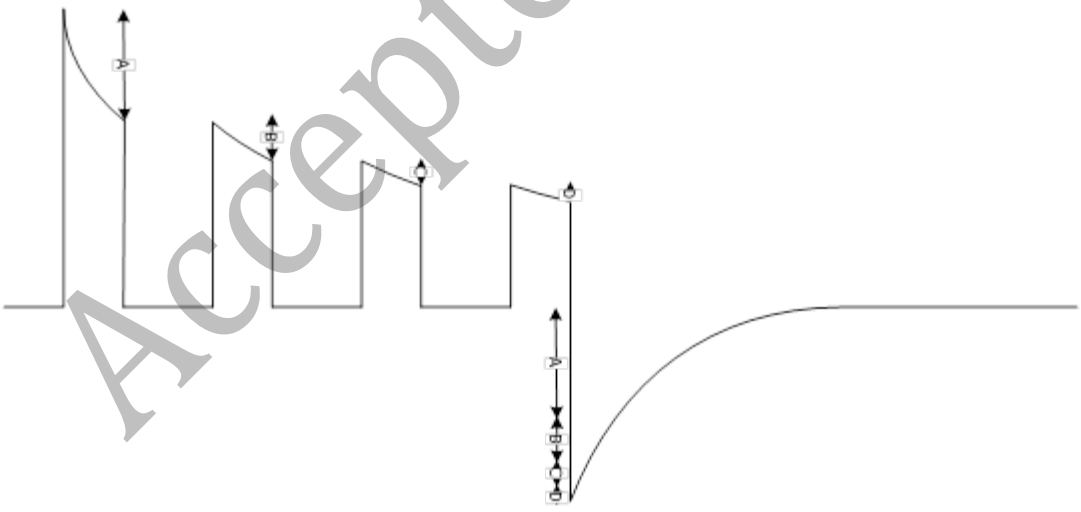

Figure 2. Graphic representation of the burst stimulation design

Programming parameters

As the study is double blinded it is crucial that patients did not feel paraesthesia. It was also important to ensure a stimulation intensity that remained 10% below the sensory threshold

regardless of the posture of the patient. This was achieved by using a stimulator capable of sensing the body posture and programmed to instantaneously adapt the voltage output at 10% below the paraesthesia threshold in any configuration. This feature (AdaptiveStim) was only available with Medtronic's RestoreSensor® SCS and the use of this particular stimulator was therefore an inclusion criterion. The RestoreSensor® is a voltage source and intensity is adjusted in mV; as such any usage of the word 'current' henceforth in the manuscript refers to voltage adjustments.

Burst stimulation (BST)

Subjects receiving BST underwent programming by the non-blinded member of the clinical team using the following steps:

I. using no more than 3 active contacts with one cathode, paraesthesia covering as much as possible of the area of pain area should be elicited with "conventional stimulation" (i.e. frequency < 150Hz) with the patient lying on his back;
II. while keeping the voltage setting below sensory threshold, the burst mode is programmed (40Hz burst of 4 spikes of each 1000μs at 500Hz per burst);
III. the voltage amplitude is progressively increased to the sensory threshold where stimulation is expected to be reported as an uncomfortable dull ache;
IV. the voltage amplitude is decreased again to the sensation threshold amplitude. The amplitude is set at 10% below the sensory threshold and recorded in the software of the stimulator;
V. the same procedure is repeated with the patient in the following posture
    a) standing
    b) lying on the left side
    c) lying on the right side
    d) lying prone

Tonic stimulation at 500Hz (T500)

Subjects receiving T500 SCS underwent the programming steps I to V as described above, by the non-blinded investigator. However, a continuous tonic stimulation at 500Hz with a pulse width of 480μs was programmed.

Sham spinal cord stimulation (Sham)

Subjects receiving Sham SCS underwent the programming steps I to V as described above, by the non-blinded investigator. However, the stimulator was switched off after completing step V.

During either sham or active stimulation phases, patients were able to revert to conventional stimulation at any time should they experience pain or side effects by contacting the pain clinic.

Outcomes

Primary outcome

The primary outcome was pain intensity using a 100 mm visual analogue scale (VAS).(16) Pain intensity was measured 3 times per day (morning, midday and evening) during 5 consecutive days at baseline (with conventional stimulation) and at the end of each 2-week study period. Each treatment phase included a washout period of 9 days (Figure 1).

Secondary outcomes

Secondary outcomes included the 7-point Patient Global Impression of Change scale (PGIC) and health related quality of life (HRQoL) using the EQ-5D-3L. Patients rated their global impression of change after each 2-weeks treatment phase. Therefore, the PGIC scores were given with reference to the last period of 2 weeks "during the last 2 weeks, my overall pain control is…" Using the PGIC scores, we adopted a responder analysis. A responder (treatment benefit) in Periods 2 or 3 is defined as a patient reporting at least 'minimally improved' on the PGIC scale (17) when BST or T500 follows sham, or at least 'minimally worse' when sham follows BST or T500. There were six possible sequences of BST, T500, and sham across 3 periods (see Table 1). Patients completed the EQ-5D-3L at baseline (with conventional stimulation) and at the end of each 2-week study period. Outcome measures were collected by a blinded observer.

Safety was assessed by means of a standardised evaluation of adverse events. Medical history, physical and neurological examination were conducted in all patients at baseline, at the end of each 2-week study periods or more often if necessary. We enquired every week about the presence of any side effects by telephone contact including the feeling of paraesthesia. We continued to follow up all subjects and report any serious adverse events (SAEs) for a period of 6 months from the end of the study. Safety was evaluated by means of patient- and assessor-based evaluations.

Table 1. Secondary outcome: PGIC

Sequence	Period 1	Period 2	Period 3	Definition of a responder on PGIC
1	SHAM	BST	T500	BST vs. sham Period 2 (Responder = minimally improved on BST)
2	SHAM	T500	BST	T500 vs. sham Period 2 (Responder = minimally improved on T500)
3	BST	SHAM	T500	Sham vs. BST Period 2 (Responder = minimally worse on sham); T500 vs. sham Period 3 (Responder = minimally improved on T500)
4	BST	T500	SHAM	Sham vs. T500 Period 3 (Responder = minimally worse on sham)
5	T500	BST	SHAM	Sham vs. BST Period 3 (Responder = minimally worse on sham)
6	T500	SHAM	BST	Sham vs. T500 Period 2 (Responder = minimally worse on sham); BST vs. sham Period 3 (Responder = minimally improved on Burst)

PGIC= Patient's Global Impression of Change
"minimally worse" or "minimally improved" means 'at least' minimally

Sample size and statistical analysis

The primary outcome is the patient's mean pain intensity score (visual analogue scale; VAS) over 5 days of monitoring. In individuals, a reduction in pain VAS of 30% typically defines a clinically important response. At the group level our targeted effect size was a mean reduction (versus sham stimulation) of 25% in pain VAS (a ratio of BST: sham or T500: sham of 0.75), assuming a small improvement (5%) in the sham condition. With 90% power, 2-sided P=0.05, and a coefficient of variation for pain VAS on the logged scale of 0.37, 35 patients were required to detect the targeted difference for the two planned comparisons.(18-20) We made no adjustment for multiple comparisons in either the sample size estimation or the subsequent analysis.(21-23) The coefficient of variation representing the within-patient variability for pain VAS scores over the course of repeat measurements in a crossover trial was derived from a previous study.(5) Given that patients were randomised to all six possible sequences of BST, T500, and sham, a multiple of six patients was required for the overall sample size. Hence, the required N was 42 allowing for missing data or withdrawals in up to 6 patients. Sample size estimation was conducted using PASS software (PASS 11 Power Analysis and Sample Size Software (2012). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

Log-transformed Pain VAS data were analysed using a linear mixed model with restricted maximum likelihood and an identity covariance structure, including fixed effects for treatment, period, treatment×period, study site and sex, and a random intercept by participant. There were two planned primary comparisons: BST versus sham and T500 versus sham. Differences in pain VAS on a log scale were back-transformed to provide ratio (percentage) differences between conditions. Point estimates and 95% confidence intervals together with the two-sided P-value are presented. We also conducted purely exploratory sub-group analyses, by including site×treatment and sex×treatment interaction terms in the model.

EQ-5D-3L index scores were reported descriptively for each condition in the trial. This reporting represents a deviation from the trial protocol, in which we planned to analyse these data using the same general model as for Pain VAS. We elected to present solely the mean and interquartile range for each condition as we now believe strongly that the EQ-5D index should be reserved for health economic analyses, rather than viewed as a patient-reported outcome measure in its own right.

All analyses are reported by intention-to-treat and compared outcomes between groups with complete data sets. Data analyses were undertaken using Stata 15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

RESULTS

We aimed to recruit 42 patients; however, our inability to recruit from the Morges site meant that our estimates were revised in consultation with the funder and ethics committee. Nineteen patients were recruited from two UK sites between October 2014 and July 2017 and followed-up for six weeks, i.e. three phases with a two-week duration each (Figure 3). Demographic characteristics are presented in Table 2. All included patients experienced failed back surgery syndrome.

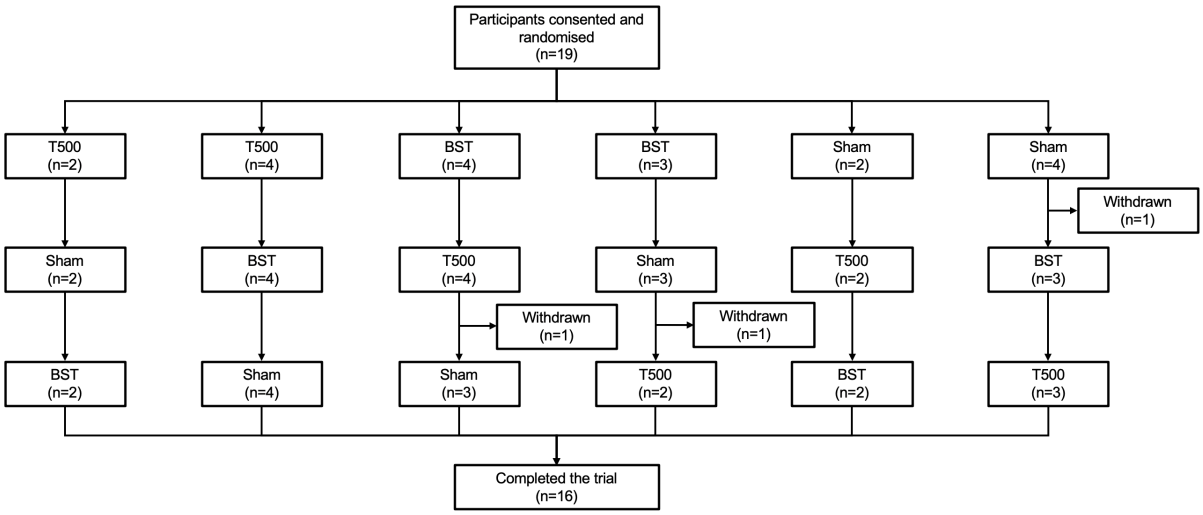

Figure 3. Flow diagram for the crossover trial

Table 2. Demographic characteristics at baseline

Variable	Summary statistic
Age, mean (SD) (n=19)	54 (9)
Sex (n)	7 men/ 12 women
Site (n)	10 JCUH/ 9 NuTH
Clinic usual Pain VAS (cm), mean (SD) (n=17)	4.4 (2.2)
EQ5-D index, median (interquartile range) (n=17)	0.620 (0.516 to 0.691)

The geometric mean pain VAS was 5.1 cm for Sham, 3.8 cm for T500, and 5.4 cm for BST. The mean reduction in pain for T500 versus Sham was 25% (95% CI, 8% to 38%; P=0.008).

Pain VAS in BST was 5% higher than Sham (95% CI, -13% to 27%; P=0.59). The 90% confidence interval for the BST versus sham comparison (equivalent to two one-sided tests each at the 0.05 level) was -10% to 23%, which statistically rules out meaningful effects (a difference in either direction of ≥25%). The two conditions are therefore practically equivalent. In a secondary head-to-head comparison of the two active treatments, the mean reduction in pain for T500 versus BST was 28% (13% to 41%; P=0.002). The model residuals were well-behaved indicating that the model is adequately specified. Analysis of the raw data, rather than log-transformed, gives very similar results with adjusted arithmetic means of 5.6 cm for Sham, 4.4 cm for T500, and 5.8 cm for BST.

In the exploratory sub-group analyses, at the JCUH site, pain VAS for T500 was 0.7× that in Sham (30% decrease), versus 0.82× at the NuTH site (18% decrease); the between-site difference in treatment effect equals a ratio of 0.85 (0.7/0.82), 95% CI, 0.57 to 1.26; P=0.41. The trial is not powered for sub-group interactions, but the point estimate for the treatment effect is substantially larger at the JCUH site. Pain VAS for T500 was 0.72× that in Sham for men (28% reduction) and 0.78× in women (22% reduction). The sex difference in the treatment effect equals a ratio of 0.92 (95% CI, 0.63 to 1.37; P=0.70).
Pain VAS for BST was 1.05× that in Sham (5% increase) at both sites (P=0.994 for the between-site difference). Pain VAS for BST was 0.97× that in Sham for men (3% reduction) and 1.13× in women (13% increase). The sex difference in the treatment effect equals a ratio of 0.86 (95% CI, 0.59 to 1.24; P=0.41).

Table 3 presents the EQ-5D-3L index scores for each condition in the trial. On average, HRQoL is substantially worse in the BST condition versus either Sham or T500 stimulation, consistent with the results of the primary analysis. However, we make no firm inferences from these data.

Table 3. EQ-5D-3L index scores for the three trial conditions (n=16 complete data sets)

Treatment	Median	Interquartile Range
Sham	0.656	0.516 to 0.691
T500	0.620	0.516 to 0.691
BST	0.516	0.002 to 0.705

With only 19 of the original target sample size recruited, combined with missing data, only 9 cases were available to assess PGIC response to T500 versus Sham and 11 for response to BST versus Sham. Hence, the data are too sparse for an informative analysis of this binary outcome. Inferential emphasis is placed solely on the primary outcome, as appropriate. Adverse events are reported descriptively by treatment phase (Table 4). Increased pain was the most commonly reported adverse event at each treatment phase. Three patients

withdrew from the study, two during the sham phase and one during the T500 phase, all due to increased pain. Patients that withdrew from the study reverted to their original conventional stimulation.

Table 4. Adverse events and side effects by study phase

Adverse events	T500 (n=17) n patients (%) / n events	BST (n=18) n patients (%) / n events	Sham (n=18) n patients (%) / n events
Increased pain	6 (35) / 7	4 (24) / 4	4 (24) / 4
Cramp in foot	1 (6) / 1	0 (0) / 0	1 (6) / 1
Pain over device	1 (6) / 1	0 (0) / 0	0 (0) / 0
Intermittent jolts of stimulation	2 (12) / 1	0 (0) / 0	1 (6) / 1
Loss of adaptive stim function	0 (0) / 0	0 (0) / 0	1 (6) / 1
Discomfort left side of neck	0 (0) / 0	1 (6) / 1	0 (0) / 0
Feeling paraesthesia	0 (0) / 0	1 (6) / 1	0 (0) / 0
Bilateral foot pain	0 (0) / 0	1 (6) / 1	0 (0) / 0
Numbness in leg	0 (0) / 0	1 (6) / 1	0 (0) / 0
Left hip pain	0 (0) / 0	0 (0) / 0	1 (6) / 1
Uncomfortable sensations	1 (6) / 1	0 (0) / 0	0 (0) / 0
Unrelated events	4 (24) / 4	3 (17) / 3	4 (24) / 4

DISCUSSION

Our findings suggest that T500 stimulation was superior to sham, but BST stimulation was not, in a group of subjects with leg and back pain habituated to tonic SCS and having achieved a stable status with tonic stimulation. Mean Pain VAS in the sham and BST stimulation conditions was practically equivalent. Our data also show that T500 was superior to BST, with a reduction in mean pain VAS of 28% (95% CI: 13% to 41%, P=0.002).

Our findings appear to contrast with one other study comparing the same stimulation modality and using a similar study design in a similar group of subjects.(7) There are however a number of programming differences between the 2 studies that may go some way to explain the different outcomes reported.

Firstly, in the current study the pulse width programming in the tonic group T500 was set at 480 mcsec for all subjects whereas in the Schu et al. study it was highly variable, with a mean (SD) of 370.8 (135.4) μsec. It is possible that the on average higher and fixed voltage charge administered in the T500 group in the current study resulted in an improved response to the stimulation.

Secondly, in the Schu et al. study both burst and tonic stimulation amplitudes were set at subthreshold in the supine/seated position and adjusted for the lowest threshold, making it likely that in standing, sitting and mobile positions the stimulation amplitude was far lower than the intended levels whereas in the current study adaptive stimulation was set to ensure that voltage amplitudes just below the threshold stimulation were constantly delivered

regardless of patient position. There is also a difference in the burst programming between the two studies; Schu et al. used a five-spike burst whereas the current study utilised a four-spike burst. The clinical impact of the number of spikes in a burst sequence remains unclear. Third, the sham programming in our study included a current leakage from the IPG in order to ensure subjects are not accidentally unblinded through the discovery that their IPG battery was repeatedly full during the sham phase. It is not clear that Schu et al. used a rigorous sham and how many of their participants were unblinded during the sham phase through the IPG charging kit showing a constantly full battery. Unintended unblinding in the sham condition could have a substantial effect on the results.

Finally, both studies recruited a relatively small number of participants n=19 and 20 respectively from the heterogeneous pool of failed back surgery syndrome patients. It is plausible, therefore, that the samples in the two studies are not comparable with respect to unmeasured prognostic factors. With respect to measured variables, mean baseline pain in the Schu et al. study was approximately 27% greater than in the current study, which could also have influenced the results.

Our results are in a way similar to those of Tjepkema-Cloostermans et al.(24) who compared five-spike burst stimulation to a low amplitude burst stimulation at 0.1 mAmp, originally intending for this to be an active sham comparator. They however found that the difference between burst and their intended sham was not clinically or statistically significant, and therefore proceeded to rebadge the sham as low amplitude burst.

Variation in the intensity of neurostimulation due to changes in body position is a problem for many patients implanted with sensation generating SCS systems because positional changes may result in changes in distance between the stimulation source and the target neural tissue in spinal cord.(25). Within the context of sensation generating SCS this often results in overstimulation or understimulation. The automatic position-adaptive stimulation feature (AdaptiveStim) was designed to detect changes in body position in real time and to automatically adjust stimulation amplitude according to patient preferences.(26) Within the context of sub-threshold SCS as used in our study, AdaptiveStim was used to retain the level of sub-threshold stimulation delivered to the spinal cord constant regardless of changes in body position. Therefore, in contrast to other sham controlled studies comparing sham to sub-threshold modes, in our study the current intensity was maintained at 90% of threshold value in a particular position through the use of AdaptiveStim. This was designed to ensure a current delivery of the same % of threshold regardless of position change.

This trial is reported in accordance with the CONSORT extension to randomised crossover trials (15) and recommendations for reporting of placebo/ sham RCTs of SCS.(8) However, our study has some limitations. Originally, we planned to include a 3rd centre in Hôpital de Morges Switzerland. Due to not being able to recruit participants from this site, our original

recruitment target could not be achieved. We powered the study a priori to detect a 25% difference in pain VAS for active treatment vs. sham, resulting in a requirement for 35 patients (n=42 allowing for 15% loss to follow up). Though we only recruited 19 patients, and data is missing completely for three of these (all from the NuTH site), our study was adequately powered ultimately because the variability was substantially lower than we predicted in advance. The power afforded by the current study to detect a difference of 25% in pain VAS (our pre-specified targeted effect size) was over 80% for both primary comparisons. We had also planned to analyse PGIC data to derive the proportions of patients responding on BST and T500 versus sham; however, the data were too sparse for an informative analysis of this binary outcome. Effectiveness of blinding was not assessed since it was felt that for a three period study the results would be difficult to interpret. Four patients had missing data for one or two periods; the linear mixed model allows us to include these participants in the analysis and is a principled method of dealing with missing outcome data in repeated measures designs. In a conventional ANOVA analysis, patients with data missing on any of the three treatments would be excluded, leaving a sample size of just twelve. With the linear mixed model, 16 patients were included in the analysis for the primary outcome.

The random allocation sequence was originally drawn up for the target sample size of 42 patients (allowing for 15% loss to follow-up), with 7 patients to be allocated to each of the six possible sequences of three treatments in three periods. The allocations of treatment order for the 19 patients recruited were reasonably well balanced, however, and in any event period effects are accounted for properly in the analysis.

The study population comprised patients with a SCS device who achieved stable pain relief with tonic stimulation. The results may not be generalisable to de novo patients. In addition, burst in the current study was employed using the highest amplitude below sensory threshold. Whether different results would be observed for burst using lower amplitudes needs further investigation.

Finally, although clinically relevant, our initial aim was not to directly compare T500 and BST modes since the study was conceived and executed before the publication of data comparing these two modes, we therefore estimated that the comparison would require a non-inferiority analysis with a much higher number of participants. A sham arm would still be required and considered the gold-standard for such a trial because one active treatment could be non-inferior to or equivalent to a reference treatment, but with neither superior to placebo/ sham. The results observed in this study for the comparison of T500 versus BST are robust considering the observed variability (i.e. the study had >80% power to detect a difference in pain of 25%) and the reduction in mean pain observed of 28% (95% CI: 13% to 41%, P=0.002) showing superiority of T500 over BST.

CONCLUSION

Our findings suggest a superior outcome from T500 stimulation over BST stimulation (versus sham) and a practical equivalence between BST and sham in a group of subjects with leg and back pain habituated to tonic SCS and having achieved a stable status with stimulation. Our findings are at odds with previous studies of similar design. This may be due to adaptive stimulation which may have enhanced the effect of T500 but not BST, use of a different sham control with a discharging IPG, and/or the potential for differing samples in relatively small studies recruiting participants from a highly heterogeneous population of people with failed back surgery syndrome.

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