Attrition with spinal cord stimulation

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Abstract

The aim of this prospective study was to investigate whether Spinal Cord Stimulation (SCS) significantly reduces pain intensity up to 18-month follow up in patients with chronic neuropathic pain. Forty eight patients were recruited. Patients rated their pain using a Visual Analogue Scale (VAS) and pain related disability using the Oswestry Disability Index (ODI) at baseline (one week prior to SCS surgery) and at six, 12 and 18-months follow-up. Pain intensity significantly decreased from baseline to all three time points $F(3,135) = 16.264$, $p<0.001$ The greatest difference in pain intensity reduction was observed between baseline ($M=7.20$, $SD=1.34$) and six-month follow-up ($M=4.60$, $SD=2.20$), $t(47)=6.741$, $p<0.001$. However, when looking at differences between six-month follow-up and subsequent assessments, statistically significant increases in pain intensity from six-months to 12-months follow-up $t(47)=-2.788$, $p=0.008$ and from six-months to 18-months follow-up $t(47)=-3.339$, $p=0.002$ could be observed. Statistically significant changes were also observed for clinical changes in pain scores, $F(2,94) = 4.972$ $p=0.009$ $F(2,84) = 4.244$ $p=0.018$. There was a significant decrease in the percentage of clinical change obtained from six ($M=33.19$, $SD=35.63$) to 12-months follow-up ($M=23.76$, $SD=33.62$), $t(47)=2.347$, $p=0.025$ and from six month to 18-months follow-up ($M=18.34$, $SD=33.51$), $t(47)=3.072$, $p=0.004$. A number of patients also reported higher levels of pain intensity at 12 and 18-month follow-up than at baseline.

Pain related disability scores significantly decreased from baseline ($M=55.04$, $SD=16.43$) to six-month follow up ($M=46.98$, $SD=19.05$), $t(47)=3.464$, $p=0.001$ and from baseline to 12-month follow up ($M=48.49$, $SD=20.94$), $t(47)= 2.918$, $p=0.005$, but not 18-month follow up ($M=51.75$, $SD=20.92$), $t(47)=1.330$, $p=.190$. There was a significant increase in pain related disability between six and 18-month follow up $t(47)=-2.188$. $p=0.034$. These findings suggest that the beneficial effect of SCS on pain intensity may diminish over time and that six-month follow up scores may reflect a placebo effect.

Key Words: Chronic pain, Spinal Cord Stimulation, Clinical Efficacy, Neuropathic pain, attrition

1. Introduction

Acute pain serves an important role in alerting the body to potential damage, in this way it can serve to protect from further injury. However there is no beneficial effect and no functional purpose in chronic neuropathic pain. The exact prevalence of neuropathic pain remains unclear, though studies have reported a prevalence rate of 8% for pain of predominantly neuropathic nature [1] and 7% for pain with neuropathic characteristics [2]. Satisfactory treatment outcomes have proved problematic to achieve [3]. An insurance database study found that health care charges were three times higher for patients with neuropathic pain disorders compared with matched controls,[4] demonstrating the impact this condition can have not only on the individual but also on healthcare services.

Spinal cord stimulation (SCS) has been used for the management of chronic pain syndromes since 1967 [5]. The concept for this implantable pulse generator (IPG) as a neuromodulator of chronic pain derives from the Gate Control Theory of Pain [6]. SCS comprises of an IPG which is connected to a number of electrodes implanted in the spinal canal. Electric fields are created using a programmed anode-cathode array, resulting in stimulation of the dorsal column fibers [7]. It is hypothesised that stimulation of these fibers facilitates supra-spinal mechanisms, leading to a decrease in activity in the ascending pain pathway (spinothalamic tract) with an increase in activity in the descending antinociceptive pathway [8]. Whilst the direct mechanisms of SCS remain unknown, SCS has an effect on certain anti-nociceptive neurotransmitters, notably GABA.

SCS is an invasive and initially expensive therapy; therefore it is necessary that this treatment be efficacious in reducing pain. Randomised controlled trials (RCT) have demonstrated the efficacy of SCS at six-month follow-up for the management of chronic regional pain syndrome (CRPS)[9] and failed back surgery syndrome (FBSS) [10,11]. Whilst SCS appears to be successful in treating certain neuropathic pain conditions at a six-month follow-up, a loss of analgesia is commonly experienced between 12 and 24 months [12].

The aim of the current research was to investigate the effectiveness of SCS in maintaining the initial (six-month) pain relief levels up to 18-months post implantation in patients with chronic neuropathic pain.

2. Methods

2.1 Participants

Recruitment took place following assessment and referral for SCS by a multidisciplinary team consisting of a pain consultant, clinical psychologist, nurse and physiotherapist. Patient suitability for SCS was assessed according to National Institute for Health and Clinical Excellence (NICE) guideline TAG159 [13]. Prior to implantation a trial period took place which evaluated individual response to SCS. Using local anaesthesia, the electrodes were inserted percutaneously whilst the patient was awake to provide feedback regarding paraesthesia coverage of the targeted painful area. The trial period lasted approximately one week. If the patient reported less than 50% pain relief, the electrical parameters would be modified to try and improve pain relief. Patients who consistently reported ≥ 50% pain relief proceeded to full implantation of the IPG. An unsuccessful trial where a patient reported less than 50% pain relief would result in the leads being removed.

All patients invited to participate in this study were over 18 years of age and gave written informed consent. All SCS patients are invited to a neuromodulation clinic every six months and the data were collected during these routine follow-up appointments. These follow-up appointments allow for reprogramming of the devices if the patients perceived a decrease of the effect, to verify the regularity of SCS use and to assess if revision surgery would be required. Ethical approval was granted by the National Research Ethics Service (NRES) committee West Midlands - South Birmingham (REC reference: 13/WM/0007).

Fifty-eight consecutive patients were initially recruited to participate in the study. Seven of the participants (12.3%) had an unsuccessful trial period, where less than 50% pain reduction was achieved. In line with current recommendations the device was not implanted for these patients [13]. Two patients (3%) had their device removed after 12-months follow

up and before 18-months follow due to inadequate pain reduction. One patient reported no longer using the stimulator at 12-months follow up due to the device having no benefit on pain levels, though the device was still implanted. A total of 48 patients were included in the final analysis.

2.2 Study procedure

The study was explained, participants were given time to consider their participation and written informed consent was obtained from all participants. Baseline assessment took place one week prior to the SCS trial period at their routine pre-operative assessment. Using a 10 cm horizontal visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst possible pain) the participants were asked to indicate on the scale where they thought their pain was for the average day. Assessments were performed at baseline (one week prior to SCS trial), six-months, 12-months and 18-months following SCS implantation. All data were collected during routine follow-up appointments.

In addition to collecting pain intensity scores, clinical change scores were calculated using the VAS scores measured at baseline, six-months, 12-months and 18-months follow-up (clinical change = (VAS pre-treatment – VAS post-treatment) / (VAS pre-treatment) x 100 [14]. In accordance with a consensus statement by Dworkin et al (2008) an improvement between 10-29% was considered as a minimally important clinical change, between 30-49% as a clinically moderate change and ≥50% as a substantial clinical change [15].

Function scores were collected using the Oswestry Disability Index (ODI). The ODI assesses the impact of pain interference on 10 daily living activities, with participants required to pick from one of six statements to reflect their ability to manage this activity. Each statement is scored from 0-5. ODI scores between 0-20% indicate minimal disability; 21-40% moderate disability; 41-60% severe disability; 61-80% crippled; and 81-100% indicate bed bound or exaggeration of symptoms [16].The ODI is considered a valid measure of condition-specific disability [16].

2.3. Data Analysis

Repeated-measures ANOVA were performed to investigate changes in pain intensity, clinical change and disability scores between all evaluable assessments. Mauchly's test was used to verify the assumption of sphericity with any violation of the sphericity assumption resulting in the use of Greenhouse-Geisser estimate of sphericity. T-tests were performed to analyse differences between two time points. Data is reported as mean ± standard deviation (range). Statistical significance was judged at 5% level. Statistical tests were carried out with the IBM Statistical Package for the Social Sciences (SPSS) Software (version 21, SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Changes in pain intensity

Forty–eight patients (25 female and 23 male) were included in the analysis (Table 1).

Table 1 Demographic Information

	N=48
Gender	F(25); M(23)
Age in Years	46.7±1.5 (27-65)
Duration of Pain in Years	9.1±1.1 (1.5-40)
Diagnosis	
FBSS	12
CRPS	18
Other[a]	18
Topography	
Back	5
Head/Neck	2
Arm/Hand	4
Buttock/Leg/Foot	23
Multiple	14

Repeated-measures ANOVA were performed to investigate changes in pain intensity between baseline, six-months, 12-months and 18-months follow-ups. Statistically significant improvements were observed for pain as measured with the VAS, $F(3,135) = 16.264$, $p<0.001$ (figure 1). Participants mean pain intensity scores reduced from baseline to six-month follow-up; however an increase in pain intensity was observed in subsequent assessments up to the 18-months follow-up post implantation.

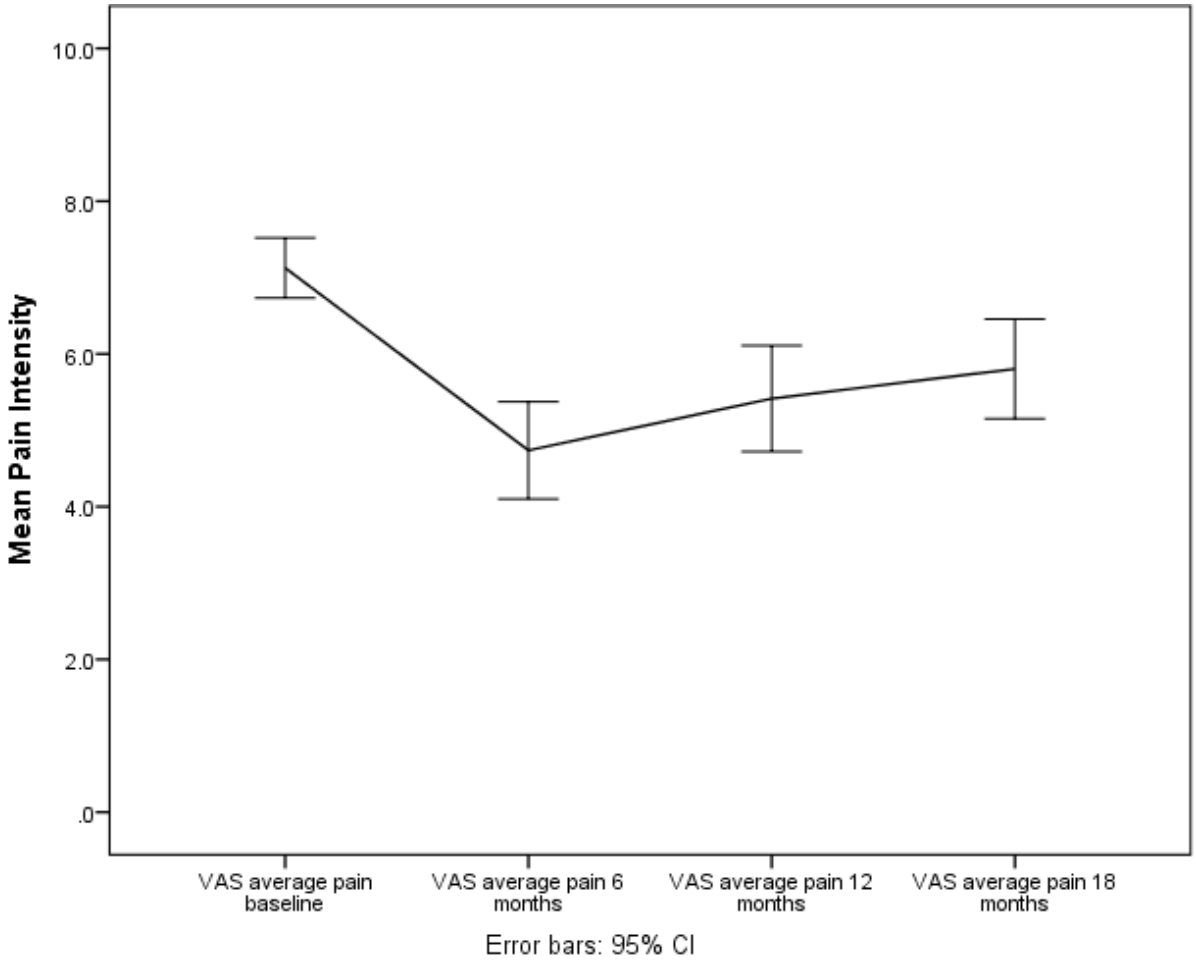

Figure 1 Mean pain intensity from baseline to 18-month follow up

A mixed between-within subjects ANOVA was performed to investigate the impact of diagnosis (FBSS, CRPS, Other) on pain intensity, across the four time point (baseline, six-months, 12-months and 18-months). There was no significant interaction between diagnosis and time point, nor was there a significant main effect of diagnosis (p =.547).

Paired samples t-tests were used to investigate changes in pain intensity between time points. Pain intensity significantly decreased from baseline to all three time points. The greatest difference in pain intensity reduction was observed between baseline (M=7.20, SD=1.34) and six-month follow-up (M=4.60, SD=2.20), t(47)=6.741, p<0.001. Statistically significant decreases from baseline to 12-months follow-up (M=5.40, SD=2.31), t(47)=5.23,

p<0.001 and to 18-months follow-up (M=5.81, SD=2.21), t(47)=4.06, p<0.001 were also identified.

However, when looking at differences between six-month follow-up and subsequent assessments, statistically significant increases in pain intensity from six-months to 12-months follow-up t(47)=-2.788, p=0.008 and from six-months to 18-months follow-up t(47)=-3.339, p=0.002 could be observed. There were no statistically significant increases in pain intensity from 12-months to 18-months follow-up (p =.301).

3.2 Clinical change

Patients demonstrated minimally important clinical changes from baseline to six, 12 and 18-months follow-up (table 2).

Table 2 Clinical change

	Six-months (n=48)	12-months (n=48)	18-months (n=48)
None (< 10%)	10	15	18
Minimal (10-29%)	14	14	13
Moderate (30-49%)	7	4	7
Substantial (≥ 50%)	17	15	10

At six-month follow-up 14 patients presented minimally important clinical changes, seven patients presented moderately important clinical changes and 17 presented substantial clinical changes. However for eight patients there was an increase in pain at six-month follow-up from baseline, in addition to two patients for which there was no change in pain from baseline. At 12-months follow-up 14 patients presented minimally important changes, four presented moderately important changes and 15 presented substantial clinical changes. Conversely at 12-months follow-up 10 patients' demonstrated an increase in pain with three patients' reporting no change from baseline and a further two patients presenting less than 10% clinical change. At 18-months follow-up the number of patients presenting minimally important changes decreased to 13, though the number of patients presenting moderately

important clinical change rose to seven. The number of patients presenting substantial clinical changes decreased to 10. Moreover at 18-month follow-up 12 patients showed an increase in pain ratings again with five patients obtaining no change from baseline, and one patients presenting less than 10% clinical change.

Repeated-measures ANOVA were performed to investigate changes in clinical change scores between six-month, 12-months and 18-months follow-ups. Statistically significant changes were observed for clinical changes in pain scores, F (2,94) =4.972 p=0.009 (figure 2).

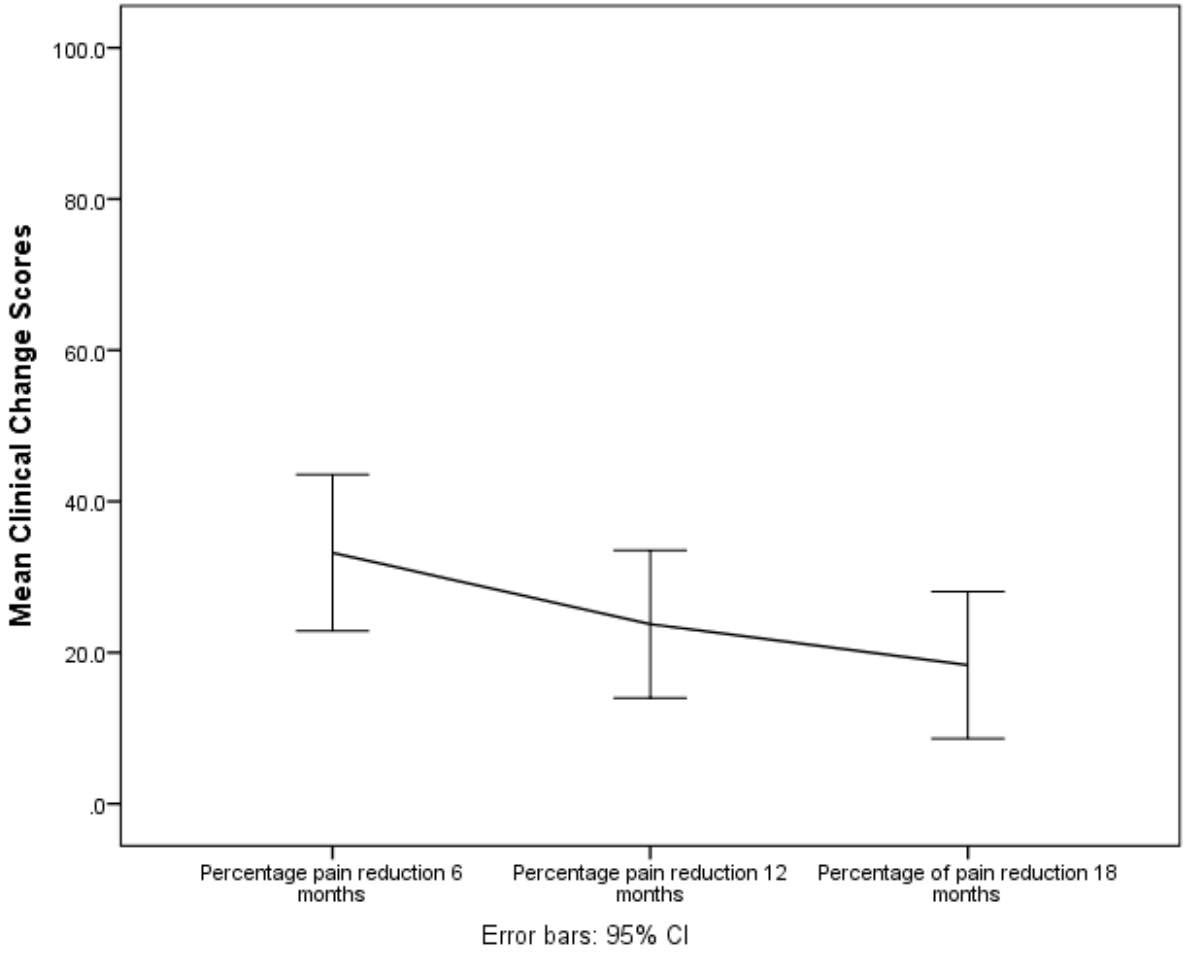

Figure 2 Mean clinical change scores up to 18-months follow up

There was a significant decrease in the percentage of clinical change obtained from six (M=33.19, SD=35.63) to 12-months follow-up (M=23.76, SD=33.62), t(47)=2.347, p=0.025 and from six month to 18-months follow-up (M=18.34, SD=33.51), t(47)=3.072, p=0.004.

There was no statistically significant difference in clinical change scores from 12-months to 18-months follow-up.

A mixed between-within subjects ANOVA was performed to investigate the impact of diagnosis (FBSS, CRPS, Other) on clinical change scores, across the time points. There was no significant interaction between diagnosis and time point, nor was there a significant main effect of diagnosis (p =.649).

3.3 Pain Related Disability

Repeated-measures ANOVA were performed to investigate changes in functional scores (ODI) between baseline, six-months, 12-months and 18-months follow-ups. Statistically significant improvements were observed for pain related disability as measured with the ODI, F (3,141) =5.010, p=0.002. As with VAS pain intensity and clinical change scores, participant's pain related disability scores reduced from baseline to six-month follow-up; however an increase in participants pain related disability scores was observed in subsequent assessments up to the 18-months follow-up post implantation.

Paired samples t-tests were used to investigate changes in pain related disability scores between time points. Pain related disability scores significantly decreased from baseline (M=55.04, SD=16.43) to six-month follow up (M=46.98, SD=19.05), t(47)=3.464, p=0.001 and from baseline to 12-month follow up (M=48.49, SD=20.94), t(47)= 2.918, p=0.005, but not 18-month follow up (M=51.75, SD=20.92), t(47)=1.330, p=.190. There was no significant change in pain related disability scores between six and 12-month follow up (p =.433), though there was a significant increase in pain related disability between six and 18-month follow up t(47)=-2.188. p=0.034. There was no significant change in pain related disability scores between 12-month and 18-month follow up (p =.184).

4. Discussion

Our findings demonstrate that SCS can effectively reduce pain intensity from baseline up to 18-months follow-up and can also result in important clinical changes being obtained up to 18-months following SCS implantation. In addition to reducing pain intensity, our findings demonstrate that SCS can effectively reduce the interference of pain on the ability to carry out daily activities, however by 18-month follow this improvement in functionality ceases to be statistically significant. Using the VAS we observed that pain intensity significantly decreased from baseline to all three time points, with reported pain intensity being at its lowest at the six-month follow-up. However, this initial pain relief at six-month follow-up failed to be maintained with reported pain intensity increasing significantly from six-month follow-up to both 12 and 18-month follow-up. The VAS has been found to be both reliable and valid in measuring subjective phenomena including pain within the chronic pain population [17,18]. A systematic review identified the VAS as the most frequently used tool for assessing pain intensity [19].

In addition to this, the level of clinical change also significantly reduced from six-month follow-up to ensuing follow-ups. The proportion of patients who reported an increase in pain intensity increased at each time point, with eight more patients reporting a greater level of pain intensity at six-month follow up than at baseline, despite a ‘successful’ trial period. Two additional patients reported the same increase at 12-month follow up and another two additional patients reported the same increase in pain at 18-month follow up.

The number of patients obtaining ≥50% clinical change reduced from 17 (35%) at six-month follow-up to 10 (21%) at 18-month follow-up. Similarly, whilst patients showed a significant decrease in pain related disability scores from baseline to six-month follow up and from baseline to 12-month follow up, from six month follow up pain related disability scores began to increase and by 18-month follow up there was no significant difference in pain related disability scores from baseline to 18-month follow up. These results suggest that a follow-up at six-months may not be an appropriate indicator as to how much pain relief and functional improvement SCS will provide in the longer term and also that efficacy may begin to

significantly decrease very early on into the treatment (prior to 12-months). These findings are in line with previous research which has found initial success of SCS in reducing pain at six-month follow up, but an inability to maintain this initial efficacy [9-11,20,21]. No differences in pain relief were observed between patients with a diagnosis of CRPS, FBSS or other. The interpretation of the subgroup analysis in this study is limited by the small number of patients per diagnosis. Future studies should take into consideration the degree of clinical change and rate of attrition per diagnosis (e.g. CRPS versus FBSS).

A RCT involving patients with CRPS found that when compared to physiotherapy alone, SCS plus physiotherapy resulted in a significantly greater reduction in pain as measured by the VAS at six-month follow-up [9]. Despite this early indication of efficacy, a five-year follow-up analysis concluded that the beneficial effects of SCS in reducing pain in patients with CRPS diminished over time [20]. At three year follow up there were no significant differences between the two groups, supporting our findings that SCS efficacy may start to decrease significantly after six to 12 months of treatment. Kumar and colleagues compared SCS with conventional medical management (CMM) in an RTC involving patients with FBSS with predominant leg pain or neuropathic origin [10]. At six-month follow-up, 24 SCS patients (48%) achieved 50% or more pain relief in the legs versus four CMM patients (9%). A follow-up analysis at 24-months found the number of patients achieving 50% or more pain relief in the legs decreased to 37% in the SCS group and 2% in the CMM group, demonstrating a decrease in SCS efficacy from six-month follow-up onwards [21]. Whilst the current findings support previous research which has shown an inability to maintain the initial high levels of pain relief provided by SCS at six-month follow up, the current research suggests that this decrease in efficacy, at least in some patients may start earlier than previously suggested by Kemler and colleagues in their five-year follow-up study which concluded that the effectiveness of SCS lasted between two to three years.

The initial success of SCS at reducing pain at six-month follow-up may be related to some placebo effects. It is likely that patients will initially have high expectations that the treatment will reduce their pain. These expectations are likely to be heightened due to the high cost of

the device and the invasive nature of the procedure leading the patient to view their pain more positively. The possibility to switch the device on and off using a remote has the potential to make the patients feel like they have more control over their pain. Expectations have been found to interact with the effectiveness of treatments [22]. This initial effect may also be linked to the additional social support received in the initial months following SCS implantation whilst the patient is adjusting to the device. Research investigating the role of perceived social support in explaining pain adjustment among chronic pain patients found that higher levels of social support resulted in decreases in pain intensity, which in turn decreased functional impairment [23]. This social support may decrease once the novelty of the device declines, resulting in an increase in pain intensity. It may be beneficial that patients are informed about this potential reduction in pain relief after the first six-months. This additional information may help the patients to cope better with the possible decrease in pain reduction in turn reducing the overall effect of this loss of analgesia. It can also be hypothesised that unspecified working mechanisms of SCS may not function indefinitely leading to an increase in pain as suggested by previous research [20,24-26].

Several hypotheses can be advanced to attempt to explain this decline in efficacy after six-months of SCS. Studies investigating predictors of SCS outcome have identified a number of possible predictive variables; however discrepancies about some of the findings limit the possibility of a consensual agreement regarding which factors may be predictive of SCS outcome. Previously, operational factors (e.g. lead positioning, electrical parameters and complications) have been speculated to be the cause of this loss in analgesia, however this has also been observed in patients with no operational complications, suggesting that other factors may play a role [27]. More recently psychological factors have been hypothesised as impacting on SCS efficacy, though a recent systematic review concluded that there were no consistent psychological predictors of SCS outcomes [28]. This review also found that depression, previously identified as being a predictor of SCS outcome may actually improve as a result of SCS questioning its predictive value [28,29]. A further systematic review found that older age and longer pain duration were predictive of poorer outcome in some studies

[27]. Future prospective research is warranted to attempt to identify predictors of long-term outcome for patients being considered for SCS.

One of the main strengths of this study is the regular follow-up allowing for detection of small changes. Previous research investigated SCS at larger incremental time points, often at six, 12 and then 24-month follow-up. Furthermore previous studies have looked at pain intensity only, as opposed to also looking at clinical change and pain related disability.

This study would benefit from studying patients over a longer period of time to identify whether efficacy stabilises or continues to progressively decrease. A limitation of this study would be the potential for assessment bias. However, all patients were given the questionnaires by a third party researcher not involved in the clinical management and completed them at their own discretion away from the pain management team, therefore reducing the risk of such bias. Other limitations include the limited number of patients and being a single centre study. Moreover the current research did not investigate concurrent analgesia use, a potential confounding variable.

In conclusion, this study observed that SCS is effective for the management of chronic neuropathic pain; although the initial pain relief experienced significantly decreased six-months following SCS implantation. A six-month assessment of pain reduction may not be indicative of long-term effectiveness as there may be too many placebo effects affecting pain perception at this time point. Some patients may actually experience an increase in pain intensity prior to 12-months following SCS implantation.

Conflict of interest statement

The authors report no conflicts of interest.

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Figure captions

Figure 3 Mean pain intensity from baseline to 18-month follow up

Figure 4 Mean clinical change scores up to 18-months follow up