Comparing the efficacy of targeted spinal cord stimulation (SCS) of the dorsal root ganglion with conventional medical management (CMM) in patients with chronic post-surgical inguinal pain: Preliminary results of the SMASHING study

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ABSTRACT

Introduction: Approximately 10% of patients who undergo a standard inguinal hernia mesh repair or Pfannenstiel incision, develop chronic (>3 months) postsurgical inguinal pain (PSIP). If medication or peripheral nerve blocks fail, surgery including neurectomies and/or mesh removal are the designated last resort treatments. A small proportion of patients, however, does not respond to any of the currently available remedial treatment modalities. Targeted spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) is found to significantly reduce chronic PSIP in specific patients.

Methods: In this multicentre, randomized controlled study, DRG SCS (Axium® SCS system, Abbott, Chicago, USA) was compared to conventional medical management (CMM; non-invasive treatments such as medication, TENS and rehabilitation therapy) in PSIP patients who were refractory to a neurectomy. Patients were recruited at a tertiary referral center for groin pain (SolviMáx, Eindhoven, the Netherlands) between March 2015 - November 2016. Suitability for implantation was assessed following the Dutch Neuromodulation Society Guidelines. Interim results in 18 of an originally calculated cohort of 78 patients were analysed. Nine patients were allocated to SCS and 9 to CMM, of whom 6 chose to cross-over to SCS treatment after 6 months. All patients kept daily pain diaries providing average Numeric Pain Rating Scale (NPRS) scores at baseline and 1-, 3- and 6- months follow-up.

Results: Fourteen of eighteen enrolled patients reached the primary 6 months endpoint and had data available for a per protocol analysis. Three SCS patients had a negative trial and were lost to follow-up. Average pain reduction was 49% in the SCS + crossover group (6.60 ± 1.24 to 3.28 ± 2.30, p=0.0029). In contrast, a 13% increase in pain was observed in CMM patients, 6.13 ± 2.24 to 6.89 ± 1.24, p=0.42. Adverse events occurred in nine SCS patients (n=19 incidents), predominantly lead dislocation and pain at the implantation site.

Conclusion: Targeted SCS stimulation of the DRG using the Axium® SCS system effectively alleviates pain in some patients with PSIP who are refractory to all other conventional treatment modalities.

INTRODUCTION

A male person in the industrialized world faces a lifetime risk of up to 27% of requiring surgery for an inguinal hernia. [1] Approximately 10-12% of these patients report moderate to severe chronic pain after the operation.[2-4] Chronic post-surgical inguinal pain (PSIP) , defined by the International Association for the Study of Pain (IASP) as 'pain beyond three months after inguinal hernia surgery', is currently the most disabling and costly complication of groin hernia surgery. In women, PSIP may also occur after a lower abdominal Pfannenstiel incision, used for example in caesarean sections.[5]

PSIP can either be nociceptive or neuropathic following nerve entrapment or damage during surgery.[6-7] Neuropathic pain is typically characterized as burning or shooting in nature. Paresthesia (tingling) and dysesthesia (spontaneous evoked unpleasant abnormal sensations) with radiation towards the associated skin area of the involved groin nerve are often reported. Pain with neuropathic characteristics is generally more severe than nociceptive pain, and is associated with a diminished health-related quality of life, with ratings as low as those of depression, coronary artery disease, myocardial infarction, or poorly controlled diabetes.[8]

Recently, a consensus was proposed concerning the management of PSIP.[9] If non-surgical options fail, a neurectomy of inguinal nerves is suggested. Success rates range from 50-100%, depending on the operative technique and experience of the surgeon. [10-12] However, few therapeutic options are currently available once these neurectomized patients demonstrate insufficient pain relief. Remaining treatments usually involve medications such as anti-neuropathics or opiates and may be supplemented by procedures such as pulsed radio frequency ablation (PRF) and transcutaneous electric neurostimulation (TENS).[13]

Spinal cord stimulation (SCS) of the dorsal root ganglion could possibly offer pain relief in these therapy resistant patients. This novel variant of traditional SCS has proved to be a significant innovation in a myriad of intractable pain conditions such as failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS) and phantom limb pain.[14-16] Its advantage opposed to traditional SCS is the direct stimulation of the inguinal dorsal root ganglia (specifically T12-L3), evading possible side-effects such as undesired sensations in structures near the groin (e.g. the bladder and urinary tract).[17] It was demonstrated to be a safe and effective therapy in small cohorts of PSIP patients, since its introduction in 2011 in Europe, but there are few large randomized controlled trials[18-20] The aim of this study was to investigate the efficacy of DRG SCS for PSIP in a randomized fashion.

METHODS

Study design, Outcomes, Patient selection and Randomization

This study set out to evaluate the efficacy of DRG SCS using the Axium® SCS System (Abbott, Chicago, USA) combined with conservative medical management (CMM) as compared to CMM alone, in PSIP patients who failed to respond favorably to an inguinal neurectomy procedure. The study design was a multicenter, randomized crossover trial. Primary outcomes were the percentage of patients experiencing pain relief and the difference in pain relief between groups, measured by average pain scores, kept for 7 consecutive days in a pain diary using a numerical rating scale (NRS) at 1, 3 and 6 months follow-up. Secondary outcomes included safety, quality of life using the EQ-5D and pain interference on daily life activities using the Brief Pain Inventory (BPI). Analysis of primary and secondary outcomes was compared to baseline values at the randomization visit.

The study was performed at 8 independent study sites with extensive experience on implantation of SCS devices. Central Review Board (IRB) approval was obtained from Maxima Medical Centre and local permission was obtained from the Board of Directors of each site. The study was registered at Clinical Trials.gov under number NCT02349659 and adhered to the Dutch Neuromodulation Guidelines.

Inclusion criteria:

- Subjects 18 years or older, able and willing to comply with the follow-up schedule
- Chronic inguinal pain (>6 months) following Pfannenstiel incision or open/laparoscopic inguinal hernia repair
- Previously undergone neurectomy procedure as a treatment for this chronic inguinal pain
- Minimum daily average baseline pain rating of 5 out of 10 in the inguinal area on an 11-point (0-10) NPRS scale
- Neuropathic pain as described by a score of ≥4 on the DN4 questionnaire

Exclusion criteria:

- Pregnant/nursing subjects or plans to become pregnant during the course of the trial
- Escalating or changing pain condition within the past month objectified by examination
- Injection or radiofrequency treatment of a target neural structure within the past 3 months
- Active implantable devices including ICD, pacemaker, SCS system or intrathecal drug pump
- Inability to operate the device

- An active infection, coagulation disorder or diagnosis of cancer in the past 2 years, except for skin malignancies such as squamous or basocellular carcinoma
- Participation in another clinical investigation within 30 days
- An ongoing condition which will probably require MRI investigation sometime in the following 2 years
- Spinal surgical procedures at or between vertebral levels T10-L2
- Progressive neurological disorders such as diabetic polyneuropathy or multiple sclerosis

Potential study patients were identified from a database of neurectomy non-responders at a tertiary referral center for groin pain (SolviMáx Center of Excellence for Abdominal Wall and Groin Pain, Eindhoven, the Netherlands) and invited for an information visit once the inclusion and exclusion criteria were met. Independent centers were also able to refer patients. Informed consent was obtained after additional screening by a multidisciplinary team of a psychologist, pain specialist and surgeon qualified as groin pain expert (inclusion requirement). Patients were randomized after the baseline visit using a centralized web-based system in a 1:1 fashion to either the DRG SCS or CMM group.

Interventions and follow-up

The DRG SCS group was referred to an implanting center nearest to their home and had one or two intake visits prior to the actual implant procedure. Patients were implanted in a protocolled two-phase procedure: leads were placed and the patients 'trialled' for a period of 1 -2 weeks with an external neurostimulator. If the subject achieved sufficient pain relief (≥ 50% pain relief), they then received an implantable neurostimulator. Follow-up visits were scheduled 4 weeks, 3 months and 6 months after final implant in the designated center. Due to reasons of patient safety, some patients did not undergo a trial period and were implanted primarily. This was discussed with the principal investigator beforehand.

The CMM group also had follow-up visits scheduled 4 weeks, 3 months and 6 months after randomization. Medication, TENS and rehabilitation therapy could be continued or initiated if monitored. Nerve root blocks, pulsed radiofrequency treatment of the dorsal root ganglia T10-L2 or epidural therapy were discouraged as these adjuncts would prevent patients from crossing over to the DRG SCS treatment at 6 months in accordance with the primary exclusion criteria. After crossover, CMM patients were followed for an additional 6 months, adhering to the schedule of the DRG SCS group.

Sample size, statistics and interim analysis

The sample size estimation was based on a responder analysis, with an estimated 10% responders (>50% pain reduction) in the CMM group and a difference in effect size of

40% between the groups. With a power of 90% and a two-tailed alpha of 0.05, it was calculated that 31 subjects were necessary in each arm to achieve the study aim. Allowing for a 20% attrition rate, the number of inclusions was aimed at 78 individuals. Unfortunately, inclusion rate was considerably lower (Figure 1). This suboptimal inclusion prompted the authors to do an interim analysis of the subjects who were included until the end of 2016, in order to validate results. A one-way repeated measures ANOVA was used on the mean pain reduction in NPRS at 4 timepoints, instead of the per protocol proposed x^2 analysis on number of favorable responders, as dictated by the low sample size. Categorical demographics were compared using the x^2 test. Continuous data were compared using the independent t-test or Mann-Whitney U test when appropriate. Results were presented as mean with standard deviation or median with range, respectively. Data were analyzed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, US).

RESULTS

Recruitment and patient flow

Study enrollment, allocation and follow-up are summarized in the CONSORT flow diagram (figure 1).[21] After IRB approval, 78 patients were screened from a database of 418 patients who underwent a neurectomy procedure between 2002-2013 and were coded as having an unsuccessful or unsatisfactory result. A total of 42 patients did not meet the study criteria. Therefore, 36 patients were contacted, of whom a further 30 were excluded or chose not to participate. In the subsequent period, between 2014-2016, 37 additional patients were evaluated after an unsuccessful neurectomy either in the tertiary referral center or referred from elsewhere. 15 of these patients met in- and exclusion criteria and were interested in participating in the study. A total of 21 patients were screened by the multidisciplinary team and 18 were deemed suitable for implantation.

From March 2015 to November 2016, these 18 patients were randomized to DRG SCS (N=9) or CMM (N=9). Three patients had a negative trial, during which the system provided no pain reduction and were not implanted and lost to follow-up. Consequently, 15 of the 18 enrolled patients reached the primary 6 months follow-up endpoint and had data available for a per protocol analysis. Six of nine patients randomized to the DRG SCS group received a permanent INS. In the other arm, 6 of 9 CMM patients chose to cross-over after 6 months follow-up and received a permanent INS. Patients in the CMM group who did not cross-over to the DRG SCS group gave reasons of fear of complications or significant comorbidity.

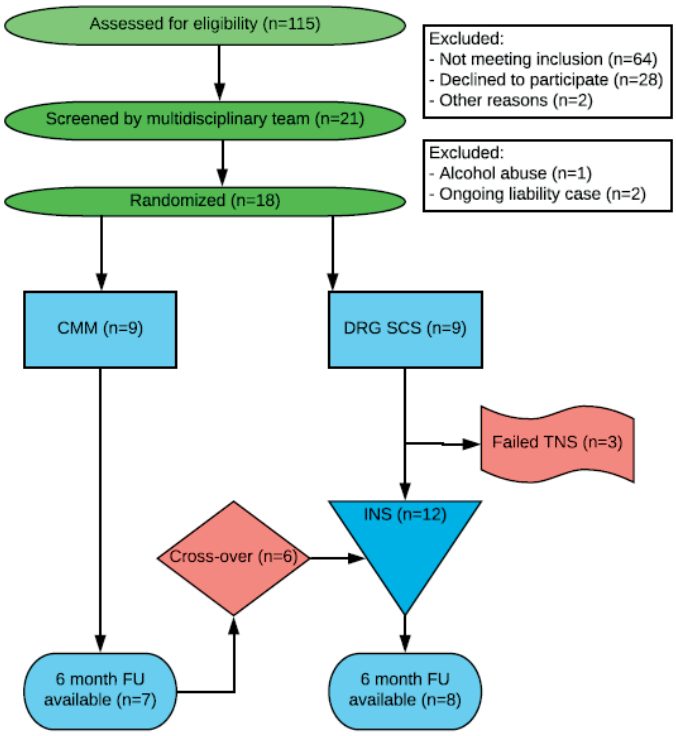

Fig. 1 Patient enrollment, allocation and flow reported following CONSORT diagram.

Baseline Characteristics and Assessments

Demographics of both groups are presented in table 1. Data were normally distributed except for duration of pain in months and least pain. There were no relevant baseline differences except for duration of pain in months. Pain distribution was equal in both groups, sometimes radiating from the inguinal area to upper leg or even back.

Table 1. Baseline characteristics represented as * means with (standard deviations) or ratios N:N.

	DRG SCS (n=9)	**CMM** (n=9)	**p-value**
Gender m : f	4:5	4:5	-
Age in years*	44 (10)	45 (15)	0.24
BMI*	26 (7)	25 (5)	0.16
Duration of pain in months*	54 (35)	64 (49)	0.02
Time since neurectomy in months*	16 (8)	16 (8)	0.40
CPIP : Postpfannestiel syndrome	4:5	4:5	-
Pain Average (NPRS)*	5,9 (1,3)	6,0 (2,1)	0.22
Pain Worst (NPRS)*	7,1 (1,7)	7,2 (1,0)	0.49
Pain Least (NPRS)*	3,8 (2,7)	4,1 (2,5)	0.33

Primary and secondary outcomes

In the pooled group of 8 implanted patients who completed the 6 months follow-up, a significant pain reduction of 49% (6.60±1.24 to 3.28±2.30, within group difference, p=0.0029) was observed (fig. 2). In contrast, a non-significant increase of 13% was observed (6.13±2.24 to 6.89±1.24, p=0.42) in the CMM patients. Group differences were highly significant over time (repeated measures ANOVA, group by time interaction, p=0.001, power 96%) and significant at 6 months follow-up (independent T-test, p=0.0047). Similarly, DRG group patients experienced an improved quality of life and decrease in pain interference, although group differences were not significant for these parameters (fig. 3 and 4).

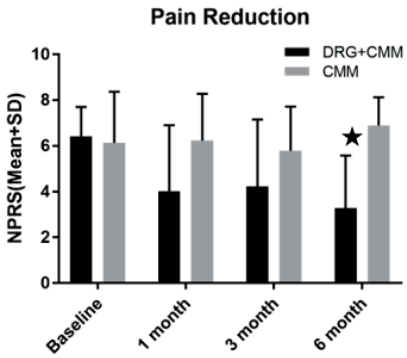

Fig. 2. Pain levels at various time points in PSIP patients receiving DRG (n=8) or standard treatment (n=6). Group differences were highly significant (p=0.001 by repeated ANOVA)

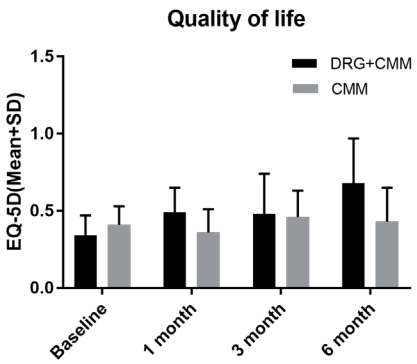

Fig. 3 Quality of life (EQ-5D) at various time points in PSIP patients receiving DRG (n=8) or standard treatment (n=6).

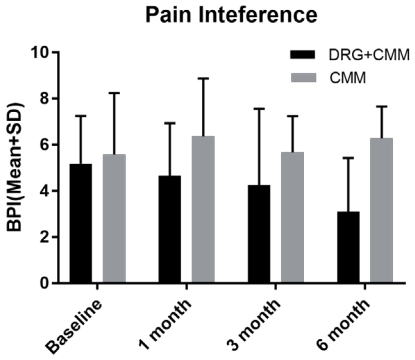

Fig. 4 Pain interference with daily life (BPI) at various time points in PSIP patients receiving DRG (n=8) or standard treatment (n=6).

There were no adverse events in the CMM group. Adverse events occurred in 9 of 15 patients receiving DRG SCS, including those with a negative TNS, with a total of 19 incidents (Table 2). Principal complications were lead migration or lead fracture, causing suboptimal stimulation, pain at the battery site and painful stimulation. One patient experienced post-spinal headache and refused permanent implantation. A second patient had a technical software problem causing low impedances, this was solved by using a new patient programmer. A third patient developed fever and pain at the site of the battery pocket. As ultrasound and laboratory testing suggested infection, intravenous antibiotics were administered leading to recovery without explantation. However, she reported fatigue and frequent episodes of relapsing sub-febrile temperatures during follow-up without abnormalities in blood tests. Finally, a fourth patient experienced a syncope and brief loss of function of the right arm, most likely unrelated to the device but caused by adjustment of medication regimens.

Table 2. Incidence of adverse events and which events consequentially required follow-up surgery.

Event etiology	Number of events (n=19)	Events requiring surgery (n=7)
Total device related	13	
Lead dislocation	6	2
Lead fracture	3	3
Painful stimulation	3	
Low impedances	1	
Technique (post-spinal headache)	1	
Total biological	5	
Pain at battery site	4	2
Infection	1	

DISCUSSION

Preliminary results in this small cohort of 18 patients with 14 subjects having a complete 6 month follow-up, indicate that DRG SCS can contribute to significant pain reduction of chronic, refractory PSIP. Substantial complications rates associated with the device were observed and some PSIP patients did not respond. Secondary outcome measures such as quality of life and functionality also improved, establishing the potential of this novel therapy for PSIP patients.

The study design of a cross-over, non-blinded RCT was inspired by a conventional SCS trial by Kumar, et al.[22] Although all patients received sub-perception threshold stimulation they could sometimes still feel stimulation, making blinding of the study very difficult. Other limitations of the study are its small sample size and the heterogeneity of the control group. Duration of pain symptoms varied slightly though significantly between groups, although it is not to be expected that a difference of 54 vs. 64 months could have any influence on the outcome. Bias could have occurred regarding the slight increase of pain complaints in the CMM group. A desire to become eligible for the DRG SCS device may have led to patients exaggerating their pain intensity (although it is both a minor and insignificant increase compared to baseline). This bias may potentially have led to an overestimation of the effect of the DRG SCS treatment.

The incidence of device related adverse events such as lead dislocation and lead fracture is higher than reported in previous studies on traditional SCS and DRG SCS, in groin patients.[23-26] Interestingly, adverse events occurred in almost every participating center in one or more patients, suggesting that hardware rather than technique was responsible. Patients who suffered from pain at the battery site or lead dislocation/ fracture had to undergo extensive revisions which may have resulted in fibrosis formation in the epidural space preventing re-implantation. Dislocation of the leads occurred several times whilst repositioning the battery. Dislocations may mask the true effect of neurostimulation at specific timepoints (most lead dislocations occurred between 1 and 3 months follow-up, resulting in higher pain scores at these moments due to suboptimal stimulation). It is therefore more likely that the efficacy of DRG SCS is underestimated due to this high complication rate.

In the literature, a non-responder rate of up to 30% has been reported.[27] In our study, the variety in treatment results could possibly be explained by the fact that covering the painful area in patients who already underwent a neurectomy is potentially challenging. Paresthesia mapping during a separate visit preceding implantation rather than 'on the table' could greatly optimize results, although this was already performed in many subjects of this study.[18]

On the other hand, it is valid to ask why these patients were non-responders to a neurectomy in the first place and whether the diagnosis of neuropathic PSIP was question-

able. We assume to have abolished any ambiguity as strict in- and exclusion criteria such as appropriate DN4-scores and psychological assessments were utilized. Furthermore, the original study protocol dictated quantitative sensory testing as a means to investigate the effect of DRG SCS on sensory deficits such as allodynia. Because of the small group size these results are not shown, but the sensory profiles of all patients at baseline were consistent with neuropathic pain, yielding disturbances such as hypo-esthesia, wind-up and allodynia.

The study was discontinued by the sponsor due to a too slow inclusion rate, the threshold for exploring a novel technique in this patient population appeared to be higher than expected. It is the explicit hope of the authors that the study will be resumed, after providing sufficient response to the findings in this article regarding preliminary results, such as the high complication rate. RCT's in the field of neuromodulation are important to assess the efficacy of DRG SCS objectively, but also to identify measures for adequate patient selection.

CONCLUSION

DRG SCS is effective in groin pain patients compared to CMM, regarding pain reduction and quality of life. Further research is warranted to define the exact position of the therapy.

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