Author's response to reviews

Title: Comparison of tonic spinal cord stimulation and high-frequency and burst stimulation in patients with complex regional pain syndrome: a double-blind, randomised placebo controlled trial

Authors:

Nadia Kriek (n.kriek@erasusmc.nl)
J George Groeneweg (j.groeneweg@erasusmc.nl)
Dirk L Stronks (d.stronks@erasusmc.nl)
Frank JPM Huygen (f.huygen@erasusmc.nl)

Version: 2 Date: 19 May 2015

Author's response to reviews: see over
May 19, 2015

Dr. C. Cornacchia  
Executive Editor  
BMC Musculoskeletal Disorders  

Manuscripts ID: MS 4345476351485680  

Dear Dr. Cornacchia,  

Dear Sir,  

We thank the reviewers for their comments regarding our manuscript. The comments of both reviewers are answered in the section below and implemented in the manuscript when needed.  

We thank the Editorial Board for the opportunity to revise our manuscript. I hope, that the improvements we have made to the manuscript as suggested by the reviewer have now made it acceptable for publication in BMC Musculoskeletal Disorders.  

All questions from the reviewers have been answered and if applicable changes in the manuscript have been made which is indicated by yellow markings along with mentioning the appropriate the page(s) and line number(s).  

With kind regards, on behalf of all authors,  

Nadia Kriek, MD  
Center for Pain Medicine  
Erasmus MC University Medical Center  
Rotterdam  
The Netherlands
1. Sample size: given the fact that three primary outcomes were selected, I wonder if a correction for multiple comparisons (such as Bonferroni or similar) has been taken into account.

The study has defined three primary outcome parameters, but the VAS score is considered as the main primary outcome parameter. We will however correct for multiple comparisons when appropriate. The “statistical analysis” paragraph in the manuscript has been rewritten to further explain the statistics that will be used and how we plan to correct for multiple comparisons:

Data are analyzed using the latest version of IBM SPSS Statistics. Descriptive statistics are used to determine the frequencies of the demographic and secondary outcome parameters, and to describe measures of central tendency and of dispersion, dependent on the shape of their distribution. The Kolmogorov-Smirnov test is used to analyze whether or not the scores on the these parameters are normally distributed. The outcome parameters are analyzed using Mixed Linear Models for repeated measurements within factors model. These Mixed Linear Models model require normality of residuals. These models are however relatively robust against violations of this assumption [81]. Therefore, the results are presented as mean ± the standard deviation (SD). Furthermore, a Bonferroni test will be performed in the pairwise comparison of the modes of stimulation only if the result of the overall analysis results in the rejection of the H0-hypothesis of no significant differences between the modes of stimulation. Therefore, to test this H0-hypothesis we will use the traditional rejection zone of five percent. The primary analysis will not make a distinction between primary implantation group vs. re-implantation group since the vast majority of the included patients will be SCS naïve. This matter should than be dealt with in a post hoc testing.

Page 12 line 18 – page 13 line 10

2. While appreciating the fact that during the initial trial, 40 Hz stimulation is the standard of care, I wonder if at least for at least short durations (perhaps one day at the time or so) other frequencies could be tested as well. This will allow patients who do not respond to the standard stimulation not to have their electrodes pulled out and give them a chance to benefit from SCS after all. This is an ethical consideration.

We have indeed considered the consequences in terms of the internal and external validity of the study and in terms of ethics of including only those patients who do respond during trial stimulation period. However due to the ethical concerns of the Institutional Regional Board we could not perform trial stimulation with other frequencies than the standard frequency that is used in daily practice.

Hence, no textual alterations in the manuscript for this item
3. It might be reasonable to consider not including a 40Hz stimulation in the statistical analysis, given the bias which arises from the initial stimulation period.

   The proposed design is based on the possibility of response shift due to the exposure of multiple other modes of stimulation. The possible recalibration in the valuing of the standard stimulation could result in it being more or less appreciated by the patients. Hence, we will include all options in the analysis.

   No textual alterations in the manuscript for this item

4. Please provide information on the randomization (computerized? blocks?)

   The manuscript has been altered to include the following lines in answer to the question of the reviewers:

   Randomization was performed with a computer based program at the beginning of the trial and no blocks were used since this is not viable in our study design. In our study design all patients in the crossover will be subjected to all five stimulation modalities in random order, resulting in 5! (120) different orders in which the stimulation modalities can be programmed. Only 48 (the required sample size) of these 120 potential different orders are selected at random by the computer to be used.

   Page 12 lines 6-10

5. Please provide clear information on the intensity of the stimulation in each treatment period. Is it going to be sub-threshold for all treatments? only for the burst stimulation? Please also give the rational for your decision.

   The following paragraph has been added to clarify the comment made by the reviewer:

   Programming the various frequencies
   The five stimulation modalities are all programmed in such a way the maximum effect pain be obtained. Standard 40 Hz stimulation will be performed above threshold which generates paresthesia in the affected area and is in accordance with normal practice. Both 500 Hz and 1200 Hz will be above threshold stimulation and will also generate paresthesia. At the time this study protocol was postulated there were no other reports available on how best to program 500 and 1200 Hz SCS based on mechanisms of action. Thus, in absence of evidence stating the contrary, we decided to program 500 and 1200 Hz SCS like standard 40 Hz stimulation with the intention to induce paresthesia and thus being an above threshold stimulation. Placebo stimulation is performed with the IPG switched off and thus does not generate paresthesia. The rationale is to evaluate how big a part of the pain relief could be attributed to the placebo effect. Burst stimulation is performed with fixed stimulation parameters and the intensity of the stimulation will be sub-threshold and therefore is does not generate paresthesia. The fixed parameters of burst stimulation are: an overall frequency of 40 Hz per burst complex. Each burst complex delivers 5 spikes with a frequency of 500 Hz and
6. Please provide the parameters for the burst stimulation.

The burst stimulation parameters have been added in the manuscript and was combined with the previous comment of the reviewer.

Burst stimulation is performed with fixed stimulation parameters and the intensity of the stimulation will be sub-threshold and therefore is does not generate paresthesia. The fixed parameters of burst stimulation are: an overall frequency of 40 Hz per burst complex. Each burst complex delivers 5 spikes with a frequency of 500 Hz and a pulse width per spike of 1 ms and an inter-spike interval of 1 ms. The charge is balanced during the 15 ms pause between the burst complexes.

Reviewer 2

Outcomes:

(1) the protocol describes 3 primary outcomes yet sample size calculation considers only one (pain VAS);

The study has defined three primary outcome parameters, but the VAS score is considered as the main primary outcome parameter. Further text has been added to the sample “size calculation paragraph” to further clarify that we have only used the VAS score in the sample size calculation.

The VAS score is considered the main primary outcome parameter out of these three.

By means of MANOVA for repeated measurements within factors, the potential differences in effect of the five different stimulation modalities will be assessed. A minimal detectable effect size (f) of 0.15 on the main primary outcome parameter pain intensity (VAS) was chosen. The required minimum number of participating patients is negatively associated with the correlation between measurements during the cross-over. Unfortunately, no data of previous research on this correlation were available at the time of setting up this study. Therefore, we made an conservative guess and a correlation of 0.6 was chosen. Thus, assuming a power of 0.8 and a significance level (α) of 0.05, an a priori sample size of 48 is required.
(2) medical history, physical examination are not (secondary) outcomes;

This will be altered in the manuscript so that the medical history and physical examination are not mentioned in the secondary outcome paragraph. They are now mentioned in the baseline measurement T0 paragraph.

The patient is invited to our medical centre to participate in various tests that are conducted as well as medical history and physical examination.

Page 14 lines 1-2

(3) provide definitions for stimulation evaluation and medication consumption will be assessed;

The manuscript has been modified to further elaborate on stimulation evaluation and medication consumption.

Stimulation evaluation requires a patient to keep a stimulation diary in which they must answer four questions; (1) the effect(s) of stimulation on pain in the CRPS effected area, (2) if they feel paresthesia and if so where do they feel it and how is the stimulation described, (3) how they would rate the ease of use of the stimulation, (4) the advantages and (5) the disadvantages per stimulation modality.

Page 16 lines 8-12

Medication consumption is assessed by taking an inventory of all (pain)medication and dosing the patients use at the time of the T0, T1 and T1 assessment. The pain medication will be stratified into the various medication groups and the sum dosage of the various pain medication groups will be calculated.

Page 11 lines 12-15

(4) it is implied that walking test will only performed if the lower extremity is compromised – clarify if only applied in this subgroup or all patient;

It is indeed correct that we only perform the walking test in the patients with CRPS in the lower extremity. This will be altered in the manuscript to make sure there is no ambiguity and it will clear for all readers.

In addition, a walking test is performed only in patients that have lower extremity CRPS. This test records how long it takes to cover a 10m distance when walking at a comfortable and maximum walking pace. Furthermore, the maximum walking distance is assessed during a 2-minute walk where the patient is instructed to cover as much distance as possible within these two minutes.

Page 9 lines 13-17
(5) physical activity level of a patient – again needs some definition;

The manuscript has been adjusted so that we can provide more information on activity and physical activity level.

The types of activity and physical activity level (PAL) of a patient is continuously measured with the VitaMove system (2M Engineering, The Netherlands) for multiple days (2-3 day), providing a detailed and continuous report on the patient’s energy expenditure, motions and postures over the course of several days [42-47]. This device is capable of interpreting various positions like sitting, standing and lying down as well as discerning various activities like walking, running, cycling or general motion of the arms, legs and trunk. The PAL can be estimated with the VitaScore software that calculates the energy expenditure with the aforementioned activities and the patients characteristics like weight, height, age and sex to estimate the basal metabolism. The energy expenditure can provide information on the level of activity of a patient that ranges from extremely inactive-extremely active.

Page 9 line 19 – page 10 line 5

(6) clarify if the outcome questionnaire is patient completed or researcher administered.

The questionnaires are completed by the patient. This will be adjusted in the manuscript on the following pages and lines:

Page 8 lines 12-13
Page 10 line 12

Design:

(1) Is 2 weeks cross-over duration sufficient? And 2 day wash out sufficient? These timings need some statement of support for their adequacy;

The duration and the rationale of the 2 weeks per period and the 2 day wash-out period are further elaborated in the discussion section of the article as a new paragraph:

The question remains if a two week test period per frequency along with a two day wash-out to counteract the possible carryover effects of the various frequencies are enough. In clinical practice a patient can conclude whether the SCS is beneficial to him/her within a two week period during trial SCS. We choose to maintain the 2 week per period analogy in the crossover period which should provide the patient with enough time to decide if one of the test frequencies is beneficial or not. Moreover, by increasing the crossover period to 3 weeks or even longer the possibility of patient withdrawal from the study increases in case one of the test
stimulations does not provide (sufficient) pain relief. This is further supported by what clinicians hear from patients that the pain returns when the stimulation is switched off. Some experience an instantaneous increase in pain while others report that it takes a few minutes or a few hours before the pain has fully returned, but never longer than 24 hours. On these arguments we decided on a wash-out period of 2 days between the various stimulation modalities to be tested.

Page 19 lines 9-20

(2) provide evidence/citation for correlation of 0.6;

This is further explained in the manuscript in the sample size calculation paragraph:

By means of MANOVA for repeated measurements within factors, the potential differences in effect of the five different stimulation modalities will be assessed. A minimal detectable effect size (f) of 0.15 on the main primary outcome parameter pain intensity (VAS) was chosen. The required minimum number of participating patients is negatively associated with the correlation between measurements during the cross-over. Unfortunately, no data of previous research on this correlation were available at the time of setting up this study. Therefore, we made an conservative guess and a correlation of 0.6 was chosen. Thus, assuming a power of 0.8 and a significance level (\(\alpha\)) of 0.05, an a priori sample size of 48 is required.

Page 11 lines 18 - page 12 line 3

(3) why is a period of standard stimulation needed?

A trial stimulation with standard stimulation was required by the Institutional Regional Board since that is the procedure in daily practice and for the reimbursement of the therapy.

The first three months with standard stimulation is needed so that the patients could recover from the operating procedures, familiarize themselves with the SCS therapy and to provide sufficient time for the therapy to have an effect. One could debate if three months with standard stimulation might be too long, but on the other hand a 1 month recovery period with standard stimulation might be too short. In both cases the patients are familiar with standard stimulation – not naive for stimulation – and we opted to choose a longer recovery period of three months to make sure recovery after the procedure was more definitive before starting the crossover period. In the crossover period we test 5 different modalities and we wanted to do everything in our power to make sure the effect that are observed are due to that stimulation modality and not a lingering effect of recovery after the SCS procedure in case of a shorter recovery time.
As for including the standard stimulation in the crossover period (see comments reviewer 1): Including the standard stimulation enables us to make a comparison between standard and other non-standard stimulation modalities and the patient will be able to weight the effects of all the different stimulation modalities and choose the one that is preferred.

*No textual alterations in the manuscript for this item*

Data analysis:

(1) how attrition be handled?

The discussion section has been updated in which we describe how attrition is handled:

Bias and in particular attrition bias is a serious problem that could affect the results of the trial. In our trial attrition bias will be handled by describing all patients that have dropped out of the trial before its completion and the reasons for dropping out/trial exit will be documented and provided in a flowchart in a separate manuscript with the results of this trial. The flowchart will adhere to the requirements of the CONSORT statement for transparent reporting of trials. Furthermore, data will be analysed using linear mixed models. Hence we can use all of the data, i.e., if a score is missing, it has no effect on other scores from that same patient.

Page 20 lines 5-11

(2) clarify if analysis will take account of the two SCS naive vs. SCS failed patients – one would expect that they may have different responses to neurostimulation effect – lack of power;

The statistical analysis section has been updated to clarify this item:

The primary analysis will not make a distinction between primary implantation group vs. re-implantation group since the vast majority of the included patients will be SCS naïve. This matter should than be dealt with in a post hoc testing.

Page 13 lines 8-10

(3) the value of T2 assessment is unclear

The value and need for a T2 assessment has been made more clear in the manuscript. The paragraph “Follow-up measurement T2” has been rewritten.
The T2 assessment is performed when a patient has completed the 3-month period with the frequency of choice. This T2 evaluation enables us to compare all the primary and secondary outcomes parameters with the T1 assessment with standard SCS and the baseline T0 assessment prior to SCS therapy. The patient is actively asked whether they want to continue with the SCS program they have chosen, or want to switch to another one based on the crossover results.