Author's response to reviews

Title: Effect of Tadalafil on blood flow, pain, and function in chronic cold Complex Regional Pain Syndrome: A randomized controlled trial

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Response to the reviewer's comments

Dear Sir,

We thank Drs. Schaller and Schwartzman for their constructive comments regarding our manuscript. The comments of the reviewers have been carefully considered and implemented as follows:

**Reviewer 1:** Hans Eberhard Schaller

1.1.) Regarding the data, significance levels are difficult to achieve with only 12 patients in each study group. We strongly encourage the authors to enclose a higher patient number in further research in this field.

We agree, that the number of patients in this study is small. We tried to recruit as many patients with CRPS as possible, but even with the assistance of the Dutch CRPS Patients Association it was hard to find enough patients fully complying with the inclusion criteria, complete with a chronic cold extremity. We went through great lengths to select a homogenous study population: Three anesthesiologists participated in the screening, and a physicist made videothermographic recordings of each screened patient during 2 years. Only one in 10 screened patients was eligible for this study, and even then many patients did not want to participate because they refused the possibility of placebo treatment. Nevertheless, we will follow your advice in the design of our future research.

1.2.) For a chronic disease like CRPS, an examination period of 12 weeks seems very low. The authors should at least indicate whether tadalafil medication was continued after the study period or not. Late results providing information about any possible tolerance to the substance or long-term side-effects would be appreciated by the reader.

The standard indication for tadalafil medication is erectile dysfunction, and it is primarily intended for male use during a short period. Up till now the medication has been used for a longer period by only one group of patients with pulmonary hypertension. This is the first study in which tadalafil has been used in male and female patients during a longer period. It took long deliberations with the Safety of Eli Lilly to get clearance for a treatment period as long as three months. Because in the Netherlands this medication has not been approved for the treatment of CRPS, a continuation of the treatment was not possible.

The primary goal of this study was to discover whether the inhibition of PDE-5 would lead to an improvement in blood flow in chronic CRPS, and whether this would improve pain and function in these patients. From our other studies we know that an improvement of blood flow and temperature could be reached in this period. (Groeneweg, G., S. Niehof, et al. (2008). "Vasodilative effect of isosorbide dinitrate ointment in complex regional pain syndrome type 1." Clin J Pain 24(1): 89-92.) We can therefore only describe the tolerance during the first 12 weeks. Most patients experienced an itching sensation, possibly related to the increase in blood flow, and two patients complained about painful muscles in their whole body during the first few weeks of the trial (page 9).
The next sentence was added to page 5, third paragraph: ‘The study medication was stopped after the study period and the patients were seen by FJPMH to discuss further conventional treatment.’

1.3.) It is well known that intensive physiotherapy is crucial in CRPS treatment, so we doubt that one treatment session, which the patients of the study population receive, is effectual. We believe that efficiency of any pharmacotherapy could be strongly enhanced by this basic treatment.

We agree with the reviewer, that intensive physiotherapy is very important in CRPS treatment. Therefore, the patients had to agree in advance to participate in a physiotherapy home exercise program, which consisted of daily exercises.

Since this was apparently not clear from the text, the third paragraph of page 5 has been altered to read: ‘All patients participated in a modified version of the physiotherapy program described by Kemler et al. [20], which is based on a graded activity approach intended to improve function, strength, and mobility of the affected extremity. The patients performed daily exercises at home, which was instructed and supervised by a local physiotherapist during one therapy session per week. The therapists received written instructions, filled in compliance reports and received feedback by telephone and email by the first author.’

1.4.) In addition to the tables showing start and end figures of the endpoints, it would increase the readability of the data if the authors would add some graphs showing time courses of the data. This would e.g. provide information if data changes are linear/nonlinear or if any plateau was reached at an early phase.

As we reported on page 5, although we did have patient contact to monitor the medication, physical therapy and adverse events, the outcome measures were only assessed at the start and end of the study. We cannot, therefore, provide these requested data in any form whatsoever. We do know, however, from the remarks of the patients, that most changes in temperature and pain appeared to take place after 4 weeks, after the medication had been doubled from 10 to 20 mg daily. Improvements in walking, as reported by the patients, seemed to take place gradually in the weeks after.

Reviewer 2: Robert Schwartzman

2.1.) Adding PT to the methods is problematic. The reader does not know anything in regard to compliance, effort and skill of therapist. This needs to be addressed.

As we stated in the answer to remark 1.3, the physical therapy protocol has been described by Kemler. The paragraph on page 5 has been adapted to make this clear.


We agree that this should be noted, therefore we added the next paragraph to page 10: ‘Our patient population is too heavily weighted towards women. The usual ratio is 4:1 [references Sandroni & de Mos], and we included 20 women and 4 men. Although it has been suggested, that the influence of hormonal etiological factors may be involved in the pathogeneses of CRPS [reference de Mos], there are no indications, that these factors still play a role in the vascular alterations in the chronic CRPS.’

2.3.) The data are sound. However, in pain studies a 30% increase over placebo is usually considered meaningful and 50% robust. The percent improvement of this study is only 15% and therefore this most important parameter of CRPS does not meet usual criterion (needs to be noted).

This suggestion has led us to add the following paragraph to page 10: ‘Pain, which is the most important parameter of CRPS, was significantly reduced compared to placebo. However, in pain studies a 30% increase is usually considered meaningful, and 50% robust. Since we found a mere reduction of 15%, this should be interpreted with care. Pain in CRPS may be due to a neuropathic cause [reference Oaklander 2006; Albrecht 2006] there may be sympathetically maintained pain [reference Wehnert 2002], or it could be caused by local ischemia [reference Koban 2003 and Xanthos 2008] perhaps even in the same patient. It seems likely, that the present reduction in pain was achieved by an improvement in local ischemia, leaving the other causes unchanged. On the other hand, an increased physical activity could consequently result in an increased awareness of pain. This needs further investigation.’

2.4.) There is a large discrepancy between reported improvements in strength, activity levels and walking with documented improvement.
This is what surprised us most when interpreting the results. Some patients improved so dramatically that they left their crutches at home, stopped using the wheelchair, and reported large reductions in pain, while others did not improve at all. Most patients appeared to respond well to tadalafil, but there were also a few completely non-responders. This may be due to a difference in disease mechanism, like for example neuropathic vs ischemic pain, or a central vs peripheral vasoactive component. Since this trial was conceived as a randomized placebo controlled trial, it is only fair to report the results of all patients and compare it to the placebo group. Growing insight in the disease mechanism thanks to this study makes us confident, that a carefully selected (and larger) group of CRPS patients with endothelial dysfunction would probably show more convincing results.

2.5.) The trend is there but the significance is not. Discussion of other factors that were not overcome such as peripheral or central sensitization or astrocytic secretion of inflammatory cytokines needs to be noted. We agree that many other factors play an important part in CRPS. Since the main focus of our article was on tadalafil, we only discussed aspects that are directly related to the vasoactive factors. We added the next few lines to page 12: ‘It has been suggested that CRPS is primarily a disease of the central nervous system [reference Janig 2003]. In any case it is a multifaceted disorder, and any effort to treat only one facet is bound to result in failure [reference Mogilevsky 2007]. However, in this trial we have solely concentrated on the question, whether the inhibition of PDE-5 could improve the blood flow in CRPS.’ As to the peripheral or central sensitization, these aspects may be subject to change, as the sensation of deep cold pain improves, when the patients’ activity pattern improves, or as a result of the physical therapy. We did, however, not measure any outcome parameters on this subject.

Our research group measured inflammatory cytokines, and found, that there is no important role for them any more in chronic CRPS. This article has been published very recently (Wesseldijk et al., Mediators of Inflammation 2008; volume 2008, article ID 469439, 8 pages).

3.1.) A few grammatical mistakes in an otherwise well written paper. The paper has been carefully re-checked, and a few textual mistakes have been corrected.

3.2.) Addition of physiologic data explaining cold CRPS (upregulation of adrenoreceptors in vasculature of affected vessels; change of small fiber innervation; changes in neuropeptide concentration (Albrecht et al Pain 2006,120(3):244-66)

In the introduction on page 3 we described that the regulatory neuronal factors were examined by Wasner et al, and we conclude the paragraph with ‘…..but secondary changes in neurovascular transmission would lead to vasoconstriction and cold skin in the chronic stage of the disease’.

We changed this sentence to read: ‘It was suggested that in CRPS, unilateral inhibition of sympathetic vasoconstrictor neurons led to a warmer affected limb in the acute stage, but secondary changes in neurovascular transmission, namely supersensitivity to circulating catecholamines and the increase of alpha-1 adrenoceptors, would lead to vaso-constriction and cold skin in the chronic stage of the disease’.

Furthermore, we added the sentence ‘A histopathologic study of skin samples in chronic CRPS showed numerous abnormal changes in vascular innervation and structure’ to the introduction on page 2, and the references of Albrecht and Oaklander are both added to the discussion on pain on page 10.

As discussed above (2.5.), we do not expect any remaining influence of cytokines in most patients with chronic CRPS, but this goes beyond the scope of this article.

3.3.) Better discussion of how changes in microenvironment (decreased blood flow) may increase pain by effects on TPRV receptors, free radical production, etc.

As mentioned above (see 2.3), we revised the paragraph on pain in the discussion on page 10.

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

With kind regards, on behalf of all authors,

George Groeneweg