Author's response to reviews

Title: Assessment of the Feasibility of High-Concentration Capsaicin Patches in the Pain Unit of a Tertiary Hospital for a Population of Mixed Refractory Peripheral Neuropathic Pain Syndromes in Non-Diabetic Patients

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Version: 6 Date: 1 May 2014

Author's response to reviews: see over
Dear Dr. Marielette Costoy,

Please find enclosed the revised version of the above manuscript. We have taken into account the comments made by the reviewers and the manuscript has been modified accordingly.

We enclose herein as a supporting document the list of changes that have been made which have been underlined or crossed out. Indeed, a clean copy is also provided.

We appreciate your comment, we believe, have permitted us to submit an improved manuscript. We hope that this revised version of our manuscript will now be deemed acceptable for publication in BMC Anesthesiology.

Sincerely yours,

Marc Giménez-Mila MD
Editorial requirements:

1. Please include the email addresses of all co-authors in the title page.

A: Done.

2. Kindly include (in the methods section of the manuscript) the full name of the Institutional Review Board that approved the study.

A: This topic was discussed in several times with the editors, previous to send the manuscript for peer review, please see e-mails date on 18 october 2013 (if it is required we can send them to the editorial office); and accordingly with the editors’ comments, the “study design section” was adapted. Now, the full name of the Institutional Review Board that approved the written informed consent has been included:

“All patients gave their written informed consent for their medical information to be used for purposes of scientific research in accordance with the ethical committee of the participating site (Hospital Clinic de Barcelona). The Ethical Committee approved the informed consent in September 2010.”
REVIEWER COMMENTS.
We thank the reviewer for the fruitful comments that we have properly addressed.

REVIEWER: Michael Serpell

Reviewer’s report:

1.- In order to gain more meaningful insight, we need to have a description of what the usual activity of your pain clinic is. You give a little information on Page 12, but please expand. For example, in our unit we have two treatment rooms on a procedure list. A patient having Qutenza would effectively block one of them for 2.5 hours. How do you work flexibly around that to reduce the negative impact of that (less patients treated)? Similarly, if I were to do this during a consultation clinic, I would have to leave the room several times to perform/supervise certain aspects of the procedure, with less patients being seen in my clinic. And that is assuming that someone else will be monitoring them whilst I go back to the clinic.

A: Following your recommendation, the following sentence has been added to the final manuscript in the first paragraph of the discussion:

“problems that may be encountered in applying this new treatment (capsaicin patch) routinely in our clinical practice. Our pain unit has three treatment rooms, three consultations rooms, and we work altogether with two specialized pain nurses leading to a flexible work minimizing the negative impact of the treatment application. During the consultation clinic the physician could develop the normal activity because the nurses were trained in performing this procedure including the patient monitoring.

2- We use our nurses to do the procedure, but similarly, they have to be in attendance all the time, and cannot do their own clinics or ward rounds during the Qutenza procedure. So we reschedule other tasks to them that can be done during certain phases of the Qutenza application. Do you do this?

You need to explain all of this in your paper, otherwise the study is meaningless to the uniformed reader.

A: In line of the previous point we have expanded in order to give more meaningfulness in the third paragraph of the discussion

“somewhat comfortable during the application. In addition, a nurse specialized in pain treatment is required for nearly 2 hours to apply the capsaicin patch, whose tasks are rescheduled to be performed during certain phases of the procedure, and also a physician must be available at the facility.”
3- Also, it looks like your practice is to apply LA before the Qutenza. This time factor does not seem to be in your calculations. Please explain.

A: We would like to comment that this issue was included in the original manuscript in methods section as it follows:

“Time to determine and mark the painful area” on the skin was defined as the total time (in minutes) needed by the physician to determine and mark the painful area. This variable includes: hair removal, washing and drying the skin, topical anaesthetic pretreatment and cutting the patch to match the size and shape of the treatment area.”

Nevertheless, in page 9 (Results Sections), second paragraph we calculate the time to determine and mark the painful area, in this time is included the application of LA. Following your comments we have added:

“The median (range) total time to determine and mark the painful area and apply local anesthetic was 9 (6-15) minutes. The median (range) total time”

4- The paper shows a worthwhile response in 40% of 20 patients (Pain VAS reduction >30%). Similar to our results (actually very good when you consider they are non-responders to many treatments for NeuP). I noted that concomitant meds were NOT increased. You would expects this as 1) you are adding a new treatment and wanting to observe the effect, and 2) they have already tried multiple treatments and presumably are on optimal doses. Could you comment on principle of reducing concomitant analgesic drug consumption in those responders?

A: In page 10 third paragraph we have made the following changes to comment this point:

“Concomitant pain medications during the 12 weeks of study are summarized in table 1. No new medication was started during the 12 weeks of study. The patients carried on with the medication administered prior to capsaicin patch treatment because they presumably were on optimal doses.”

Specific comments. Compulsory revisions
Page 4, Methods - para 1, line 4 -- "your study", should this be "the study taking place"

A: Done.

Page 4, Methods, para 2, line 2 - Blood Pressure measured with cuff, not controlled.

A: Done

Page 5, para 3. What happened if the previous week, a patient had had application of Qutenza at the clinic? What then would then be your reference day?
A: The situation you mention just had happened once in the study. In this case as reference days were the two same days of the previous week (two different weeks) when capsaicin was not applied.

In order to clarify this point the following sentence has been included in the new manuscript (results section, fifth paragraph):

“Only in one case two patient were treated in two consecutive weeks and in the same day of the week, being the reference day the two same days of the previous week (two different weeks) when capsaicin was not applied.”

Page 5, last para - time to determine & mark the painful area - if this includes application of LA, then the time ranges measured are too short as the LA pre-treatment needs to be applied for 60 mins. Recent research evidence has demonstrated that LA preparation can be be ommitted and procedure pain adequately controlled with Tramadol PO instead. Can you comment on whether this was done in your centre during Oct 2010 to Sept 2011? If not, then new changes would reduce time to do the whole procedure.

A: .
We totally agree with your comment. As we mention before, the variable time to determine and mark the painful area includes the application of LA.
In our patients the time between LA and capsaicin patch application was short, probably due to this the main adverse event was pain. However we would like to highlight that the intensity of the pain related to capsaicin patch was mild (one to three in NRPS scale; page 9 third paragraph).

In the time the study was performed there was few evidence regarding the application of LA vs tramadol vo. Actually we give oral drugs to avoid the pain related to capsaicin application.

Page 8, RESULTS, para 2 - CRPS I is not a form of peripheral neuropathic pain (CRPS II is)

A: This is a controversial topic, the patient with CRPS I had pain in the upper extremity related to a bone fracture. That was the main reason to classify the pain in peripheral, because the involvement of the wrist. However we are aware of the complex physiopathology of this disease with the involvement of central nervous system and peripheral mechanisms.
The following references has been revised:


Page 9, para 2 - you do not mention any time for application of LA. Was this your practice? You do mention this later on (bottom of Page 9), it needs to be mentioned earlier and these times needs to be included in the analysis as it adds a minimum of one hour to the whole procedure time!!!

A: we consider that this has been clarified with the previous points.

Page 11, para 1. What was the change in EuroQol in the responders? Fig 1 unclear. I would suggest to include total N for each pain condition.

A: The following data has been included (last paragraph of results):

“and the median (range) of change (baseline minus at 12 weeks) in the EuroQol VAS was of 12.5 (-20, 50) [mean (sd): 16.9 (23.7)] in responders and of 10 [-70, 30] in non-responders [mean (sd): 0.4 (27.3)].”

The legend of the fig 1 has been changed

Figure 1: Responders to the capsaicin patch treatment by peripheral neuropathic pain diagnosis [PH: post-herpetic neuralgia (n: 6); TKA: total knee arthroplasty post-surgical pain (n: 3); PS: painful scar (n:4); NFC: Femoral cutaneous neuropathy (n: 2); N: neuroma (n: 3); CRPS-I: complex regional pain syndrome type I (n: 1); HIV: HIV-associated neuropathy (n: 1)].

Level of interest: An article of limited interest
Quality of written English: acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: 'I declare that I have no competing interests'
REVIEWER: David M Simpson

Reviewer’s report:
Major compulsory revisions:
1. The authors’ data on feasibility has limited value given the very small number of treated patients. Why would the authors’ believe that treating no more than 1 patient/day or 2/week would have significant impact on patient flow in their clinic?

A: We understand that this issue was reflected in the original manuscript, in following paragraph of the discussion section:
“In spite of the time required to manage this treatment, capsaicin patch application time did not affect the number of patients treated per day in our Pain Unit”. Therefore, we think that given that the number of patients did not change per day nor per week when the capsaicin patch was applied.

2. Why was such intensive BP monitoring and pre-/post-procedure EKG done? This is well beyond standard of care.

A: We agree with the reviewer, this performance is beyond the standard care. As we mentioned in the answers of the other referee, according with summary of product characteristics of capsaicin patch, we performed BP monitoring and pre-/post-procedure EKG as a safety measure, since that these 20 patients were the first treated with the capsaicin patch in our center, and we did not previously have experience with this treatment. In fact, these measures were only implemented for these first patients treated with capsaicin patch in our clinical practice.

3. Efficacy and QOL data from a small open label study of limited significance

A: We totally agree with the reviewer’s comment. Our intention is to show only a descriptive data, and we did not want to take any conclusion about this data. Therefore, in line with this comment, in the third paragraph of the discussion we point out this issue on efficacy: “Conclusions on the effectiveness of capsaicin patch could not be drawn due to the study design, the low number of patients included and to the variability of indications of peripheral neuropathic pain tested”. Likewise, only descriptive explanations about these results were included in the discussion of the original manuscript.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published

A: Following the suggestions of the reviewer, the new version of the manuscript has been revised by a native English teacher, which has caused some little changes along the manuscript.