

# The Efficacy of topical Capsaicin in the management of painful diabetic peripheral neuropathy: A unicenter double-blind, randomized clinical trial

**Batakeh Ba Agoons** (✉ [bbagoons@gmail.com](mailto:bbagoons@gmail.com))

Bafang District Hospital <https://orcid.org/0000-0002-5516-8770>

**Mesmin Dehayem**

National Obesity center, Endocrinology and Metabolic disease unit, Yaoundé Central Hospital

**Martine Claude Etoa Etoga**

Department of clinical sciences, Faculty of Medicine and Pharmaceutical sciences, University of Douala, Douala, Cameroon. 2) National Obesity Center, Endocrinology and Metabolism Unit, Yaounde Central Hospital.

**Dayawa Da Agoons**

UPMC Pinnacle Hospital, Department of Medicine, Harrisburg, Pennsylvania

**Faustin Yepnjio**

Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon

**Anne Ongmeb Boli**

Department of Internal Medicine and Specialties, University of Yaoundé 1, Yaoundé, Cameroon

**Yves Florent Wasnyo**

Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon

**Jean-Claude Njabou Katte**

Department of Public Health, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon

**Eliane Stella Tcheundjio Ngassam**

National Obesity Center, Endocrinology and Metabolic disease Unit, Yaoundé Central Hospital

**Ariane Nkamgna**

National Obesity Center, Endocrinology and Metabolic disease unit, Yaoundé Central Hospital

**Sobngwi Eugène**

National Obesity Center, Endocrinology and Metabolic disease unit, Yaoundé Central Hospital. 2) Department of Internal Medicine and Specialties, University of Yaoundé 1, Yaoundé, Cameroon.

**Jean-Claude Mbanya**

National Obesity Center, Endocrinology and Metabolic disease unit, Yaoundé Central Hospital.  
2)Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences,  
University of Yaoundé 1, Yaoundé, Cameroon

---

## Research article

**Keywords:** Pain, Neuropathy, Diabetes, Capsaicin

**Posted Date:** March 25th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-19190/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

## Background:

Painful peripheral neuropathy is a common complication of diabetes and its management is difficult. Neurotropic drugs, which are the drugs of choice, have moderate efficacy due to high first pass metabolism. Topical Capsaicin, derived from the capsicum plant, is effective in relieving the pain of diabetic peripheral neuropathy in Caucasians. Due to an intercultural bias in pain treatment response, we evaluated the efficacy of Capsaicin on painful diabetic neuropathy in sub-Saharan subjects

## Methods:

22 subjects with type 2 diabetes having painful diabetic polyneuropathy were randomly assigned using a 1:1 blocking pattern, with parallel design, to an intervention group of capsaicin cream, or to a control group of Miconazole cream. Participants and investigators were blinded to the randomization. Both groups applied the supplied drug topically three times daily for 08 weeks. Pain intensity was noted in both groups, using a visual analogue scale, at intervals of 2 weeks. The trial took place at the national obesity center in Cameroon. The primary analysis was intention-to-treat, and compared the reduction in the mean pain score from baseline, per 2 week period.

## Results:

Twenty-two patients, aged  $55 \pm 7$  years, with an average pain intensity of 6.3 units in the Capsaicin group and 5.8 units in the placebo group were included; at inclusion, there was no significant difference in the 2 groups ( $p=0.52$ ). After 02 weeks, the mean value of pain intensity was  $3.3 \pm 0.9$  vs  $5.4 \pm 1.7$  ( $p=0.004$ ), at week 4,  $3.2 \pm 0.9$  vs  $4.7 \pm 1.2$  ( $p=0.015$ ), at week 6,  $3.5 \pm 1.3$  vs  $4.8 \pm 1.3$  ( $p=0.018$ ) and at week 8,  $6.6 \pm 1.1$  vs  $5.4 \pm 1.0$  ( $p=0.55$ ) for capsaicin and placebo respectively. The main side effect in the capsaicin group was burning sensations in the application zones

## Conclusion:

Capsaicin significantly reduced neuropathic pain in the intervention group; however the pain worsened at week 8. It therefore has a transient positive effect on neuropathic pain in sub-Saharan subjects

# Background

Peripheral neuropathy in people living with diabetes mellitus is frequent, affecting about 50% of the population, ensuring it is the most common diabetic microvascular complication [1]. This peripheral neuropathy can clinically be motor, sensory, mixed or autonomic in nature. Pain, or painful paresthesias when present, can interfere with daily activities, work, and sleep, greatly reducing the quality of life of its sufferers.

The treatment of painful diabetic neuropathy, according to the Ad Hoc Panel on Endpoints for Diabetic Neuropathy Trials management is first to assure optimal glucose control, symptomatically treat the pain, and thirdly with the use of ancillary therapies directly interfering with the pathophysiologic cycle of diabetic neuropathy [2]. Symptomatic therapies for painful diabetic neuropathy include Tricyclic antidepressants, anticonvulsants, Gamma Amino Butyric Acid analogs, Selective Serotonin reuptake inhibitors, and rarely opioids. Despite this seemingly rich availability of options to treat painful diabetic neuropathy, effective treatment of diabetic neuropathic pain remains a challenge for both physicians and patients [3]. Most of these drugs are orally administered, and thus present with a high risk of systemic side effects and decreased drug bioavailability due to first-pass mechanism [4].

Capsaicin (Trans-8-methyl-N-vanillyl-6-nonenamide) is the active ingredient found in various species of chili peppers, and exhibits pharmacologic effects on type C nociception nerve fibers, which are necessary for conduction of slow neuropathic pain. Its application is topical and repeated applications result in functional injury to peripheral nerves, resulting in desensitization to painful stimuli [5]. This peculiar characteristic of capsaicin is the basis for its usage in relieving the pain of HIV neuropathy, post-herpetic neuralgia and surgical post-op pain [6]. Topical Capsaicin has been proven to have moderate efficacy in diabetic peripheral neuropathy in Caucasians. Pain perception threshold shows ethnic and racial differences with treatment response in Africans different from Caucasians [7]. In this population milieu, there is a lack of data indicating the efficacy of capsaicin in painful diabetic neuropathy. We therefore hypothesized that an 8-week treatment course using Capsaicin 0.075% would significantly improve pain sensation associated to diabetic distal peripheral neuropathy and overall quality of life of sub-saharan patients with type 2 diabetes involved in the study. We also investigated the possibility of occurrence of side effects with Capsaicin treatment.

## Methods

### Trial design

This was a unicenter, balanced 1:1 randomized double-blind, placebo-controlled clinical trial, with a parallel design, conducted at the National obesity center, Cameroon.

### Participants

Twenty-two participants with painful symmetrical diabetic neuropathy were recruited for this study, and were randomized to receive either capsaicin or the placebo cream. All were patients with type 2 diabetes who had daily pain or painful paresthesias in a neuropathic or radiculopathic distribution, intensity between 4 and 7 on a visual analogic scale, interfering with daily activities, work or sleep for at least 3 months duration.

Excluded, were patients with;

- History of allergies to any capsaicin product

- Diabetic patients with other diagnosed etiology responsible for peripheral neuropathy such as hepatitis, AIDS, Nutritional deficiencies (folate, vitamin B12)
- Presence of open skin lesions at the site of application of the study medication
- Signs of infection on limbs or amputations
- Pregnant or lactating females
- Subjects with other topical medication at site of application of study cream.
- All eligible patients who did not give their signed informed consent to participate.

### **Intervention**

The study took place at the National Obesity Center of the Yaoundé Central Hospital, from January to April 2018.

Painful peripheral neuropathy was diagnosed using the *Douleur Neuropathique 4* criteria and the *Toronto Neuropathy Score* [8]. Hepatitis screens, and HIV serology was done to exclude these as causes of the neuropathy. At baseline, Laboratory tests, physical examinations, vital signs and anthropometric characteristics such as body weight, height, blood pressure and general characteristics including age, duration of diabetes, history of hypertension, pain characteristics (intensity, duration, associated symptoms, and effect on quality of life) and ongoing medications were recorded at the beginning of the study.

### **Outcomes**

The Primary outcome/endpoint of the study was the reduction in the mean pain score from baseline, as assessed by the Visual analogic scale (0-10 points). (Figure 1)

The secondary outcome was the level of improvement in quality of life score after intervention. This was evaluated using the *physician's global evaluation* Score (Table 1).

### **Sample size**

The Whitley formula was used to calculate the sample size

$$n = \frac{P1(1 - P1) + P2(1 - P2)}{(P1 - P2)(P1 - P2)} \times f(\alpha, \beta)$$

Where P1 is the proportion of patients experiencing relief from capsaicin

P2 is the proportion of patients experiencing relief from a placebo

According to a study carried out by Rub Tandan et al on capsaicin efficacy and neuropathy,

P1= 73% or 0.73

P2= 21% or 0.21

From statistic tables,  $\alpha$  was set at 5% and  $\beta$  at 20% to obtain a power of 80%, giving a value of 7.9. This gave a minimum sample size of 11 patients per group.

### **Randomization and blinding**

Randomization was done using computer software, with a 1:1 varying blocking type to preserve internal validity. Thus, randomization divided the eligible candidates into two groups 1 and 2, equally. Generation of the random allocation sequence, enrollment of participants, and distribution of drug type to participants was done by different members of the study group. The study drugs were Capsaicin 0.075% gel and Miconazole cream, in identical no-label white tubes. Both drugs were dispensed to patient according to randomized group assignment. Participants applied either of the drugs topically on the feet 3 times daily. Evaluations of the patients including assessment of the pain severity, assessment of quality of life, vital signs and examination, and questioning regarding the adverse effects were performed at each of a 2-week follow-up visit. Compliance was assessed by direct questioning.

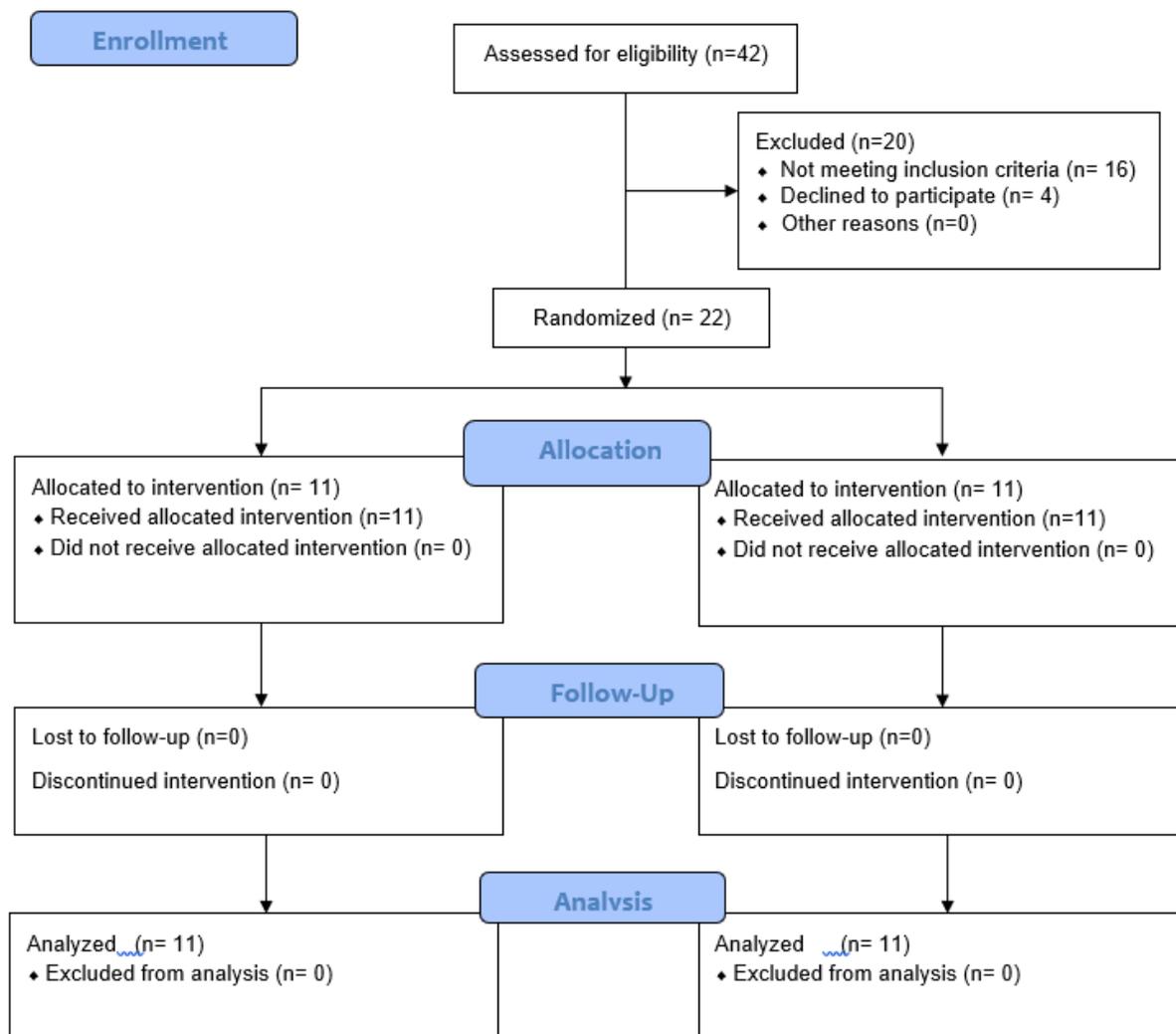
A data and safety monitoring board was setup and could decide to withdraw a study participant, if there was development of any serious harm as a result of the trial. At the end of the 8<sup>th</sup> week, the study was stopped. Equipoise was assured by making sure all investigators, participants and data analysts were blinded to the allocation. Only members of the data and safety monitoring board were aware of the subjects per allocated arm. The data and safety monitoring board was accessible by telephone to all participants throughout the study.

### **Statistical analysis**

The student t test was used to compare means for continuous variables between both groups. Categorical variables were compared using the chi square test. The primary analysis was intention-to-treat and involved all patients who were randomly assigned. The efficacy endpoint was the change in mean bi-weekly pain score on the Visual analogic scale. Values were expressed as means with ranges, and numbers and percentages. Statistical significance was set for  $p \leq 0.05$

## **Results**

The flowchart below shows the numbers of participants who were randomly assigned, received intended treatment, and analyzed for the primary outcome.



### Baseline characteristics of the patients

The study was conducted between January and April 2018. Patients' baseline characteristics were comparable between the two groups of treatments (Table 2)

### Outcomes and estimation

Table 3 shows the results of the effect of our intervention on the pain intensity values for each group per time period.

There is strong evidence that participants who applied capsaicin cream attested to a more favorable change, as shown by the primary efficacy parameter, than subjects who applied the placebo cream. There was a decrease in mean pain intensity value in the capsaicin group within 2 weeks of drug administration, maintained as such till the sixth week. At the eighth week however, there was a rebound in pain intensity in the capsaicin-treated group, greater than baseline values (**figure 2**)

Quality of life analysis was done using data from the fourth and eighth week of the study. Comparison for both groups revealed no statistically significant improvement as shown in Table 4.

## Harms:

Of the 11 participants allocated to receive the drug, 8 complained of a burning, stinging sensation at site of application only. 2 participants, in addition to this burning sensation, complained of sneezing and tearing eyes upon administration, and another 1, complained of diffuse redness on site of application, in addition to the burning. These side effects were noticed upon first administration and were significantly reduced or absent two weeks later.

The eleven participants assigned to the placebo group had no side effects throughout the duration of study (Table 5).

## **Discussion**

### Limitations:

The limitations of our study were the short duration of study and the lack of nerve conduction studies, which are the best methods in diagnosing and determining the type of neuropathy.

### Interpretation

The results of our double-blind placebo controlled randomized study in sub-Saharan participants with diabetic painful neuropathy show that 0.075% capsaicin cream significantly reduces neuropathic pain for 6 weeks of use. In this study, burning or heat sensations at site of administration was the most frequent adverse effect, which was tolerable, and decreased with repeated continuous administration. This shows that topical capsaicin may be of some value in the symptomatic management of painful diabetic neuropathy in cases where conventional agents fail to elicit a favorable response.

Ten out of eleven of the participants taking the topical capsaicin achieved a drop in their pain levels from baseline within 14 days from the start of therapy [9]. Our study demonstrated a pain reduction between weeks 2 to 6 which was statistically significant for Capsaicin versus placebo (3.08 units drop vs. 1.46,  $p=0.02$ ).

At the end of the 8<sup>th</sup> week, there was no statistically significant reduction in mean pain value in the capsaicin group, (-0.3 vs. 0.44,  $p=0.55$ ) but rather an increase in mean pain intensity compared to pre-treatment values. Capsaicin mediates its effect by defunctionalizing c fiber nociceptors (neurolysis). It is a TRPV1 agonist and its prolonged activation of TRPV1 results in loss of receptor functionality, causing impaired local nociception for extended periods. [10] Also defunctionalization of peripheral nerve fibers is partially as a result of capsaicin-induced substance p depletion, along with other sensory mediators in the spinal dorsal root ganglia. Regeneration or reinnervation of these nerve fibers after a functional insult is completed after about 6-8 weeks, explaining this increased pain intensity.

There was an improvement in the Quality of life at Week 4 analysis of the capsaicin participants, manifested by better sleep and less interference in physical activities and emotion. 9 out of 11 of these

experienced a positive change to Quality of life. However, comparison to the placebo group yielded no significant difference ( $p=0.28$ ) despite a significant mean pain level difference. Our findings can be explained by the fact that we limited our patient recruitment to those with a maximum pain level of 7. Thus, their baseline Quality of life was likely to be acceptable, and as such a large change unlikely. Quality of life comparisons at the 8<sup>th</sup> week were not significant either and comparatively impaired in the capsaicin group. This was most likely due to the worsening pain intensity due to nerve reinnervation.

Our study also sought to identify the safety profile of topical Capsaicin. All the 11 participants undergoing treatment complained of a Burning or stinging sensation at site of application of drug. This side effect gradually decreased with continuous application of drug, and was greatly reduced or tolerable by the second week of treatment. This finding corresponds to capsaicin-induced initial hyperalgesia of nociceptors followed by desensitization [11]. 1 participant out of the 11 complained of an on-site burning pain associated with erythema. This redness is due to the release of histamine from mast cells. [5]

## Conclusion

The above findings show that topical capsaicin has a transitory superb short term effect on neuropathic pain, but without any modification to clinical neuropathy severity grading, indicating it can be used as a symptomatic add-on option in periods of exacerbation of neuropathic pain. It also appears less likely to cause major side effects and improves quality of life modestly. The initial burning that capsaicin induces, may negatively impact compliance, and hence the drug's efficacy.

## Declarations

### List of Abbreviations

HIV: Human Immunodeficiency Virus

### Ethics and consent to participate

The study was approved by the Centre Regional Ethics Committee for Human Health Research, Cameroon (ethical clearance N<sup>o</sup> 0076/CRERSHC/2018) and the Institutional review board of the Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1 (ethical clearance N<sup>o</sup>0055/UY1/FMSB/VDRC/CSH). Signed informed consent was obtained from all the participants.

### Consent to publish

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare no competing interest.

## Funding

The funding for this study was supplied by the primary investigator. BBA was involved in the conception, design of the study, interpretation of data and drafting of the manuscript.

*AsacPharma* laboratories Cameroon provided the capsaicin drug, as a free sample.

## Authors' contributions

BBA was involved in the conception, design of the study, interpretation of data and drafting of the manuscript. DM, MCE and YF were involved in the study conception, design, protocol writing, critical review and revision of the manuscript. DDA and YFW were involved in data analysis and interpretation. NE, JCK, NA and AOB were involved in the training of workers for subject follow up and data collection, and critical review of this manuscript. SE and MJC were involved in the conception of the study, its design and general supervision. All the authors have read and agreed to the final manuscript.

## Acknowledgements

We thank the staff of the National Obesity center of the Yaoundé central hospital for their assistance in this study. We also thank the *AsacPharma* laboratories Cameroon, for providing the capsaicin drug, as a free sample.

## Author's Information

Not applicable

This study adheres to CONSORT guidelines for reporting clinical trials.

## **References**

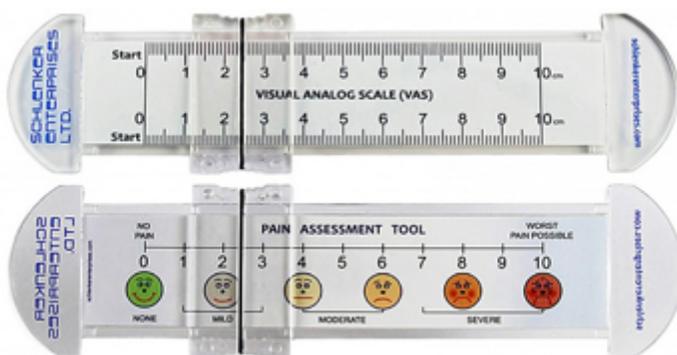
1. Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy. American Diabetes Association American Academy of Neurology. *Diabetes Care*;11(7):592–7.
2. Huizinga MM, Peltier A. Painful Diabetic Neuropathy: A Management-Centered Review. *Clin Diabetes* . American Diabetes Association; 2007 Jan 1;25(1):6–15.
3. Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P. 0.025% Capsaicin Gel for the Treatment of Painful Diabetic Neuropathy: A Randomized, Double-Blind, Crossover, Placebo-Controlled Trial. *Pain Pract*. 2013 Jul;13(6):497–503.

4. Stanos SP, Galluzzi KE. Topical Therapies in the Management of Chronic Pain. *Postgrad Med.* 2013 Jul 2;125(sup1):25–33.
5. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth.* 2011 Oct;107(4):490–502.
6. Katz NP, Mou J, Paillard FC, Turnbull B, Trudeau J, Stoker M. Predictors of Response in Patients With Postherpetic Neuralgia and HIV-Associated Neuropathy Treated With the 8% Capsaicin Patch (Qutenza). *Clin J Pain.* 2015 Oct;31(10):859–66.
7. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag.* NIH Public Access; 2012 May;2(3):219–30.
8. Bril V, Tomioka S, Buchanan RA, Perkins BA, mTCNS Study Group the mTCNS S. Reliability and validity of the modified Toronto Clinical Neuropathy Score in diabetic sensorimotor polyneuropathy. *Diabet Med.* Wiley-Blackwell; 2009 Mar;26(3):240–6.
9. Simpson DM, Robinson-Papp J, Van J, Stoker M, Jacobs H, Snijder RJ, et al. Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study. *J Pain.* Churchill Livingstone; 2017 Jan 1 ;18(1):42–53.
10. Groninger H, Schisler RE. Topical capsaicin for neuropathic pain #255. *J Palliat Med.* Mary Ann Liebert, Inc.; 2012 Aug;15(8):946–7.
11. Knotkova H, Pappagallo M, Szallasi A. Capsaicin (TRPV1 Agonist) Therapy for Pain Relief. *Clin J Pain.* 2008 Feb;24(2):142–54.

## Tables

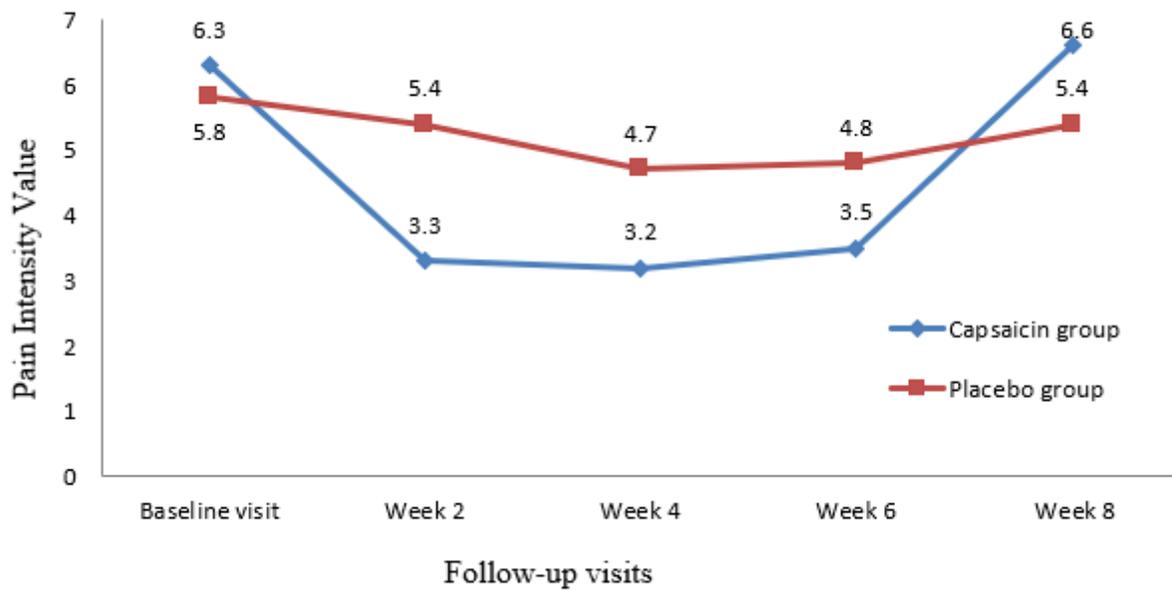
Due to technical limitations, all tables are only available for download from the Supplementary Files section.

## Figures



**Figure 1**

10 point visual analogic scale



**Figure 2**

Evolution of mean pain intensity value per 2 week period, in both treatment arms

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables.docx](#)