Efficacy of 0.0125% Capsaicin Patch at Acupuncture Point for Pain Relief in Knee Osteoarthritis: A Randomized Controlled Trial

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ABSTRACT

Objective: To study the efficacy of 0.0125% capsaicin patch at acupuncture point for pain relief in knee osteoarthritis (OA).

Methods: This randomized, double-blind, placebo-controlled clinical trial was conducted during September 2014 to March 2015. Sixty-two ambulatory patients over 50 years of age with a diagnosis of knee OA were included. All enrolled patients had a pain score of 4-7 out of 10. Participants were randomized into either the treatment (capsaicin, n=31) or control (placebo, n=31) group.

Interventions: Capsaicin vs. placebo patch at ST34 (1), SP10 (2), ST35 (3), EX-LE4 (Neixiyan) (4), ST36 (5), and SP9 (6) acupuncture points for 4 weeks. Main outcome measure: Pain subscale of modified Thai version of Western Ontario and McMaster (WOMAC) Osteoarthritis Index was assessed at baseline, 2, 4, 6, and 8 weeks after treatment.

Results: Pain subscale of modified Thai version of WOMAC showed no significant difference between groups at baseline, 2, 4, 6, and 8 weeks after treatment. After 2 weeks of treatment, the pain subscale score in the treatment group was significantly decreased from baseline ($p<0.001$). After 4 weeks of treatment, the pain subscale score in the placebo group was significantly decreased from baseline ($p<0.006$).

Conclusion: Capsaicin patch at acupuncture point for pain relief in knee OA yielded no significant difference between groups. However, significant pain relief from baseline was observed in the treatment group after 2 weeks of treatment and in the placebo group after 4 weeks of treatment. Further study with higher capsaicin concentration and/or larger size patch should be considered.

Keywords: Capsaicin patch; acupuncture point; knee osteoarthritis (Siriraj Med J 2018;70: 382-390)

INTRODUCTION

Osteoarthritis (OA) is a major cause of pain and locomotor disability in the older population.[1] Knee OA is one of the most common forms of osteoarthritis and the most frequent chronic condition leading to functional limitation in older adults.[2] Prevalence of knee OA in an older Thai population with a mean age of 67.8 years was 34.5-45.6 percent.[3] Current treatment guidelines recommend that optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities. Surgical intervention is normally used in severe cases as the final treatment option.[4,5] However, oral pharmacologic management is often accompanied by gastrointestinal, cardiovascular, and/or renal side effects. Thus, the demand for safe and noninvasive therapies to treat the symptoms of OA is increasing.

Topical capsaicin is increasingly used in OA, because it reversibly desensitizes nociceptive C fibers by acting on VR-1 vanilloid receptors. Sound evidence has been

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reported regarding the efficacy of capsaicin in knee OA[6] and no systemic side effects were reported.[5] Multiple preparations of topical capsaicin (0.0125%, 0.025%, and 0.075%) were used in a 4-week, double-blind, randomized, placebo-controlled trial for treatment of painful joints from rheumatoid arthritis (RA) and osteoarthritis (OA).[6-8] In these studies, a local burning sensation was the only side effect noted, although none of the patients withdrew from any of these studies because of this side effect. These findings suggest that topical capsaicin is a safe and potentially useful drug for the treatment of painful OA.

Capsaicin patch was developed for ease of application and accuracy of drug dosage release. Several indications for capsaicin patch have been reported, including chronic lower back pain, reducing postoperative analgesic requirement after orthognathic surgery, prevention and reduction of postoperative nausea and vomiting after surgery, and treatment of notalgia paresthetica and post-herpetic neuralgia.[9-15] Previous studies applied capsaicin patch at acupuncture points to reduce postoperative analgesic requirement and to prevent postoperative nausea and vomiting after surgery.[10,11,13,15] However, the efficacy and point of application of capsaicin patch for pain relief in knee OA has not been reported. The objective of this study was to evaluate the efficacy of 0.0125% capsaicin patch at acupuncture points for pain relief in knee OA.

MATERIALS AND METHODS

Preparation of 0.0125% capsaicin patch

Capsaicin patches (0.0125% concentration) were produced by the Herbal Medicine and Products Manufacturing Unit at the Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, with manufacturing quality controlled according to standards of Good Manufacturing Practice and British Pharmacopoeia 2008. The patch has been made from polyacrylate-based products which allow the active substances in patch form (sustained release) to treat during normal activity of the human body. A single 0.0125% capsaicin patch contained 1 μg or 0.25 μg/cm^2 of capsaicin. Patches were stored at room temperature in a well-closed container and kept dry and clean.

Study design

This study was conducted at the outpatient rehabilitation clinic of Siriraj Hospital – Thailand's largest university-based tertiary referral center (Bangkok, Thailand). We equally allocated 62 patients between 2 study groups in a double-blind, randomized, placebo-controlled trial designed to compare the efficacy of 0.125% capsaicin patch vs. placebo patch for relief of pain in knee OA. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University (Si 204/2556). This trial was registered with the Thai Clinical Trials Registry (TCTR) (TCTR20141111001).

Participants

Eligible patients were recruited during the September 2014 to March 2015 study period from the Outpatient Unit, Department of Rehabilitation Medicine, Faculty of Medicine Siriraj Hospital using the following inclusion criteria:

1. Outpatients who attended the outpatient rehabilitation clinic that were diagnosed with knee OA according to American College of Rheumatology (ACR) clinical criteria for classification of idiopathic (primary) OA[16]; and
2. Ambulatory patients over 50 years of age; and
3. Pain score according to numerical rating scale (pain on weight bearing) of 4-7 out of 10; and
4. Willing to participate in this study.

Patients with one or more of the following were excluded:

1. History of hypersensitivity to capsaicin or related compounds, paracetamol, naproxen or NSAIDs;
2. Skin lesion at the affected (treated) knee;
3. History of acupuncture for knee pain relief within 1 month prior to screening;
4. History of lower extremity surgery within 6 months prior to screening;
5. Other rheumatological diseases potentially affecting knee joint, such as rheumatoid arthritis or gouty arthritis;
6. Disease of spine or other lower extremity joints that could affect walking ability;
7. Treatment with other drugs potentially affecting bone or cartilage metabolism, such as:
   - Chronic systemic corticosteroids;
   - Glucosamine or chondroitin sulphate treatment within the last 15 days;
   - Hyaluronan injection into the affected knee within the previous 6 months;
   - Diacerin treatment within the last 12 months.

Interventions

Sixty-two participants were randomly assigned to receive capsaicin or placebo patch. The first participant was randomized in September 2014 and the last participant assessment took place in March 2015.

Using the www.randomization.com website,

randomization was performed into blocks of 8 8 8 8 8 6 8 8 in a 1:1 ratio to receive capsaicin or placebo patch. Staff of the Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University provided capsaicin or placebo patches in opaque packages according to the generated randomization list. Study investigators, assessors, and participants were blinded to treatment assignment.

Participants in both groups received identical looking patches (2x2 centimeters in size) and instructions to apply 2 patches at 2 acupuncture points (one each) on the affected knee for at least 6 hours twice daily during the first week and once daily during the second to the fourth week.

A combination of two of the following six acupuncture points for knee OA were selected: ST34 (1), SP10 (2), ST35 (3), EX-LE4 (Neixiyan) (4), ST36 (5), and SP9 (6). The acupuncture point combinations were: 1 & 4, 2 & 3, 4 & 5, and 3 & 6, respectively – as shown in each patient's treatment diary (Fig 1).

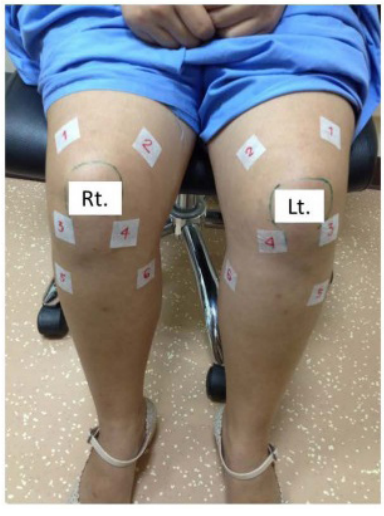

Fig 1. Locations of six acupuncture points in each knee.

All patients in both groups received basic education on knee OA and quadriceps exercise technique. Paracetamol 500 mg (Tylenol®; Johnson & Johnson, Ayutthaya, Thailand) every 4-6 hours or naproxen 250 mg (Berlin Pharmaceutical Industry Co., Ltd., Bangkok, Thailand) every 12 hours were allowed as a rescue medication, if necessary. Patients attended to their normal daily routines and were instructed not to seek, participate in, or take any other treatments (e.g., physical therapy, other pain relief medicines). Patients maintained a treatment diary that included the times patches were applied and removed, type and amount of medications used, and side effects, such as skin irritation and burning sensation.

Participants were seen in the clinic at baseline, 4 weeks, and 8 weeks after treatment for primary and secondary outcome evaluation, and interviewed via telephone at 2 weeks and 6 weeks after treatment for primary outcome evaluation.

Outcomes

The primary outcome was the pain subscale of modified Thai version of WOMAC osteoarthritis index for knee OA (measured on a 0- to 50-point scale, with higher scores indicating greater level of pain) at baseline, 2, 4, 6, and 8 weeks after treatment.[17,18]

Predefined secondary outcomes were modified Thai version of WOMAC osteoarthritis index for knee OA stiffness subscale (0-20), functional subscale (0-150), and total WOMAC score (0-220); visual analogue scale (VAS) for pain (0-10); Timed Up and Go test (seconds); participants' global assessment of improvement by asking participants to rate how much their knee pain had changed since using the patches (measured on a Likert scale from 1 [very much better] to 7 [very much worse]); participants' satisfaction of treatment (measured on a Likert scale from 1 [very satisfied] to 5 [very unsatisfied]); VAS for burning sensation (0-10); and, side effects from treatment.

Sample size

For the primary outcome of pain subscale of modified Thai version of WOMAC score, we initially estimated that 26 participants would be needed in each group to detect a difference of 3.42 between groups with a standard deviation (SD) of 4.3 (from previous study)[7], with a two-tailed α of 0.05 and a statistical power of 80% for comparison of 2 independent means. Based on a potential 20% withdrawal rate assumption, the final calculated sample size was 31 participants per group or a total sample of 62 participants.

Statistical Analysis

Data were reported using mean ± standard deviation (SD), median (min, max), or number. To compare quantitative data between 2 groups, independent t-test was used for normally distributed data and Mann-Whitney U test was employed to analyze for non-normally distributed data. Analysis of covariance (ANCOVA) was used to compare pain subscale of modified Thai version of WOMAC score between capsaicin and placebo groups. To compare quantitative data within group, repeated measures ANOVA was used with Bonferroni corrections for multiple comparisons. Chi-square test or Fisher's exact test was used to compare qualitative data between groups. For intention-to-treat (ITT) analysis, the last available score was carried forward. All statistical

analyses were performed using SSPS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A p-value<0.05 was considered to be statistically significant.

RESULTS

A total of 80 patients were screened for eligibility. Sixty-two patients met the eligibility criteria and were randomized between September 2014 and March 2015 (Fig 2). Baseline demographic and clinical characteristics were similar between groups (Table 1). Pain subscale of modified Thai version of WOMAC score between capsaicin and placebo groups at baseline and at each visit showed no significant difference between groups (Table 2). Pain subscale of modified Thai version of WOMAC score within group (pre-post treatment) at baseline and at each visit (weeks 2, 4, 6, and 8) in the capsaicin group showed pain subscale of modified Thai version of WOMAC was significantly decreased from baseline after 2 weeks of treatment (p<0.001 for all). In the placebo group, modified Thai version of WOMAC pain subscale was significantly decreased from baseline after 4 weeks of treatment (p=0.108, p=0.004, p=0.005, and p=0.004, respectively) (Table 3). Trend of pain subscale of modified Thai WOMAC score improvement from baseline to each follow-up visit in the capsaicin and placebo groups is shown in Fig 3.

Stiffness subscale, functional subscale, and total modified Thai version of WOMAC score at baseline and at each visit showed no significant differences between groups (Table 2). VAS for pain, Timed Up and Go test (seconds), participants' global assessment of improvement, and participant satisfaction with treatment at baseline and at each visit showed no significant differences between groups (Tables 4, 5).

A significant difference between groups was observed for burning sensation VAS at week 4 (p=0.029) (Table 5). Only one subject in the placebo group mention about burning sensation. This was probably because of the uncomfortably feeling from patch was miss-interpreted to burning sensation in the questionnaire in that particular patient.

Five out of 31 patients in each group described feeling uncomfortable wearing patches. Reported side effects included allergy, rash, itching, and ankle swelling (Table 6). None of the patients in either group withdrew as a result of any of these side effects.

The amounts of medication used to control knee pain over the 8-week course of patch treatment for paracetamol and naproxen was not significantly different between groups (p=0.227 and p=0.789 respectively) (Table 5).

Patient treatment compliance was recorded in each patient's treatment diary. Twenty-seven patients (87.1%) in the treatment group and 29 patients (93.5%) in the placebo group had good compliance (over 80% compliance), with no significant difference between groups (p=0.671).

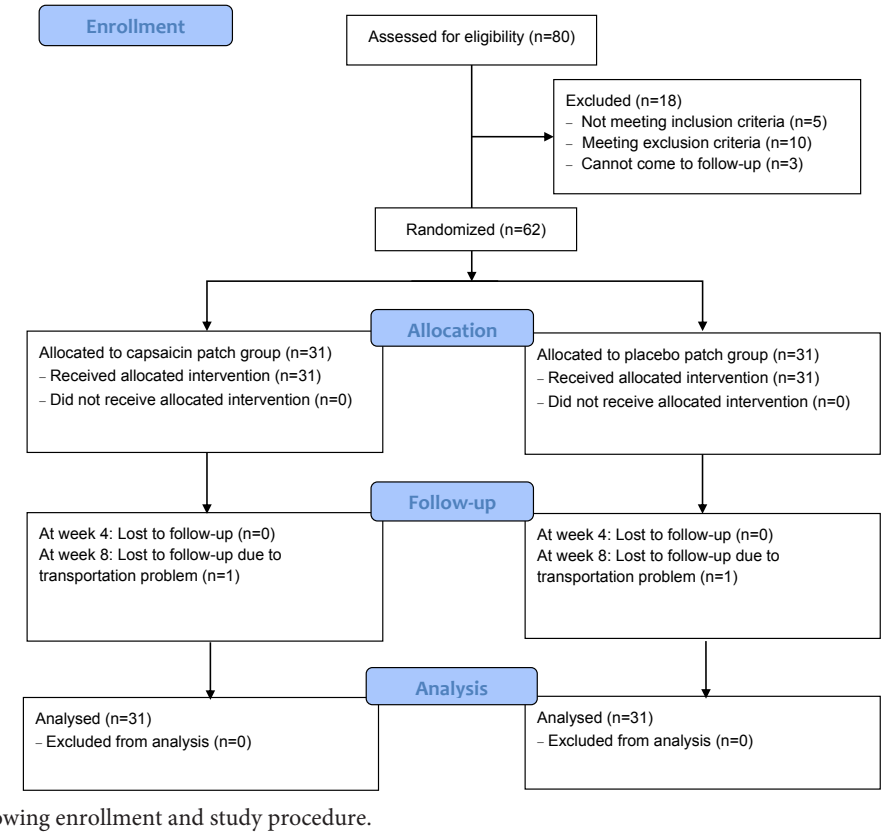

Fig 2. Flow diagram showing enrollment and study procedure.

TABLE 1. Clinical characteristics of study population at baseline.

	Treatment (n=31)	Placebo (n=31)	*p*-value
Age	63.3±8.9	62.8±6.3	0.767
Gender (female:male)	27:4	30:1	0.354
Body Mass Index	26.3±4.8	25.9±5.2	0.792
Affected knee (right:left)	18:13	14:17	0.309
Duration of pain (years)	3 (0.2, 10)	2 (0.2, 20)	0.876
WOMAC pain	22.0±9.7	20.7±7.9	0.556
WOMAC stiffness	8.5±5.2	8.9±4.2	0.727
WOMAC function	58.5±33.7	57.7±27.0	0.927
WOMAC total	89.0±46.5	87.4±36.4	0.880
VAS for pain	5.38±1.84	5.20±1.61	0.685
Timed Up and Go test	14.18±4.22	12.64±3.31	0.117

Data presented as mean±SD, median (min, max), or number

Abbreviations: WOMAC = Western Ontario and McMaster Osteoarthritis Index, VAS = visual analogue scale

TABLE 2. Comparison of WOMAC subscale and total scores between treatment and placebo groups at baseline and at each follow-up visit.

	Week	Treatment (n=31)	Placebo (n=31)	*p*-value
Pain subscale	0	22.0±9.7	20.7±7.9	0.556
	2	17.5±9.8	17.0±7.2	0.745
	4	15.0±10.8	14.9±7.2	0.630
	6	13.2±10.4	14.7±7.3	0.225
	8	13.5±11.1	14.4±8.5	0.432
Stiffness subscale	0	8.5±5.2	8.9±4.2	0.727
	4	5.2±4.6	5.6±3.7	0.691
	8	5.2±4.8	4.5±3.5	0.490
Functional subscale	0	58.5±33.7	57.7±27.0	0.927
	4	45.6±32.6	44.3±23.1	0.858
	8	43.2±35.2	44.9±28.5	0.837
Total WOMAC score	0	89.0±46.5	87.4±36.4	0.880
	4	65.7±46.0	64.8±30.5	0.923
	8	62.0±50.0	63.8±37.5	0.873

Abbreviation: WOMAC = Western Ontario and McMaster Osteoarthritis Index

TABLE 3. Comparison of pain subscale of modified Thai version of WOMAC score between baseline and each follow-up visit within group (pre-post treatment) for the capsaicin and placebo groups (repeated measures ANOVA).

Week	Treatment (n=31)	Placebo (n=31)
0 *vs.* 2	*p*<0.001	*p*=0.108
0 *vs.* 4	*p*<0.001	*p*=0.004
0 *vs.* 6	*p*<0.001	*p*=0.005
0 *vs.* 8	*p*<0.001	*p*=0.004

p-value <0.05 indicates statistical significance

TABLE 4. Comparison of pain VAS and Timed Up and Go test at baseline and at each follow-up visit between capsaicin and placebo groups.

	Week	Treatment (n=31)	Placebo (n=31)	*p*-value
Pain VAS	0	5.38±1.84	5.20±1.61	0.685
	4	3.57±2.09	3.9±2.05	0.526
	8	3.45±2.56	3.93±2.74	0.477
Timed Up and Go test	0	14.18±4.22	12.64±3.31	0.116
(seconds)	4	12.36±3.57	11.67±2.53	0.381
	8	12.56±4.28	10.93±2.00	0.062

Abbreviation: VAS = visual analogue scale

TABLE 5. Comparison of global change after treatment, patient satisfaction, burning sensation VAS and number of medication used (tab) between capsaicin and placebo groups.

		Treatment (n=31)	Placebo (n=31)	*p*-value
Global change after treatment	Week 4	2 (1, 5)	3 (1, 6)	0.246
	Week 8	2 (1, 4)	2 (1, 7)	0.341
Patient satisfaction	Week 4	2 (1, 3)	2 (1, 4)	0.994
	Week 8	2 (1, 4)	2 (1, 3)	0.943
Burning sensation VAS	Week 4	0 (0, 9.46)	0 (0, 6.88)	0.029
	Week 8	0 (0, 9.46)	0 (0, 0)	N/A
Amount of medications used	Paracetamol	0 (0, 62)	0 (0, 25)	0.227
	Naproxen	0 (0, 48)	0 (0, 15)	0.789

Data presented as median (min, max), *p*-value <0.05 indicates statistical significance

Abbreviations: N/A = not applicable, VAS = visual analogue scale

TABLE 6. Comparison of side effects between capsaicin and placebo groups (patients can have more than 1 side effect).

Side effect	Treatment (n=5)	Placebo (n=5)	*p*-value
Allergy	1	1	1.000
Rash	3	3	1.000
Itching	4	4	1.000
Other	0	1*	1.000

*Ankle swelling

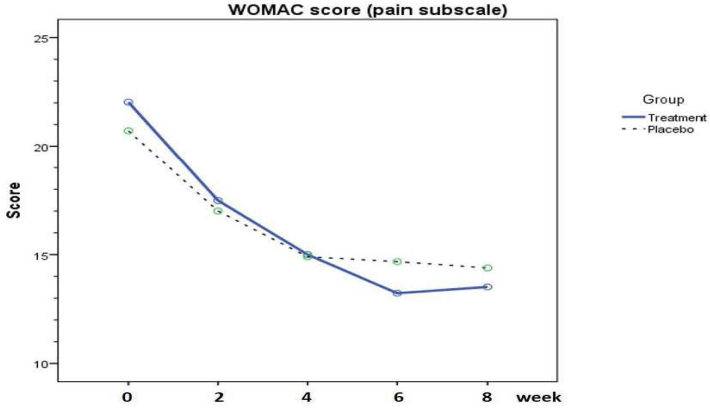

Fig 3. Pain subscale of modified Thai version of WOMAC score at baseline and at each visit in the capsaicin and placebo groups.

DISCUSSION

In this study and relative to the pain subscale of modified Thai version of WOMAC score, the treatment group showed early significant improvement after 2 weeks of treatment and the placebo group demonstrated significant improvement after 4 weeks of treatment. However and overall after 8 weeks of treatment, there was no significant difference in reduction of pain subscale of modified Thai version of WOMAC score between groups.

Possible explanations why there was no statistical difference in overall pain subscale of modified Thai version of WOMAC score between groups include: (1) insufficient concentration and volume of capsaicin; (2) acupuncture point effect; (3) effect of education and/or exercise; and, (4) placebo effect.

Based on our review of the literature specific to preparations of topical capsaicin and acupuncture point in knee OA, we decided upon using the lowest concentration of capsaicin preparation, which is 0.125%.[7] In addition, only 2 of 6 acupuncture points were used at each patch treatment (for a total of 4 different acupuncture point combinations) in order to avoid local side effect, as two local points may be sufficient to treat knee OA.[19] The concentration and volume of capsaicin used in this study may have been insufficient. As such, additional studies using a higher concentration of capsaicin and/or a larger size of the patch should be conducted.

Stimulation of acupuncture point with capsaicin or placebo patch may have acupuncture effect, which can reduce pain via gate control theory.[20] Additionally, placebo patch may replicate sham acupuncture, which may also have some therapeutic effects.[21] Education and exercise might also affect outcome of treatment. From the results, pain subscales were decreased in both groups, partially because quadriceps strengthening exercises were advised for every subject in this study. There is evidence that a 5-week isometric quadriceps exercise program showed beneficial effects on quadriceps muscle strength, reduction in pain intensity, and improvement in function in patients with osteoarthritis of the knee.[22] However, in this study, the decrement of pain subscale between both groups showed no statistically significant difference probably because the effect size of quadriceps exercise is over and above the effect of capsaicin patch alone.

From a systematic review of the effects of alternative placebo types on pain outcomes in knee OA, Bannuru, *et al.*

reported a 0.20 (95% CI: 0.02-0.38) effect size for topical placebo.[23] Administration of a placebo with higher efficacy will decrease the apparent effect size of the active treatment in a between-group comparison. Thus, the magnitude of the placebo effect can influence the results of a randomized controlled trial. Accordingly, there might have been a placebo effect relative to pain reduction in this study.

Study limitations

This study accomplished its research objective, but not without some mentionable limitations. First, the follow-up period was relatively short, although longer-term follow-up was not available. Second, rescue drugs for pain relief were authorized in all patients in both groups since all initial pain scores ranged from 4 to 7 out of 10 on visual analog scale, which we considered to be moderate pain. Third, although all patients were prescribed the same behavior modification and exercise regimens as co-interventions, data relating to frequency and intensity of exercise were not recorded by our patients. Finally, only patients with moderate knee pain were recruited for this study. Therefore, the findings of this study cannot be considered generalizable to patients with mild or severe knee pain.

CONCLUSION

Capsaicin patches (0.0125% concentration) at acupuncture points for pain relief in moderately painful OA knees yielded no significant difference in pain relief between groups. However, significant pain relief from baseline was observed in the treatment group after 2 weeks of treatment and in the placebo group after 4 weeks of treatment. Further study with higher capsaicin concentration and/or larger size patch should be considered.

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Conflict of interest declaration: The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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