Randomized Trial

Efficacy and Safety of 0.625% and 1.25% Capsaicin Patch in Peripheral Neuropathic Pain: Multi-Center, Randomized, and Semi-Double Blind Controlled Study

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Background: Topical capsaicin therapy may be of benefit in providing pain relief in patients with peripheral neuropathy.

Objectives: To investigate the efficacy and safety of 0.625% (50 μg/cm^2) and 1.25% (100 μg/cm^2) capsaicin patches (CPs) compared to conventional 0.075% capsaicin cream or placebo patches in patients suffering from peripheral neuropathy.

Study Design: Early Phase II, multi-center, randomized, semi-double-blind, and placebo-controlled clinical trial.

Setting: Two medical college teaching hospitals.

Methods: Sixty patients were randomized to the 0.625% CP, 1.25% CP, placebo-controlled patch, or 0.075% capsaicin cream. The primary efficacy endpoint was the mean difference in the change of daily numerical rating scale (NRS) pain score. Secondary endpoints included values for the Daily Sleep Interference Scale, the percentage of patients achieving a ≥ 30% or ≥ 50% reduction in pain, and data for Global Impression Change (GIC) and EQ-5D.

Results: Patients treated with the 0.625% CP and 0.075% capsaicin cream showed statistically significant improvements in pain after 6-weeks of test drug application. Daily sleep disorder scores were improved only for those patients applying the 0.075% capsaicin cream. For patient-derived GIC scores, the majority (11 of 12) of patients in the 0.625% CP group reported that their pain was improved. For the safety evaluation, 2 severe adverse events were reported for the 0.075% capsaicin cream group only. Repetitive patch application was related to minor skin problems such as a burning sensation, erythema, pruritus, and vesicles in 28 patients (46.67%).

Limitations: The small sample size and relatively high dropout rates.

Conclusion: Our data indicate that the 0.625% CP may prove to be an effective and safe alternative with which to treat patients with peripheral neuropathy and could replace the high concentration (8%) CP. Further studies are now needed to definitively establish efficacy.

Key words: Capsaicin, patch, CP, topical capsaicin, neuropathic pain, peripheral neuropathic pain, PNP, high concentration CP

Trial Registration: ClinicalTrials.gov, NCT02228928

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Peripheral neuropathic pain (PNP) is a sensory abnormality that arises as a consequence of a disease affecting the afferent neurons of the peripheral nervous system (1,2). It manifests several clinical characteristics including burning, electric shock-like pain, and stimulus-induced hypersensitivity such as allodynia and hyperalgesia (1,3). A myriad of diseases such as diabetic polyneuropathy (DPN), postherpetic neuralgia (PHN), or HIV-associated distal sensory polyneuropathy (HIV-DSP) can provoke PNP, which is considered a clinical entity (1).

Current treatments for neuropathic pain include oral antidepressants, anticonvulsants, and opioid analgesics (4) that can incur systemic side effects and often fail to achieve satisfactory pain relief (5). These limitations have prompted interest in nonsystematic therapies for PNP. For example, topical creams containing 0.025% or 0.075% capsaicin have been marketed for the management of a wide range of PNP conditions (6-10). Capsaicin, a highly selective agonist of the transient receptor potential vanilloid (TRPV) receptors, can reduce the quantity of neuropeptide released by nerve terminals (11). Despite its mode of action, a recent Cochrane review failed to make any recommendations concerning the use of 0.075% capsaicin cream for the treatment of PNP in clinical practice, with the authors basing their decision on a lack of data (12).

Uncertainties surrounding the efficacy of low-dose capsaicin cream prompted the development of a high concentration (8%) capsaicin patch (CP), licensed since 2009. Based on positive clinical trials, the European Union (EU) approved its use for PNP in nondiabetic patients, with the US Food and Drug Administration approving its use in the USA to treat PHN alone (13-18). However, patients treated with 8% CPs may experience a severe burning sensation during or after patch application (19). Hence, it has been recommended that patients receive pretreatment with a topical anesthetic such as lidocaine before patch application, or that the skin be cooled during patch application (20,21). Furthermore, treatment with the 8% CP should only be carried out under the supervision of a physician or a health care professional (22).

The discomfort associated with the application of the high dose CP has led to the development of lower-dose 0.625% and 1.25% CPs for PNP treatment, both of which exceed the concentration of capsaicin found in conventional cream (0.075%). To evaluate the efficacy and safety of these 0.625% and 1.25% CPs, we performed an early phase II, multi-center, randomized, semi-double-blind, and placebo-controlled clinical trial.

Methods

This study was approved by the Institutional Review Boards at 2 participating hospitals (Seoul National University Hospital and Seoul National University Bundang Hospital), and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participating patients prior to initiating study-related procedures. This study was a randomized, semi-double-blind, placebo-controlled, and early phase II clinical trial. Patient enrollment took place from February 2009 to April 2010.

Criteria for study inclusion were patients aged > 18 years of age, with chronic PNP related to a diagnosis of either PHN or DPN; patients with chronic PNP for > 3 months with an 11-point Numeric Rating Scale (NRS) pain score ≥ 4; and patients diagnosed with PHN with an interval of at least 3 months since shingles vesicle crusting. Further, patients with DPN and well-controlled diabetes were asked to maintain a stable dose of oral hypoglycemic or insulin for at least 35 days before study enrollment and during the study. Patients taking concomitant pain medications (anticonvulsants, antidepressants, anxiolytics, and opioids, including tramadol) were required to maintain a stable dose for at least 5 weeks before study enrollment and during the study period. Also, any conservative therapies such as TENS, physical therapy, chiropractic, massage, biofeedback, or yoga had to cease at least 5 weeks before enrollment and were not permitted during the study period. Women of childbearing age were required to have a negative pregnancy test within 14 days of study enrollment and were asked to agree to the use of an effective method of contraception for at least 28 days after the last exposure to study medication.

Exclusion criteria were as follows: significant pain of an etiology other than PHN or DNP; other severe medical or psychiatric conditions or laboratory abnormality that may increase the risk associated with study participation or, in the judgment of the investigator, would make the patient inappropriate to participate in the study; painful PHN areas located on the face or above the scalp hairline; an implanted medical device for the treatment of neuropathic pain; use of topically applied agents including capsaicin-containing products, a 5% lidocaine patch or similar products, local anesthetics or steroids within the past 14 days; a known hypersensitivity to capsaicin; the current use of any class 1 anti-arrhythmic drug; and uncontrolled diabetes mellitus or uncontrolled hypertension. Any use of

oral nonsteroidal anti-inflammatory drugs (NSAIDs) or a COX2 inhibitor had to cease at least 2 weeks before randomization (acetaminophen for pain control was permitted up to 4 g per day).

The study included a 7-day baseline screening period (Visit 1) followed by randomization (Visit 2), a 6-week treatment period with clinic visits at weeks 2 (Visit 3), 4 (Visit 4), and 6 (Visit 5), then a 4-week post-treatment assessment visit (Visit 6).

During the screening period, patients had to record a daily diary for their NRS pain score and sleep interference scale. We only enrolled participants who recorded their diary at least 4 days a week while having an average NRS pain score of ≥ 4, which was used as a baseline NRS pain score.

A 2-step randomization process occurred at Visit 2, using a random sampling number table. First, eligible patients were randomized to receive either a plaster application or 0.075% capsaicin cream (Diaxen, Republic of Korea) at a 3:1 ratio. The plaster application group was then blindly randomized into one of 3 groups, the 0.625% (50μg/cm^2) CP group, 1.25% (100 μg/cm^2) CP group, and the placebo-controlled patch group, at a ratio of 1:1:1. Patients in patch application groups were unaware as to which group they belonged to as all plasters were identical in size, shape, and color. Physicians and all related participants were blinded as to this group randomization. However, it was impossible to place patients into the capsaicin cream group blindly due to the differences in the formulation of the patch versus cream. Consequently, this study was semi-double-blinded.

Patients in all plaster groups were directed to apply one or more plasters to the lesion site according to lesion size for 3 days, and then leave a one-day interval (4-day cycle). In the capsaicin cream group, patients were instructed to apply 0.075% capsaicin cream to the painful area 3 or 4 times daily, rubbing the cream in until it had vanished. Hands were to be washed thoroughly immediately after the capsaicin cream application. Detailed training regarding study medication packaging, dispensing, administration, storage, and accountability were provided in a separate training module.

The primary efficacy end point was a mean difference in the change of daily NRS pain score, an 11-point scale ranging from 0 (no pain) to 10 (the worst pain possible) (23), scored from baseline (Visit 2) to week 6 (Visit 5) in each study group. The daily diary, comprising NRS pain scores and the Daily Sleep Interference Scale (DSIS) was to be completed every evening, from Visit 1 – 5, throughout the 6-week drug application period to assess average pain over the past 24 hours. After Visit 2, daily NRS pain scores were evaluated every 2 weeks at Visits 3, 4, and 5. At least 4 entries in the daily diaries were needed within the past 7 days to calculate a mean score.

Secondary efficacy end points included a comparison of NRS pain scores at Visit 5 among groups, the percentage of responders (30% reduction), and the percentage of patients achieving a ≥ 50% reduction in NRS pain score at Visit 5. Altered DSIS values over time in each group were also compared. DSIS, which measures the severity of sleep interference, was based on an 11-point scale from 0 (no interference of sleep) to 10 (complete interference, i.e., they didn't sleep at all the previous night), and was recorded every morning in the individual's daily diary (24).

A rating for Clinical Global Impression of Change (CGIC) was derived by a physician at Visit 5 together with a patient-reported Global Impression of Change (PGIC), to evaluate subjective perceptions of decreased pain intensity. (Table 1) The CGIC and PGIC are self-administered instruments that measure change in a patient's overall status on a scale ranging from 1 (very

Table 1 *Clinical global impression of change (CGIC) rated by physicians and patient global impression of change (PGIC) reported by patients, at Visit 5.*

		Capsaicin Cream (n = 13)	Capsaicin Patch		Placebo Patch (n = 12)
			50 μg/cm^2 (n = 12)	100 μg/cm^2 (n = 9)	
PGIC	1	1	0	0	0
	2	3	2	2	3
	3	5	9	4	4
	4	3	1	3	5
	5	1	0	0	0
	6	0	0	0	0
	7	0	0	0	0
CGIC	1	0	0	0	0
	2	4	2	2	3
	3	5	9	4	4
	4	3	1	3	5
	5	1	0	0	0
	6	0	0	0	0
	7	0	0	0	0

1 = Very much improved, 2 = Much improved, 3 = Minimally improved, 4 = No change, 5 = Minimally worse, 6 = Much worse, and 7 = Very much worse

much improved) to 7 (very much worse). The recall period was from the start of study medication (25).

At Visits 2 and 5, patients completed the EQ-5D Health Survey with EQ-5D Visual Analogue Scale (EQ-VAS) score. The EQ-5D Health Survey is a self-administered questionnaire designed to assess health-related quality of life (HRQOL) in terms of a single index value or utility score (26), and comprises 5 questions relating to the 5 dimensions of HRQOL: activity, self-care, daily life, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-point scale. Cross-cultural adaptation and validation of the Korean version of the EQ-5D was used in this study (27). Additionally, patients were asked to rate EQ-VAS in terms of their own health on a vertical 20 cm VAS, which was included with the EQ-5D (28). The scale ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The recall period of the EQ-5D was "right now."

Safety assessments during the 10-week study included adverse events (AEs), prevalence of side effects, vital signs, targeted neurologic sensory examination (light brush, pinprick, warmth, vibration, and allodynia), a physical examination including skin and subcutaneous tissue disorders, medication use for treatment-associated discomfort at each visit, and 12-lead centrally read electrocardiograms (ECGs) for Visit 1 alone. Clinical laboratory tests, including HbA1C, were performed at visits 1 and 5. Four weeks after the last application of patch or cream, patients in all groups were followed for the last time to evaluate their safety and tolerability (Visit 6). Until Visit 6, patients in all groups were informed not to apply any type of topical agents to their pain site. MedDRA (Medical Dictionary for Regulatory Activities) was used to code the AEs.

To evaluate the local effect of capsaicin plaster without systemic side effects, the blood concentration of capsaicin was analyzed. Venous blood samplings were taken from patients who had provided signed informed consent separately from the study. Blood was drawn 3 times from each patient. The first blood sample was taken just prior to the application of the test drug (Visit 2), with a second and third sample drawn one day and 2 weeks after test drug application, respectively. Blood samples were taken at the study hospitals then transported to an independent institute for analyses.

All data were collected, analyzed, and reviewed by an independent company and the academic author. Since this study was designed primarily as an exploratory study to test a preliminary hypotheses rather than a definitive efficacy study, statistical adjustments for multiple comparisons were not deemed necessary. Therefore, we decided to enroll 15 patients per group, as an early phase II study. Demographics were analyzed based on the intent-to-treat (ITT) population with Fisher's exact tests or t-tests. Efficacy analyses were performed on both the ITT population and the per-protocol (PP) population for the primary endpoint, and on the PP alone population for the secondary endpoints. The last observation carried forward (LOCF) method was used to handle missing values in the ITT population, with safety analyses based on the ITT population.

The efficacy and safety endpoints were analyzed with the paired t-test, with ANOVA, Chi-square test, Fisher's exact test, or McNemar test, as appropriate. These outcomes were reported as mean ± SD (min, max) or frequency (%). $P \leq 0.05$ was considered statistically significant for all analyses.

Results

Figure 1 shows the progression of patients in the study arms. A total 60 patients (30 from Seoul National University Hospital and 30 from Seoul National University Bundang Hospital) were randomized and received study medications at Visit 2. Ultimately, 46 patients were included in the PP group analysis. There were no statistically significant differences in terms of patient demographics (Table 2).

Table 3 shows the change in mean NRS pain scores. At baseline, these scores were similar for all study groups, indicating moderate pain. The mean reductions in NRS pain scores from Visits 2 to 5 represented a statistically significant fall for the 0.625% CP group and the 0.075% capsaicin cream group in ITT analyses. In contrast, there were no statistically significant reductions in pain scores for the 1.25% CP or placebo patch groups.

We identified more patient responders (≥ 30% pain reduction in NRS pain score at Visit 5) in the 0.075% capsaicin cream group (n = 6) than in either the 0.625% CP group (n = 3), the 1.25% CP group (n = 1), or the placebo patch group (n = 1), although these differences were not statistically significant ($P = 0.1369$). In addition, when comparing groups, there was no statistically significant difference in the number of patients achieving a ≥ 50% reduction in NRS pain score at Visit 5 (one in the 0.625% CP group, 0 in the 1.25% CP group, 0 in the placebo patch group, and 3 in the 0.075% capsaicin cream group; $P = 0.2261$).

Table 4 shows DSIS scores for Visits 2 – 5 in each group. A statistically significant improvement of sleep

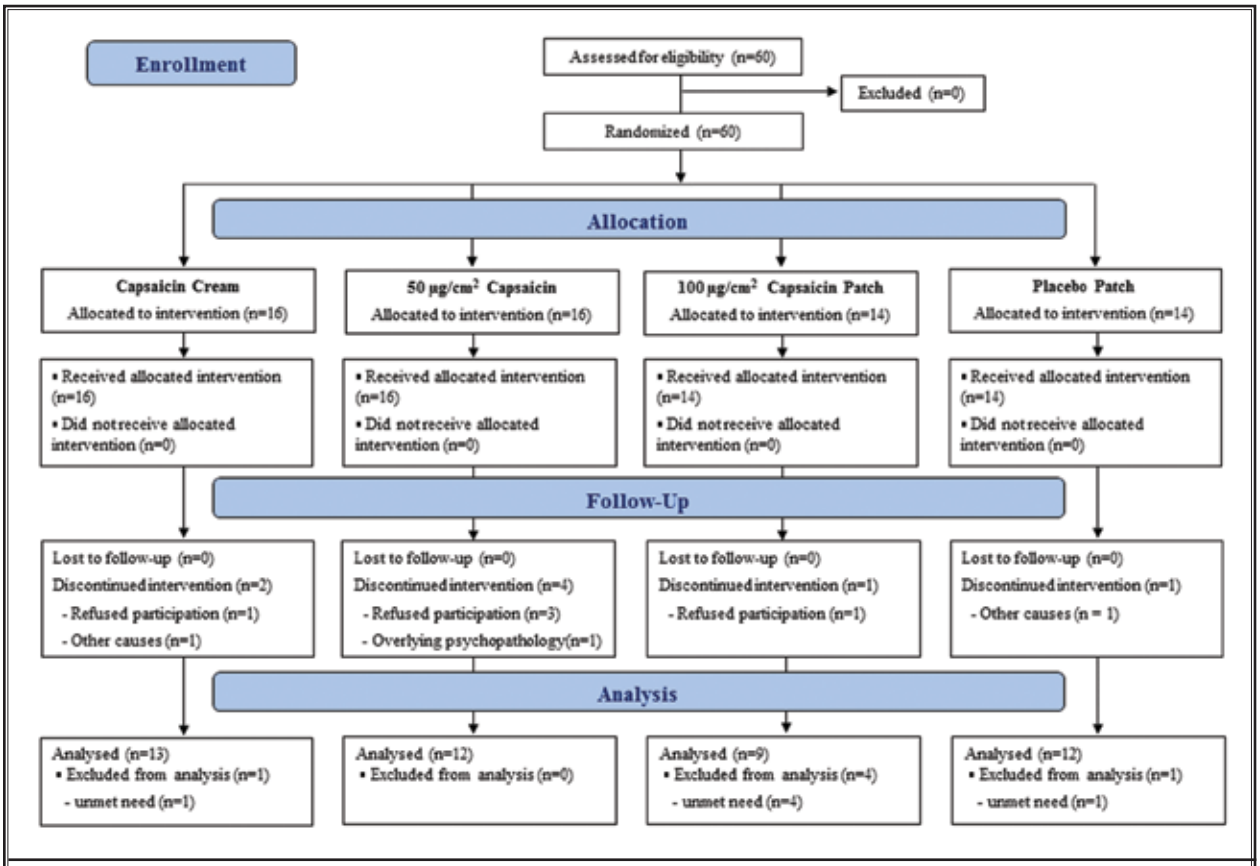

Fig. 1. *Enrollment*.

Table 2. *Baseline demographics and clinical features stratified by treatment group among patients randomized to one of the capsaicin patch groups or the capsaicin cream group.*

	Capsaicin Cream	Capsaicin Patch		Placebo Patch	Total	*P* value
	n = 16	50 µg/cm2 n = 16	100 µg/cm2 n = 14	n = 14	n = 60	
Age	71.1 ± 7.4 (58.0 – 83.0)	67.0 ± 8.2 (46.0 – 83.0)	70.0 ± 11.2 (50.0 – 86.0)	70.4 ± 5.4 (61.0 – 80.0)	69.6 ± 8.2 (46.0 – 86.0)	0.53
Gender						
Male	4 (25.0%)	7 (43.8%)	8 (57.1%)	9 (64.3%)	28 (46.7%)	0.14
Female	12 (75.0%)	9 (56.3%)	6 (42.9%)	5 (35.7%)	32 (53.3%)	
Height (cm)	156.1 ± 6.4 (144.7 – 168.0)	160.0 ± 7.8 (141.0 – 174.3)	160.6 ± 9.7 (144.0 – 176.2)	162.6 ± 7.8 (145.0 – 174.0)	159.7 8.1 (141.0 – 176.2)	0.17
Weight (kg)	60.3 ± 7.6 (42.2 – 71.2)	64.4 ± 9.6 (48.6 – 80.3)	60.3 ± 1.0 (41.9 – 76.0)	63.5 ± 9.9 (43.5 – 76.9)	62.1 ± 9.2 (41.9 – 80.3)	0.49
Duration of pain (mon)	23.5 ± 19.2 (3.1 – 60.0)	46.9 ± 36.5 (4.0 – 132.0)	42.9 ± 38.2 (6.9 – 108.0)	33.5 ± 24.2 (4.0 – 78. 0)	36.6 ± 31.2 (3.1 – 132.0)	0.15
Diagnosis						
DPN[a]	0 (0.0%)	2 (12.5%)	0 (0.0%)	3 (21.4%)	5 (8.3%)	0.09
PHN[b]	16 (100.0%)	14 (87.5%)	14 (100.0%)	11 (78.6%)	55 (91.7%)	

[a]DPN = diabetic polyneuropathy and [b]PHN = postherpetic neuralgia
Data indicate mean values ± SD (min, max) or frequency (%).

Table 3. *Changes in numerical rating scale pain score during the 6-week drug application.*

	Capsaicin Cream	Capsaicin Patch		Placebo Patch	*P*-value (ANOVA)
		50 µg/cm²	100 µg/cm²		
Visit 2 (baseline)	5.27 ± 1.18 (16) [4.00 – 8.00]	6.02 ± 1.31 (16) [4.29 – 8.71]	5.90 ± 1.64 (14) [4.00 – 10.00]	5.57 ± 1.24 (14) [4.00 – 8.71]	0.41
Visit 3	4.49 ± 1.49 (15) [2.47 – 7.86]	5.61 ± 1.44 (12) [2.31 – 8.00]	6.0 5 ± 1.56 (13) [4.31 – 9.77]	4.75 ± 1.67 (14) [1.71 – 8.36]	0.04
Visit 4	3.83 ± 1.44 (14) [1.19 – 6.71]	5.16 ± 1.47 (12) [2.07 – 8.00]	5.54 ± 1.62 (13) [3.60 – 9.14]	4.93 ± 1.62 (13) [2.07 – 8.08]	0.04
Visit 5	3.39 ± 1.47 (14) [0.92 – 5.87]	4.74 ± 1.46 (12) [2.00 – 8.00]	5.36 ± 1.63 (12) [3.29 – 9.07]	5.01 ± 1.72 (13) [2.14 – 8.00]	0.01
Visit 5 (LOCFa)	3.87 ± 1.93 (16) [0.92 – 8.15]	5.10 ± 1.92 (13) [2.00 – 9.50]	5.42 ± 1.54 (14) [3.29 – 9.07]	4.77 ± 1.87 (14) [1.71 – 8.00]	0.12
Difference [Visit 5–Visit 2]	-1.40 ± 1.19 (16) [-3.93 – 0.15]	-0.97 1.04 (13) [-2.57 – 0.79]	-0.48 0.93 (14) [-2.33 – 1.00]	-0.79 1.58 (14) [-4.09 – 2.12]	0.22
P-value (paired t-test)	0.0003	0.0056	0.0791	0.0824	

Data indicate mean values ± SD (n) and [min, max].
[a]LOCF = last observation carried forward

Table 4. *Changes in daily sleep interference scale from visits 2 (baseline) to 5.*

	Capsaicin Cream (n = 13)	Capsaicin Patch		Placebo Patch (n = 12)	*P*-value (ANOVA)
		50 µg/cm² (n = 12)	100 µg/cm² (n = 9)		
Visit 2 (baseline)	3.89 ± 2.15 [1.00 – 7.88]	3.48 ± 2.71 [0.00 – 7.43]	2.67 ± 2.12 [0.00 – 6.86]	2.80 ± 2.37 [0.00 – 8.00]	0.57
Visit 5	2.49 ± 1.92 [0.00 – 5.87]	2.80 ± 1.94 [0.00 – 5.79]	2.23 ± 1.57 [0.00 – 4.79]	3.64 ± 2.58 [0.00 – 8.00]	0.40
Difference [Visit 5 – Visit 2]	-1.40 ± 1.46 [-3.69 – 1.75]	-0.68 1.68 [-3.50 – 3.21]	-0.44 1.04 [-2.93 – 0.37]	0.84 1.46 [-0.88 – 3.55]	0.04
P-value (paired t-test)	0.0047	0.1864	0.2412	0.0695	

Data indicate mean values ± SD (n) and [min, max].

interference was found for the 0.075% capsaicin cream group alone (*P* = 0.0047).

PGIC data indicated that just under three-quarters of the patients (n = 33, 71.7%) perceived an improvement in their pain. Twenty-two (47.8%) reported minimal improvement, 10 (21.7%) were much improved, and one (2.2%) was very much improved. Notably, 11 of 12 patients (92%) in the 0.625% CP group responded with improved pain. "No change" was most commonly reported in the placebo patch group (n = 5, 41.7%); there were no statistically significant differences for PGIC between the 4 study groups (*P* = 0.5603). Physician-derived CGIC results were in line with those reported by patients (PGIC). Thirty-three patients (71.7%) were reported as "pain was improved," but again with no statistically significant differences (*P* = 0.7655).

In the EQ-5D survey, no statistically significant differences were found at baseline, or at Visit 6, when comparing the 4 groups in terms of their mobility, pain discomfort, or anxiety-depression. With respect to the EQ-5D VAS, scores were slightly increased indicating an improvement of their QOL across all study groups, but again with no statistically significant differences within or between groups.

During the 10-week study period, the proportion of patients with adverse drug reactions (ADRs) was 46.67% (n = 28), with 44 events. However, there were no serious adverse events (SAE). Mild to moderate AEs were caused by the capsaicin formulation being applied to skin. Two severe adverse events occurred in the 0.075% capsaicin cream group. One patient complained of severe constipation and the other reported paresthesia at the capsaicin application site. Subsequently the

patient reporting paresthesia discontinued cream application and withdrew from the study.

For the evaluation of validity of the capsaicin plaster, 63 analyses of the blood concentration of capsaicin were performed for 22 patients. From their first to third blood draws, no peak of capsaicin concentration was determined using chromatography.

Discussion

In the study we investigated the efficacy and safety of low concentration (0.625% and 1.25%) CPs compared to either conventional (0.075%) capsaicin cream or a placebo patch. In terms of the efficacy evaluation, patients using the 0.625% CP and 0.075% capsaicin cream showed statistically significant improvements in their pain after a 6-week application of the test drugs. For the safety evaluation, 2 severe AEs were reported for the 0.075% capsaicin cream group, with one patient (reporting paresthesia) discontinuing drug application then withdrawing from the study.

Capsaicin is a natural alkaloid that is extracted from red chili peppers (11). The continuous application of capsaicin can deplete a pain neurotransmitter, resulting in functional inactivation, which is suggested to be the principal mechanistic action of capsaicin in alleviating neuropathic pain (29). Capsaicin has long been available in various formulations as lotions or creams at low concentration (< 0.075%) capsaicin. However, its extremely short, 2-hour elimination half-life, requires several daily applications in order to achieve an optimal effect when using low-concentration capsaicin (30). Moreover, patients who use capsaicin cream should be advised not to use their bare hands, making it inconvenient to apply. A single application of a high-concentration 8% CP (640 µg/cm2) has been shown to be highly effective (14-17), although this patch failed to demonstrate drastic pain improvement compared with either placebo or a low concentration capsaicin patch in randomized double-blind controlled studies. Irving et al (16) reported that the proportion of patients who achieved a ≥ 50% decrease in pain score from baseline to weeks 2 – 8 was 29% for the high concentration CP group vs. 20% for the low concentration (0.04%) CP group (P = 0.04). Moreover, 96% of the recipients of the high concentration CP experienced at least one AE at their patch administration site (13). To remedy the inconvenience of low concentration capsaicin cream and a safety issue with the high concentration patch, a low-concentration CP could be an attractive alternative with which to manage neuropathic pain. In our study, the 0.625% CP showed clinical efficacy in treating patients with PNP, particularly PHN, unlike the 1.25% CP; both concentrations were safe and well tolerated compared to their high concentration counterpart.

Although the Cochrane review on the efficacy of < 1% capsaicin cream in the treatment of neuropathic pain concluded a lack of sufficient data with which to derive firm conclusions (12), the American Academy of Neurology's evidence-based guideline suggests 0.075% capsaicin cream as a (probably effective) option to treat DPN (31). On the other hand, the European Federation of Neurological Societies has not cited capsaicin cream as an effective treatment for DPN (32). In this study, the use of a 0.625% CP resulted in an improvement of PNP, particularly PHN, comparable to that achieved with the 0.075% capsaicin cream. Although almost all patients in the 0.625% CP group reported pain relief, even minimally, in PGIC reporting, patients with substantial levels of pain relief (≥ 50%) were rare (one and 3 for the 0.625% CP and 0.075% capsaicin cream groups, respectively). Our results suggest that low concentration capsaicin cream and patches can be recommended as an alternative treatment for PNP (Level B evidence) (31), although they may produce modest rather than dramatic pain relief.

The most significant unanswered question is why the 1.25% CP failed to provide any beneficial pain relief compared to either the 0.625% CP or the 0.075% capsaicin cream. We had assumed that the 1.25% CP and 0.075% capsaicin cream might be of similar effectiveness because of their comparable concentrations. However, the 0.625% CP proved to be a better comparator to the 0.075% capsaicin cream used in this study. Similarly, a previous study reported that a 0.025% capsaicin gel failed to provide any significant pain relief in patients with DPN (33), whereas the same preparation at a lower concentration (0.0125%) provided tangible pain relief in excess of that provided by the vehicle gel in patients with osteoarthritis (34). We would suggest that the statistical insignificance reported here may reflect the small sample sizes, both in total, and for the 1.25% CP group, which comprised 14 individuals instead of 16 in the 0.625% CP and 0.075% capsaicin cream groups. In addition, although there were no statistically significant differences in demographics between groups, a slightly higher ratio of individuals with a longer medical history was observed for the 1.25% CP group [over the 5 years: 50 µg/cm2 CP (n = 5, 31.25%), 100 µg/cm2 CP (n = 6, 42.86%), placebo patch (n = 2, 14.29%), and 0.075% capsaicin cream (n = 1, 6.25%)].

According to a previous article, the highest treatment response to the capsaicin 8% cutaneous patch was observed in patients with a history of pre-existing PNP of < 6 months duration, suggesting that early initiation of topical treatment might be indicated (35). Finally, the number of used patches (mean) in the 1.25% CP group was smaller than for other patch groups; poor patient compliance with these products is often cited as a likely contributor to limited efficacy (36).

As mentioned above, the major limitations of the present study include its small sample size and high dropout rates. The possibility of baseline differences in clinical and demographic variables tends to be minimized by large groups of patients, which are now needed to evaluate efficacy. Our present study, which corresponds to a smaller phase-I or early phase-II study, carries the risks inherent with a small sample size in terms of patient bias. The partial-blinding can be noted as another limitation of this study. To mitigate this effect, we could have included additional study groups such as a placebo cream group and a 0.075% patch group.

Conclusion

In conclusion, the result of this study indicates that the 0.625% CP may prove to be an effective and safe alternative with which to treat PNP patients. While these preliminary data are encouraging, further studies are now warranted to firmly establish efficacy.

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References

1. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010; 9:807-819.
2. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology 2008; 70:1630-1635.
3. Arning K, Baron R. Evaluation of symptom heterogeneity in neuropathic pain using assessments of sensory functions. *Neurotherapeutics* 2009; 6:738-748.
4. Park HJ, Moon DE. Pharmacologic management of chronic pain. *Korean J Pain* 2010; 23:99-108.
5. Harden N, Cohen M. Unmet needs in the management of neuropathic pain. *J Pain Symptom Manage* 2003; 25:S12-S17.
6. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol* 1989; 21:265-270.
7. Biesbroeck R, Bril V, Hollander P, Kabadi U, Schwartz S, Singh SP, Ward WK, Bernstein JE. A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. *Adv Ther* 1995; 12:111-120.
8. Ellison N, Loprinzi CL, Kugler J, Hatfield AK, Miser A, Sloan JA, Wender DB, Rowland KM, Molina R, Cascino TL, Vukov AM, Dhaliwal HS, Ghosh C. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncol1997*; 15:2974-2980.
9. Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther* 1993; 15:510-526.
10. Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. *Pain* 1995; 62:163-168.
11. 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; 107:490-502.
12. Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2012; 9:CD010111.
13. Baranidharan G, Das S, Bhaskar A. A review of the high-concentration CP and experience in its use in the management of neuropathic pain. *Ther Adv Neurol Disord* 2013; 6:287-297.
14. Backonja MM, Malan TP, Vanhove GF, Tobias JK; C102/106 Study Group. NGX-4010, a high-concentration CP, for the treatment of postherpetic neuralgia: A randomized, double-blind, controlled study with an open-label extension. *Pain Med* 2010; 11:600-608.
15. Clifford DB, Simpson DM, Brown S, Moyle G, Brew BJ, Conway B, Tobias JK, Vanhove GF; NGX-4010 C119 Study Group. A randomized, double-blind, controlled study of NGX-4010, a capsaicin 8% dermal patch, for the treatment of painful HIV-associated distal sensory polyneuropathy. *J Acquir Immune Defic Syndr* 2012; 59:126-133.
16. Irving GA, Backonja MM, Dunteman E, Blonsky ER, Vanhove GF, Lu SP, Tobias J; NGX-4010 C117 Study Group. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration CP, for the treatment of postherpetic neuralgia. *Pain Med* 2011; 12:99-109.
17. Webster LR, Tark M, Rauck R, Tobias JK, Vanhove GF. Effect of duration of postherpetic neuralgia on efficacy analyses in a multicenter, randomized, controlled study of NGX-4010, an 8% CP evaluated for the treatment of postherpetic neuralgia. *BMC Neurol* 2010; 10:92.
18. Webster LR, Malan TP, Tuchman MM, Mollen MD, Tobias JK, Vanhove GF. A multicenter, randomized, double-blind,

controlled dose finding study of NGX-4010, a high-concentration CP, for the treatment of postherpetic neuralgia. *J Pain* 2010; 11:972-982.

19. Wallace M, Pappagallo M. Qutenza®: A capsaicin 8% patch for the management of postherpetic neuralgia. *Expert Rev Neurother* 2011; 11:15-27.
20. Knolle E, Zadrazil M, Kovacs GG, Medwed S, Scharbert G, Schemper M. Comparison of cooling and EMLA to reduce the burning pain during capsaicin 8% patch application: A randomized, double-blind, placebo-controlled study. *Pain* 2013; 154:2729-2736.
21. Höper J, Helfert S, Heskamp ML, Maihöfner CG, Baron R. High concentration capsaicin for treatment of peripheral neuropathic pain: Effect on somatosensory symptoms and identification of treatment responders. *Curr Med Res Opin* 2014; 30:565-574.
22. Kern KU, England J, Roth-Daniek A, Wagner T. Is physician supervision of the capsaicin 8% patch administration procedure really necessary? An opinion from health care professionals. *J Pain Res* 2013; 6:571-575.
23. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149-158.
24. Vernon MK, Brandenburg NA, Alvir JM, Griesing T, Revicki DA. Reliability, validity, and responsiveness of the daily sleep interference scale among diabetic peripheral neuropathy and postherpetic neuralgia patients. *J Pain Symptom Manage* 2008; 36:54-68.
25. Busner J, Targum SD. The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007; 4:28-37.
26. EuroQol Group. EuroQol: A new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16:199-208.
27. Kim MH, Cho YS, Uhm WS, Kim S, Bae SC. Cross-cultural adaptation and validation of the Korean version of the EQ-5D in patients with rheumatic diseases. *Qual Life Res* 2005; 14:1401-1406.
28. Brooks R. EuroQol: The current state of play. *Health Policy* 1996; 37:53-72.
29. Cortright DN, Szallasi A. Biochemical pharmacology of the vanilloid receptor TRPV1. An update. *Eur J Biochem* 2004; 271:1814-1819.
30. Babbar S, Marier JF, Mouksassi MS, Beliveau M, Vanhove GF, Chanda S, Bley K. Pharmacokinetic analysis of capsaicin after topical administration of a high-concentration CP to patients with peripheral neuropathic pain. *Ther Drug Monit* 2009; 31:502-510.
31. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: Treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011; 76:1758-1765.
32. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T; European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17:1113-1123 (e67-e88).
33. 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; 13:497-503.
34. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. *J Med Assoc Thai* 2010; 93:1188-1195.
35. Maihöfner CG, Heskamp ML. Treatment of peripheral neuropathic pain by topical capsaicin: Impact of pre-existing pain in the QUEPP-study. *Eur J Pain* 2014; 18:671-679.
36. 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; 107:490-502.