Observational Study

Capsaicin 8% for Peripheral Neuropathic Pain Treatment: A Retrospective Cohort Study

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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 06-26-2021
Revised manuscript received: 12-23-2021
Accepted for publication: 02-04-2022

Free full manuscript: www.painphysicianjournal.com

Background: Chronic neuropathic pain is a disabling condition that affects quality of life. Despite recommendations and guidelines, treatment remains suboptimal as it often does not result in significant symptom relief. Capsaicin 8% patch has been used for the treatment of several peripheral neuropathic pain etiologies with encouraging results.

Objectives: To assess the results of capsaicin 8% patch on neuropathic pain by evaluating pain intensity and the painful treatment area.

Study Design: Observational retrospective cohort study.

Setting: All patients submitted to capsaicin treatment at the Chronic Pain Unit of the Hospital Centre of Tondela Viseu, from 2011 through 2019.

Methods: Records of capsaicin treatments were reviewed, and the data collected. The primary outcome was pain intensity and painful treatment area reduction between the first and last treatment. Also, the number of treatments performed, neuropathic pain duration, anatomic location, pain etiology, and concomitant oral pain medication at baseline and upon treatment conclusion was also listed.

Results: Postsurgical neuropathic pain was the most common etiology (49%), followed by postherpetic (28%). The median (interquartile range [IQR]) baseline pain intensity assessed by the Numeric Rating Scale (NRS-11) was 6 (5-8) and the median (IQR) final NRS-11 was 3 (1-5), with a median (IQR) relative difference of -0.5 (-0.85-0.17) with statistically significant differences ($P < 0.001$) between baseline and last pain intensity, regarding all groups. Also, there was a reduction in the painful treatment area between baseline and the last evaluation, with a median (IQR) relative difference of -0.4 (-0.625-0.167).

Limitations: A relatively small sample and occasional different timing for pain intensity and pain treatment area assessment due to logistical difficulties.

Conclusions: Capsaicin 8% patch is a valuable option for the treatment of peripheral neuropathic pain, providing a significant reduction in pain intensity and painful area. It is well tolerated and has a high treatment compliance.

Ethics Committee Reference Number: 16/16//04/2021

Key words: Capsaicin, chronic pain, neuralgia, neuropathic pain, topical administration

Pain Physician 2022: 25:E641-E647

The newly developed International Classification of Diseases 11th Revision defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" (1).

The prevalence of chronic pain with neuropathic descriptors in the general population has been estimated to be between 6.9% to 10% (1), with significant effects on quality of life.

Neuropathic pain can have a central or a peripheral origin. Peripheral neuropathic pain involves a lesion or disease of the peripheral somatosensory nervous system. Common causes include posttraumatic nerve injuries, postsurgical, as well as postherpetic neuralgia.

It is generally estimated that about 60% of neuropathic pain conditions are identifiable as localized neuropathic pain (LNP), defined as "a type of neuropathic pain characterized by consistent and circumscribed area(s) of maximum pain associated with negative or positive sensory signs and/or spontaneous symptoms characteristic of neuropathic pain" (2).

According to the 2015 Special Interest Group on Neuropathic Pain recommendations (3), first-line treatments include tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors and calcium channel α2-δ ligands. However, these drugs have significant side effects that often hinder their tolerability. Topical treatments, such as the capsaicin 8% patch, have proved their value to treat several etiologies of localized neuropathic pain, such as HIV-induced neuropathy and postherpetic neuropathy (4,5). In fact, a recent review recommended topical patches as a first line treatment for LNP (6). Moreover, topical capsaicin is approved by the US Food and Drug Administration for the treatment of neuropathic pain associated with postherpetic neuralgia and for the treatment of neuropathic pain associated with diabetic peripheral neuropathy.

Capsaicin is a potent and selective agonist of the TrpV1 channel, a transmembrane receptor–ion channel complex that is preferentially expressed on nociceptive nerve fibers. By binding to these receptors, capsaicin causes an initial burning and warming sensation that subsides with continued exposure and evolves to desensitization and degeneration of the nociceptors (7). Its topical application is usually well tolerated, with most adverse reactions referred to the area of patch application and is a valuable alternative to systemic medication.

In our Pain Unit, capsaicin 8% patch has been used since 2009 for peripheral neuropathic pain. This retrospective study aimed to assess the results of capsaicin 8% patch on LNP by evaluating pain intensity and painful treatment area (PTA).

Methods

An observational retrospective cohort study was performed at the Chronic Pain Unit of the Tondela Viseu Hospital Center. The study was approved by the hospital Ethics Committee. We included 100 adult patients with peripheral neuropathic pain who were administered at least one capsaicin 8% patch treatment, from 2011 through 2019. Patients' consent for the treatment was previously obtained.

Data Collection

Records were reviewed, and the following data collected: age, gender, neuropathic pain duration, anatomic location, and pain etiology (postherpetic, posttraumatic, postsurgical or others). The total number of capsaicin treatments and concomitant oral pain medication at baseline and upon treatment conclusion was also listed.

Pain intensity was measured at baseline, at 48 hours, and 1-3 months after each capsaicin 8% patch application, during a visit to the pain clinic or upon telephone contact. Subsequent treatments were scheduled after 12 weeks if a significant increase in pain intensity was referred during the follow-up period. Pain intensity and dynamic allodynia were graded according to the Numeric Rating Scale (NRS-11). The PTA was identified through mechanical allodynia, quantified (in cm^2) and recorded at baseline and after the last treatment.

Data Analysis

Parametric data are presented as mean and standard deviation (SD) and independent samples t test, one-way analysis of variance with Bonferroni correction or Pearson χ^2 were performed as appropriate. Nonparametric data are presented as median and interquartile range (IQR), and tested using the Mann-Whitney U test, Kruskal-Wallis test or Fisher's exact test. The normal distribution of the variables was assessed using the Kolmogorov-Smirnov test with Lilliefors Significance Correction or the Shapiro-Wilk test. Equality of variances was assessed using Levene's test. Significance was assumed as a P value < 0.05. Statistical analysis was performed using IBM SPSS Statistics Version 22 and Excel 2013 (Microsoft).

Results

From the 100 patients included, 66% were women, the mean (SD) age was 63 (13) years, with a median (IQR) duration of neuropathic pain of 2 (0.79-3.25) years (Table 1). Four patients died during the follow-up period due to other morbidities, and one patient missed the treatment appointment. The thorax was the most common painful anatomical location (38%).

Postsurgical neuropathic pain was the most common etiology (49%), followed by postherpetic (28%), post-

traumatic (14%) and other causes (9%). These included neuropathic pain secondary to chemotherapy and radiotherapy, neuropathic pain due to pressure ulcer, idiopathic neuropathy, and one case of diabetic polyneuropathy.

Anticonvulsants (68%) and opioids (56%) were the most common pharmacological classes. Sixty-five percent of patients were on 2 or more classes of oral pain medication, and 11% (n = 11) of patients took no medication. The most common prescriptions were anticonvulsants alone (n = 20), followed by the combined use of anticonvulsants and opioids (n = 18) and by no use of medication (n = 11). After the last capsaicin treatment, most patients maintained (n = 41) or reduced (n = 33) oral pain medication. At this point, the most common prescriptions were still anticonvulsants alone (n = 23), followed by anticonvulsants plus opioids (n = 17) and no medication (n = 16).

The median (IQR) number of treatments was 2 (1-5) without statistically significant differences between etiologies, with a maximum of 12 treatments per patient.

The median (IQR) baseline NRS-11 was 6 (5-8); there were no statistically significant differences between etiologies. The median (IQR) final NRS-11 was 3 (1-5). There was an absolute difference of -3 (-5 - -1), and a median (IQR) relative difference of - 0.5 (-0.85-0.17) with statistically significant differences ($P < 0.001$) between baseline and last pain intensity, regarding all groups. In the posttraumatic and postherpetic pain etiologies, there was a relative difference of -0.5 between baseline and last NRS-11 intensity, whereas in the postsurgical etiology there was a relative difference of -0.43 (-1; -0.2). The group "Others" presented a relative difference of -0.16 (-0.9; 0) between the first and last NRS-11 evaluations.

Table 1. *Demographics and clinical characteristics.*

	Total	Posttraumatic (PT)		Postsurgical (PS)		Postherpetic (PH)		Others (O)		*P* value
Demographics										
Gender, n (%)										0.75[a]
Men	34 (34)	3	(21.4)	17	(34.7)	11	(39.3)	3	(33.3)	
Women	66 (66)	11	(78.6)	32	(65.3)	17	(60.7)	6	(66.7)	
Age (years), mean(SD)	63,2 (13,4)	55,7	(12.3)	58,2	(13.2)	73	(7.3)	71,6	(10.1)	< 0.001[b]
Clinical characteristics										
Duration of NP (years) - median (IQR)	2 (0.8-3.3)	3	(1.5-3.5)	2	(1-4)	0.8	(0.5-1)	2	(1.1-4.5)	< 0.01[c]
Anatomical location - n (%)										< 0,001[a]
Abdominal	4 (4)	0	(0)	4	(8.2)	0	(0)	0	(0)	
Thorax	38 (38)	1	(7.1)	17	(34.7)	19	(67.9)	1	(11.1)	
Upper limb	13 (13)	4	(28.6)	7	(14.3)	1	(3.6)	1	(11.1)	
Lower limb	31 (31)	9	(64.3)	12	(24.5)	3	(10.7)	7	(77.8)	
Groin	4 (4)	0	(0)	3	(6.1)	1	(3.6)	0	(0)	
Other	10 (10)	0	(0)	6	(12.2)	4	(14.2)	0	(0)	
Baseline oral pain medication, n (%)										
Anticonvulsants	68(68)	5	(7.5)	35	(51.5)	21	(30.9)	7	(10.3)	0.48[d]
Antidepressants	29(29)	4	(13.8)	21	(72.4)	3	(10.3)	1	(3.45)	0.02[a]
Opioids	56(56)	7	(12.5)	32	(57.1)	12	(21.4)	5	(8.93)	0.38[a]
Others[e]	32(32)	5	(15.6)	20	(62.5)	5	(15.6)	2	(6.25)	0.16[a]

Abbreviations: n = total number; % = percentage; SD = standard deviation; IQR = interquartile range; NP = neuropathic pain.

[a] Fisher's exact test;

[b] One-way ANOVA test (t test comparisons - O vs PS $P = 0.01$; O vs PT $P = 0.01$; O vs PH P = 1.00; PS vs PH $P < 0.001$; PS vs PT $P = 1$; PH vs PT $P < 0.001$);

[c] Kruskal-Wallis test (Mann-Whitney U test for comparisons - O vs PS $P = 0.96$; O vs PH $P = 0.05$; O vs PT $P = 0.74$; PC vs PH $P < 0.01$; PS vs PT $P = 0.56$; PH vs PT $P = 0.01$);

[d] χ^2test.

[e] Lidocaine patch 5%, acetaminophen + thiocolchicoside,{this drug is not US-FDA approved} acetaminophen + codeine, acetaminophen + tramadol, ibuprofen, dipyrone, etoricoxib, celecoxib, cyclobenzaprine

Sixty-nine percent of patients had a greater than 30% reduction in pain intensity between baseline and after the last treatment. Of those, 26% achieved near-complete pain relief, with a pain intensity ≤ 1 at the last NRS-11 assessment.

The median (IQR) baseline allodynia was 6.5 (5-8) and after the last treatment was 2.5 (0-6). There were no differences between etiologic groups. There was a statistically significant reduction in allodynia between baseline and the last measure in the postherpetic and postsurgical groups.

Median (IQR) baseline PTA was 266 (99-280) cm^2 in the posttraumatic group, 240 (140-385) cm^2 in the postherpetic group, 150 (53-280) cm^2 in other causes, and 83 (47-210) cm^2 in the postsurgical group.

In general, a reduction in the PTA between baseline and the last evaluation was seen, with a median (IQR) absolute difference of -29.5 (-168-14), and a median (IQR) relative difference of -0.4 (-0.625-0.167) (Table 2).

There was a statistically significant difference between the first and last treatment areas in the postherpetic group ($P < 0.01$), with a relative difference of -0.5 (-0.8-0.1). In the posttraumatic group, there was a median IQR) relative difference of -0.5 (-0.8-0.1) between PTA baseline and final evaluation. In the postsurgical group, the relative difference was of -0.16 (-0.6-0.3) and in the group "Others" there was a relative difference of -0.43 (-0.7-0.2).

Discussion

Our results evidenced significant reductions in both pain intensity and PTA, even in neuropathic pain etiologies where capsaicin patch use is not so well established, such as posttraumatic and postsurgical neuropathic pain (4,8). However, we do acknowledge the relatively small sample for some of the etiologies. Treatments were very well tolerated, without major adverse effects encountered, which led to a high compliance rate.

In our unit, analgesia for a capsaicin treatment session was initially achieved using oral medication, mostly acetaminophen or nonsteroidal anti-inflammatory drugs, with tramadol rarely needed. However, since the beginning of 2019, we started to perform skin cooling with ice pads placed over the area of patch application during the treatment, which we found to improve tolerance and reduce the capsaicin burning sensation. Since then, rescue analgesia was very rarely needed.

According to the most recent recommendations issued by the Special Interest Group on Neuropathic Pain (NeuPSIG) (3) previously mentioned, capsaicin is referred as a second line therapy for peripheral neuropathic pain. However, it is also stated that topical treatments can be considered as first line in some specific cases, particularly in elderly patients. In fact, first line systemic medications have several adverse effects and interactions that can hamper patients' compliance and treatment tolerability. Moreover, several expert consensus statements have recommended topical treatment with capsaicin or lidocaine patches as first line for LNP (5,7,9,10).

Postsurgical pain is one of the most common causes of neuropathic pain (11) and will continue to rise as the number of surgeries performed increases. Although there seems to be a decrease in nociceptive postsurgical pain over time, the neuropathic component appears to increase and persist (11). The surgical procedures most likely to cause chronic postsurgical neuropathic pain are breast surgery and thoracic surgery (11). This is in accordance with our data since postsurgical etiology was the most common (49%), mainly after thoracic and orthopedic surgeries, while postherpetic neuropathic pain represented only 28%. This also explains most common pain locations being the thorax and inferior limb.

In a review by Derry et al (4), evidence of moderate improvement was found in postherpetic neuralgia, HIV neuropathy, and peripheral diabetic neuropathy after topical capsaicin treatment. At the time of that review, only one study was included regarding postsurgical pain (8), which made it impossible to draw conclusions concerning this etiology. Few studies have been made regarding capsaicin for postsurgical pain since then (12-14). However, Bischoff et al (8) did not find a significant difference in pain relief between placebo and capsaicin patch in patients with severe, persistent inguinal postherniorrhaphy pain, but we found a significant decrease in pain intensity of 43% in the postsurgical group (Table 2). These results were in line with other case reports where a significant reduction in pain intensity was achieved (13,15).

Posttraumatic etiology includes causes such as cuts, strains, dislocations, and burns. This neuropathic pain etiology has not yet been clearly evaluated in clinical studies regarding treatment with capsaicin (3). Nevertheless, this group revealed a 50% reduction in pain intensity from baseline to last treatment, alongside a 50% reduction in the PTA.

Capsaicin 8% patch treatment for postherpetic neuralgia has been found to be effective (4,16). Pain reduction, as well as allodynia and PTA reduction,

Table 2. *Treatment results*.

	Total	n	Posttraumatic (PT)	n	Postsurgical (PS)	n	Postherpetic (PH)	n	Others (O)	n	*P* value
NRS-11, median (IQR)											
Baseline	6(5-8)	97	7.5 (5-8)	14	6 (5-7)	47	5 (5-7)	27	5 (4-7.5)	9	0.50[b]
Last	3 (1-5)	94	4 (3-4.8)	12	3 (0-5)	48	3 (1.8-4)	26	5 (0.5-7)	8	0.30[b]
Absolute difference	-3 (-5- -1)	92	-3 (-4.8 - -1)	12	-3 (-5 - -1)	47	-3 (-4 - -1.5)	25	-1 (-2-0)	8	0.35[b]
Relative difference	-0.5 (-0.9 - -0,2)	92	-0,5 (-0.6 - -0,2)	12	-0.43 (-1 - -0.2)	47	-0.5 (-0.7 - -0.3)	25	-0.16 (-0.9-0)	8	0.54[b]
P value for baseline vs last measurement a	< 0.001		< 0.01		< 0.001		< 0.001		0.17		
Allodynia, median (IQR)											
Baseline	6.5 (5-8)	62	6.5 (5-8)	12	6 (5-8)	29	7 (5-8)	18	7 (6.5-7.5)	3	0.93[b]
Last	2.5 (0-6)	46	6 (4-8)	7	0 (0-6)	23	2.5 (0-5.3)	14	4.5 (0-9.5)	2	0.06[b]
Absolute difference	-2.5 (-6.3-0)	34	0 (-1-1)	7	-4 (-8- -0.8)	14	-4 (-6.8- -0.5)	12	-	0	0.03[c]
Relative difference	-0.42 (-1-0)	34	0 (-0.2-0.1)	7	-0,66 (-1- -0.1)	14	-0.54 (-1- -0,1)	12	-	0	0.03[d]
P value for baseline vs last measurement a	< 0.001		0.66		< 0.01		< 0.01		-		
TA (cm^2), median (P25;75)											
Baseline	150 (62-280)	100	266 (99-280)	14	83 (47-210)	49	240 (140-385)	28	150 (53-280)	9	<0.01[e]
Last	115 (55-184)	63	140 (63-178)	9	70 (32-157)	29	140 (103-245)	21	32 (17-146)	4	0.05[b]
Absolute difference	-29.5 (-168-14)	63	-140 (-214-12.5)	9	-7 (-70-23)	29	-120 (-285-12)	21	-59.5 (-67- -12)	4	0.10[b]
Relative difference	-0.4 (-0.6-0.2)	63	-0.5 (-0.8-0.1)	9	-0.16 (-0.6-0.3)	29	-0.5 (-0.8-0.1)	21	-0.43 (-0.7-0.2)	4	0.34[b]
P value for baseline vs last measurement a	< 0.001		0.05		0.3		< 0.01		0.14		
Number of treatments, median (IQR)	2 (1-5)	100	2.5 (1-8.5)	14	2 (1-3)	49	3 (15)	28	1 (1-3)	9	0.27[b]

Abbreviations: n = total number of observations; % = percentage; SD = standard deviation; IQR = interquartile range; NRS-11 = numeric rating scale; TA = treatment area.

[a] Wilcoxon signed-rank test between baseline and last measurements;

[b] Kruskal-Wallis test;

[c] Kruskal-Wallis test (Mann-Whitney U test for comparisons - O vs PS $P = 0.35$; O vs PH $P = 0.23$; O vs PT $P = 0.11$; PS vs PH $P = 0.8$; PS vs PT $P = 0.01$; PH vs PT $P = 0.02$);

[d] Kruskal-Wallis test (Mann-Whitney U test for comparisons - O vs PS $P = 0.28$; O vs PH $P = 0.32$; O vs PT $P = 0.12$; PS vs PH $P = 0.98$; PS vs PT $P = 0.01$; PH vs PT $P = 0.02$);

[e] Kruskal-Wallis test (Mann-Whitney U test for comparisons - O vs PS $P = 0.39$; O vs PH $P = 0.17$; O vs PT $P = 0.54$; PS vs PH $P < 0.001$; PS vs PT $P = 0.05$; PH vs PT $P = 0.55$).

were statistically significant in this group, with a 50% decrease, which was consistent with previous studies (16).

Contrary to Anand et al (17), where the authors found significant pain relief in chemotherapy-induced peripheral neuropathy, the 2 patients in our study with this diagnosis did not improve with treatment. However, the patient with neuropathic pain secondary to radiotherapy had a substantial pain reduction, from an NRS-11 of 6 to 0.

From the population studied, 29 patients found no relief in pain intensity between the first and last patch application, although in 4 of them, there was a greater than 30% decrease in PTA. Gustorff et al (18)

also noticed that nonresponders were found to have a significant decrease in the painful area, despite a lack of significant pain intensity relief. On the other hand, Allegri et al (5), in their treatment algorithm for localized neuropathic pain, considered a reduction greater than 30% in pain intensity or in PTA to be a good response to patch application.

In accordance with previous studies, our results highlight the safety of several capsaicin patch treatments.

Concerning oral medication, our patients' prescriptions were in line with the NeuPSIG recommendations previously mentioned, since the major pharmacological class was anticonvulsants (gabapentin and pregabalin). Opioids were the second most common pharmacological class, probably because tramadol, a weak opioid, is one of the recommended oral medications that can be added as an adjunct (3,6).

Study limitations include the relatively small sample, the coexistence of oral pain medication, and the size asymmetry between groups. Also, timing for pain intensity and PTA assessment was not always precisely the same due to logistical difficulties.

Conclusions

Capsaicin 8% patch proved to be a valuable option to treat peripheral neuropathic pain, providing a significant reduction in pain and allodynia intensity, as well as a reduction in the painful area (19,20). It is well tolerated and has a high treatment compliance (21). Its topical route of administration makes it a valuable option for a growing patient population with several comorbidities and polypharmacy. Our study shows pain intensity and painful area reduction with capsaicin treatment in several peripheral neuropathic pain etiologies, such as postsurgical and posttraumatic neuropathic pain.

Research complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013) and was approved by the authors' Institutional Review Board (Reference Number 16/16//04/2021).

All authors accept responsibility for the entire content of this manuscript and approve its submission.

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