

Observational Report

8% Capsaicin Patch in Treatment of Peripheral Neuropathic Pain

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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: 01-10-2020
Revised manuscript received:
02-28-2020
Accepted for publication:
03-30-2020

Free full manuscript:
www.painphysicianjournal.com

Background: Neuropathic pain is a complex condition that is difficult to control and has a high impact on quality of life. 8% Capsaicin patch can be a therapeutic strategy in the treatment of peripheral neuropathic pain.

Objectives: This study aims to (1) evaluate clinical efficacy and (2) tolerability of 8% capsaicin patch in a Pain Unit.

Study Design: Retrospective observational study

Setting: Portuguese Pain Unit

Methods: A sample of 120 patients diagnosed with peripheral neuropathic pain, underwent treatment with the 8% capsaicin patch between February 2011 and February 2019 in a Portuguese Pain Unit. Patients were included in one of the following groups according to the etiology of pain: postherpetic neuralgia (PHN), chronic post-surgical pain (CPSP), post traumatic neuropathic pain (PTNP), diabetic neuropathy (DN), regional pain syndrome, complex I and II (CRPS I / II), HIV-associated neuropathy (HIVN), lumbar neuropathic pain (LNP), trigeminal neuralgia (TN) and other neuropathies (O). The evaluated parameters were: pain intensity according to unit protocol (numerical rating scale), pain characteristics, location, size of the painful area. The evolution of pain intensity after treatment (patients were considered as responders to therapy if the decrease in NRS was equal to or greater than 30%; patients with a decrease in NRS of 50% or more were also analyzed), the area of pain and the need for adjuvant analgesic therapy, as well as the tolerability to treatment and the identification of eventual predictors of its efficacy were evaluated, at 15 days, 8 weeks and 12 weeks after 8% capsaicin patch.

Results: Of the 120 patients in the sample, 40.8% had a $\geq 30\%$ decrease in basal pain intensity 15 days after treatment, 43.3% after 8 weeks and 45.0% after 12 weeks. 30.8% of patients had $\geq 50\%$ decreased basal pain intensity 15 days after treatment, 27.5% after 8 weeks and 30.0% after 12 weeks. Pain area decreased in 36.7% of patients and 18.3% reduced chronic analgesic therapy within 12 weeks after 8% capsaicin patch application. There was only one case of intolerance to the treatment.

Limitations: This study has the limitations inherent to a retrospective study. The study period was only 12 weeks and some diagnostic groups included a small number of patients.

Conclusion: Treatment of peripheral neuropathic pain with 8% capsaicin patch seem to be effective in the short and medium term, both in decreasing pain intensity and in reducing the painful area. Its application is tolerated by most patients.

Key words: 8% capsaicin patch, peripheral neuropathic pain, pain intensity, painful area

Pain Physician 2020; 23:E541-E548

Neuropathic pain is defined as pain that results from an injury or dysfunction affecting the somatosensory system; pain may be central or peripheral (1). It is clinically characterized by the presence of dysesthesia, allodynia, and hyperalgesia.

Its prevalence in Europe is estimated at approximately 7% to 8%, with a major impact on quality of life (2). The high prevalence of this condition, particularly in patients with comorbidities, has represented a challenge in therapeutic management. Drugs commonly used as the first line of treatment have limited efficacy and potential for drug interaction, addiction, or adverse effects (2). Topical formulations have added one more therapeutic option.

Capsaicin, a capsicum pepper extract, is a highly selective agonist of type 1 vanilloid transient potential receptors (TRPV-1), located in C fibers and some A delta skin fibers (3). Activation of these receptors by heat or substances with acid pH triggers the sensation of local heat, burning, and/or itching. Capsaicin is available as low- concentration skin cream (0.025%-0.1% capsaicin) or high-concentration skin patch (8% capsaicin) (4). Prolonged activation of TRPV-1 receptors as with application of high concentration capsaicin patch results in receptor dysfunction and blockage of painful impulse transmission. Induced neurolysis is usually temporary, with reinnervation a few weeks after treatment is completed (3).

The analgesic activity of capsaicin has been explored since 1860 and is currently indicated in many countries for the treatment of peripheral neuropathic pain (5,6).

This study aimed to evaluate the tolerability and clinical efficacy at 12 weeks of the 8% capsaicin patch for the treatment of various peripheral neuropathic pain syndromes.

METHODS

A retrospective observational study, approved by the local ethics committee, was conducted, which included all patients with peripheral neuropathic pain undergoing 8% capsaicin patch treatment between February 2011 and February 2019 at the Centro Hospitalar e Universitário de São João, Portugal. Patients with incomplete clinical records were excluded. During this period, patients with peripheral neuropathic pain refractory to first-line therapy (this is, according to the Portuguese Directorate-General for Health guidelines: anticonvulsants (AC) for trigeminal neuralgia and tricyclic antidepressants (TCAs), selective serotonin and

norepinephrine reuptake inhibitors (SRNI), or gabapentinoids (GB) for the remaining syndromes) were eligible for capsaicin patch treatment. All patients (or legal representative) consented to treatment and underwent psychological assessment prior to the treatment and at all follow-up appointments. Although the safety of the 8% capsaicin patch at pediatric age and on the face has not been established, 2 children, 12 and 16 years old, and 4 cases of chronic facial pain were included in the sample. Basal pain intensity was recorded prior to treatment via the Numeric Rating Scale 0-10 (NRS-11). Patients were administered 1 g of paracetamol orally one hour before patch application unless they had a drug allergy. No other topical therapy was given during treatment. After identification of the limits of the painful area, the 8% capsaicin patch was applied over this area, up to a maximum of 4 patches, for a period of 30 to 60 minutes (30 minutes if applied to the feet and 60 minutes in the remaining body zones), according to the manufacturer's standards and under medical supervision. Pain intensity according to the NRS-11 was recorded one hour after treatment. This was followed by a 12-week follow-up period, with periodic medical consultations for pain assessment (NRS-11) and analgesic medication adjustment after 15 days, 8 weeks, and 12 weeks.

The statistical treatment of the data was performed using the patients' clinical information, which was retrospectively consulted through the individual computerized process. The following variables were recorded for the 120 patients included in the sample: demographic data, diagnosis, pain location, evolution of the pain area, and ongoing analgesic therapy. Patients were included in one of the following groups according to the etiology of pain: postherpetic neuralgia (PHN), chronic postsurgical pain (CPSP), posttraumatic neuropathic pain (PTNP), diabetic neuropathy (DN), complex regional pain syndrome I and II (CRPS I/II), HIV-associated neuropathy (HIVN), lumbar neuropathic pain (LNP), trigeminal neuralgia (TN), and other neuropathies (O). Analgesic drugs were categorized into weak opioids (such as tramadol and codeine), strong opioids (morphine, oxycodone, buprenorphine, hydromorphone, fentanyl), and adjuvants. Patients who reduced analgesic medication over the 12 weeks of follow-up were identified. Pain intensity (NRS-11) was recorded prior to treatment, one hour after treatment, after 15 days, after 8 weeks, and after 12 weeks. Pain level was classified as mild (NRS-11: 1-3), moderate (NRS-11: 4-6), and severe (NRS-11: 7-10). The evolution of pain

intensity from baseline was analyzed, and patients were considered as responders to therapy if the decrease in their NRS-11 score was equal to or greater than 30% ("responders \geq 30%"). Patients with a decrease in their NRS-11 score of 50% or more ("responders \geq 50%") were also analyzed. The primary objective of this study was to evaluate the change in basal pain intensity (proportion of patients with a decrease in basal NRS-11 of \geq 30% and \geq 50%) at 15 days, 8 weeks, and 12 weeks after application of the 8% capsaicin patch. Secondary objectives included the study of the evolution of the area of pain, the need for systemic analgesic therapy, tolerability to treatment, and the identification of eventual predictors of 8% capsaicin patch efficacy. We used SPSS Version 25 (IBM Corporation, Armonk, NY) for all analyses. The threshold significance level for all tests was set at $P = .05$.

RESULTS

Patients

A total of 120 patients were included in the sample, 81 women (67.5%) and 39 men (32.5%), with a minimum age of 12 years and a maximum of 90 years, and a mean age of 57.1 ± 16.7 years (Table 1). Age was normally distributed. The most frequent diagnoses were CPSP ($n = 38$; 31.7%) and PHN ($n = 34$; 28.3%).

CRPS I/II, TN, and DN were found to be associated with a higher mean basal pain intensity. The painful syndromes included in the sample mostly involved the limbs and chest. Of the patients studied, 55.8% were on chronic opioid therapy when treated with 8% capsaicin patch, and 86.7% were receiving adjuvant drugs such

as TCAs, SRNI, AC, GB, topical local anesthetics (TLA), muscle relaxants (MR), or corticosteroids (CCT). Only 2.5% of patients in the sample were not taking any chronic analgesic medication at the time of treatment (Table 2).

Therapeutic efficacy

Table 3 and Fig. 1 show the evolution of mean pain intensity (NRS-11) at different assessment times.

Of the 120 patients in the sample, 40.8% had a baseline NRS-11 decrease of \geq 30% ("responders \geq 30%") 15 days after treatment, 43.3% after 8 weeks, and 45.0% after 12 weeks (Figs. 2-4). No statistically significant differences were identified by age group (age < 18 years, 18-65 years, > 65 years) at 15 days (chi-square test; $P = .26$), 8 weeks ($P = .74$), or 12 weeks ($P = .52$). Similarly, there was no statistically significant influence of gender at the 3 assessment times (chi-square test; $P = .53, .56, .18$, respectively).

Regarding "responders \geq 50", 30.8% of patients had a decrease in their baseline NRS-11 score of \geq 50% 15 days after treatment, 27.5% after 8 weeks, and 30.0% after 12 weeks. Also in this group, there were no statistically significant differences in pain intensity reduction after 15 days, 8 weeks, and 12 weeks, by gender (chi-square test; $P = .25, .05, .45$, respectively) or age ($P = .43, .47, .72$, respectively).

Significantly lower treatment response was noted in patients with moderate basal pain intensity (NRS-11 score: 4-6) at 15 days and 8 weeks (chi-square test; $P = .04$ and $.047$, respectively). At 12 weeks, even if it existed, this difference was no longer statistically significant ($P = .08$).

Table 1. Demographic characteristics.

			Diagnosis							T		
			CPSP (n = 38)	PHN (n = 34)	PTNP (n = 12)	CRPS I/II (n = 12)	HIVN (n = 6)	LNP (n = 5)	DN (n = 5)	TN (n = 4)	O (n = 4)	(n = 120)
Age (yrs) Average \pm SD			50.5 \pm 13.6	72.6 \pm 10.8	48.6 \pm 15.4	49.7 \pm 14.2	46.0 \pm 11.9	63.9 \pm 7.5	50.6 \pm 21.2	56.0 \pm 26.6	51.0 \pm 16.7	57.1 \pm 16.7
Gender	F	n	28	18	9	11	1	3	4	4	3	81 (67.5%)
		%	73.7%	52.9%	75.0%	91.7%	16.7%	60.0%	80.0%	100%	75.0%	
	M	n	10	16	3	1	5	2	1	0	1	39 (32.5%)
		%	26.3%	47.1%	25.0%	8.3%	83.3%	40.0%	20.0%	0.0%	25.0%	
T (%)			31.7	28.3	10.0	10.0	5.0	4.2	4.2	3.3	3.3	100

Abbreviations: F, female; M, male; SD, standard deviation; T, total

Table 2. Baseline pain characterization.

		Diagnosis n (%)								T (n = 120)	
		CPSP	PHN	PTNP	CRPS I/II	HIVN	LNP	DN	TN		O
		(n = 38)	(n = 34)	(n = 12)	(n = 12)	(n = 6)	(n = 5)	(n = 5)	(n = 4)		(n = 4)
Baseline NRS-11 Average ± SD		6.2 ± 2.7	5.8 ± 2.4	6.7 ± 2.1	7.3 ± 2.4	5.5 ± 1.9	6.9 ± 1.9	7.2 ± 3.1	7.3 ± 3.2	4.7 ± 1.6	6.3 ± 2.4
Body zone	Head	2 (5.3%)	3 (8.8%)	0	0	0	0	0	4 (100%)	0	9 (7.5%)
	Chest	13 (34.2%)	25 (73.5%)	1 (8.3%)	0	0	0	0	0	3 (75%)	42 (35.0%)
	Abdomen	7 (18.4%)	1 (2.9%)	1 (8.3%)	0	0	0	0	0	0	9 (7.5%)
	Upper limb	4 (10.5%)	4 (11.8%)	6 (50%)	9 (75%)	0				1 (25%)	24 (20.0%)
	Lower limb	12 (31.6%)	1 (2.9%)	4 (33.4%)	3 (25%)	6 (100%)	5 (100%)	5 (100%)	0	0	36 (30.0%)
Drugs	Weak opioids	10 (26.3%)	14 (41.2%)	1 (8.3%)	5 (41.7%)	1 (16.7%)	3 (60.0%)	0	0	1 (25.0%)	36 (30.0%)
	Strong opioids	10 (26.3%)	7 (20.6%)	4 (33.3%)	1 (8.3%)	2 (33.3%)	2 (40.0%)	2 (40.0%)	2 (50.0%)	1 (25.0%)	31 (25.8%)
	Adjuvants ^a	31 (81.6%)	26 (76.5%)	11 (91.7%)	11 (91.7%)	5 (83.3%)	5 (100%)	5 (100%)	4 (100%)	3 (75.0%)	104 (86.7%)

Abbreviations: Numeric Rating Scale, NRS-11

^a Adjuvant drugs: TCAs, tricyclic antidepressants; SNRI, serotonin and norepinephrine reuptake inhibitors; AC, anticonvulsants; GB, gabapentinoids; TLA, topical local anesthetics; MR, muscle relaxants; CCT, corticosteroids.

Table 3. Pain evolution.

		Diagnosis median ± DP								T (n = 120)	
		CPSP	PHN	PTNP	CRPS I/II	HIVN	LNP	DN	TN		O
		(n = 38)	(n = 34)	(n = 12)	(n = 12)	(n = 6)	(n = 5)	(n = 5)	(n = 4)		(n = 4)
Baseline NRS-11		6.2 ± 2.7	5.8 ± 2.4	6.7 ± 2.1	7.3 ± 2.4	5.5 ± 1.9	6.9 ± 1.9	7.2 ± 3.1	7.3 ± 3.2	4.7 ± 1.6	6.3 ± 2.4
NRS-11 after one h		5.3 ± 2.5	5.2 ± 3.4	5.6 ± 3.4	4.5 ± 4.0	3.3 ± 2.4	4.8 ± 1.9	7.4 ± 2.1	9.0 ± 1.2	3.8 ± 1.1	5.3 ± 3.0
NRS-11 after 15 d		4.6 ± 2.5	4.6 ± 2.8	4.7 ± 2.4	3.5 ± 3.0	3.7 ± 2.3	6.3 ± 1.2	5.4 ± 1.9	3.5 ± 0.6	3.5 ± 1.1	4.5 ± 2.5
NRS-11 after 8 wks		4.7 ± 2.9	4.2 ± 2.7	5.8 ± 2.5	3.7 ± 3.1	2.5 ± 3.2	8.1 ± 1.5	6.0 ± 2.9	3.5 ± 2.9	4.7 ± 1.6	4.7 ± 2.9
NRS-11 after 12 wks		4.8 ± 3.2	4.2 ± 2.8	5.1 ± 3.0	3.6 ± 3.4	2.2 ± 2.1	8.2 ± 0.8	4.8 ± 2.5	1.8 ± 2.1	6.5 ± 0.9	4.5 ± 3.0

Pain area decreased in 36.7% of patients, being more frequent in patients with CRPS I/II (66.7%), CPSP (42.1%), and PTNP (41.7%). Only 18.3% of patients were able to reduce chronic analgesic therapy within 12 weeks of applying the 8% capsaicin patch (Table 4).

Tolerability

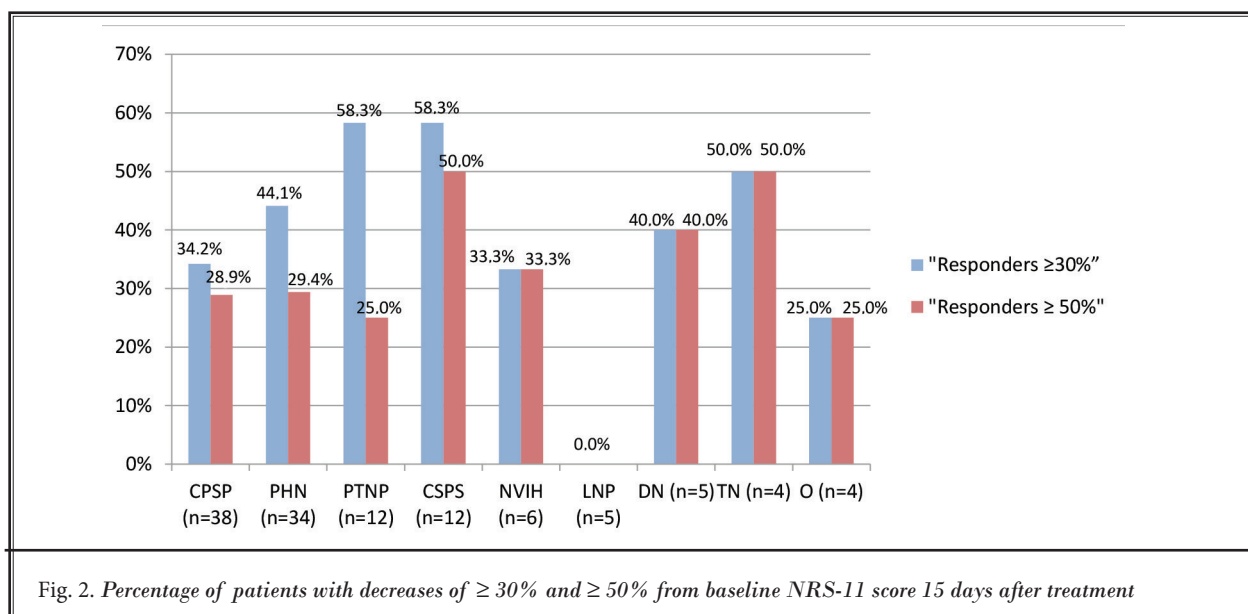
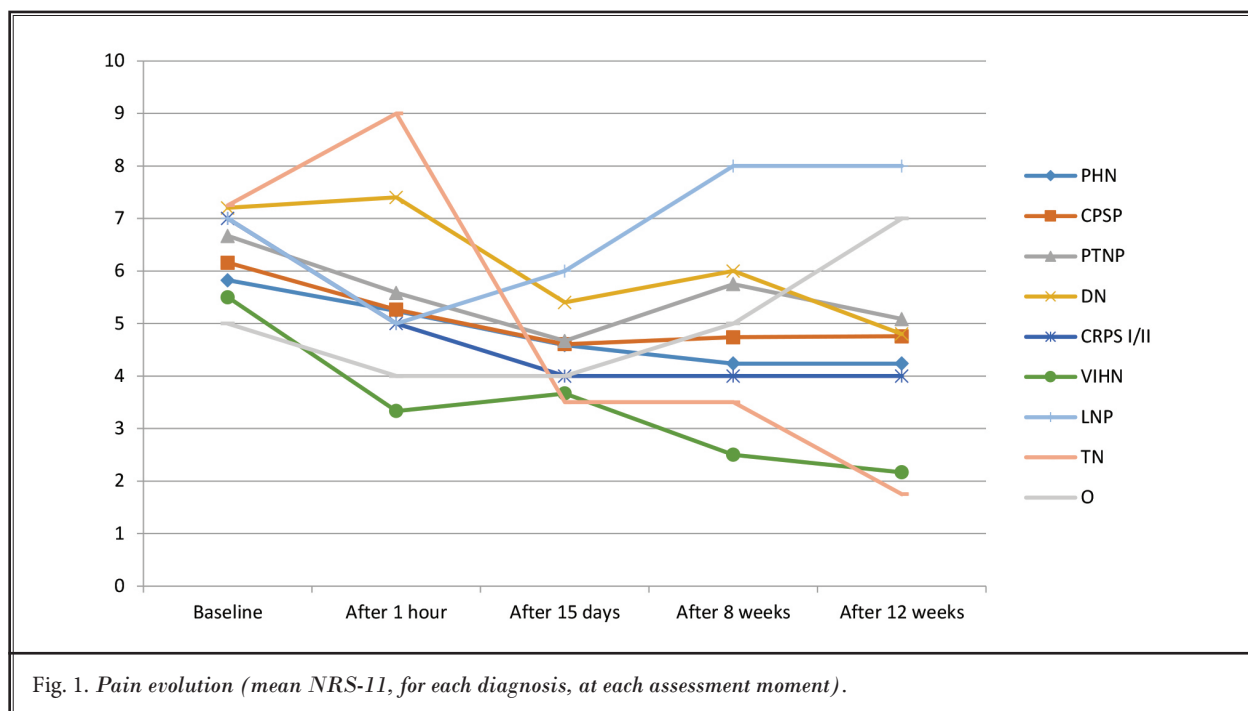
Of the 120 patients in the sample, 20.8% increased

their pain one hour after 8% capsaicin patch application (Table 3), and rescue systemic analgesia was administered in one patient for sustained severe pain. There was only one case of need for early adhesive removal due to pain intolerance. In the patients included in the sample, no major treatment-related adverse reactions were reported.

DISCUSSION

With chronic pain being a worldwide scourge,

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there is a growing concern to find effective and safe therapeutic solutions for these patients (7).

This retrospective study showed that the 8% capsaicin patch decreases pain intensity in several syndromes associated with peripheral neuropathic pain. In fact, more than 40% of patients experienced a decrease in

baseline pain intensity $\geq 30\%$ over 12 weeks, with this relief being more significant in about 30% of the study population, who experienced a decrease of $\geq 50\%$ in their NRS-11 scores. Pain relief over weeks after a single application is one of the advantages of this therapeutic option. These results are in line with the efficacy levels

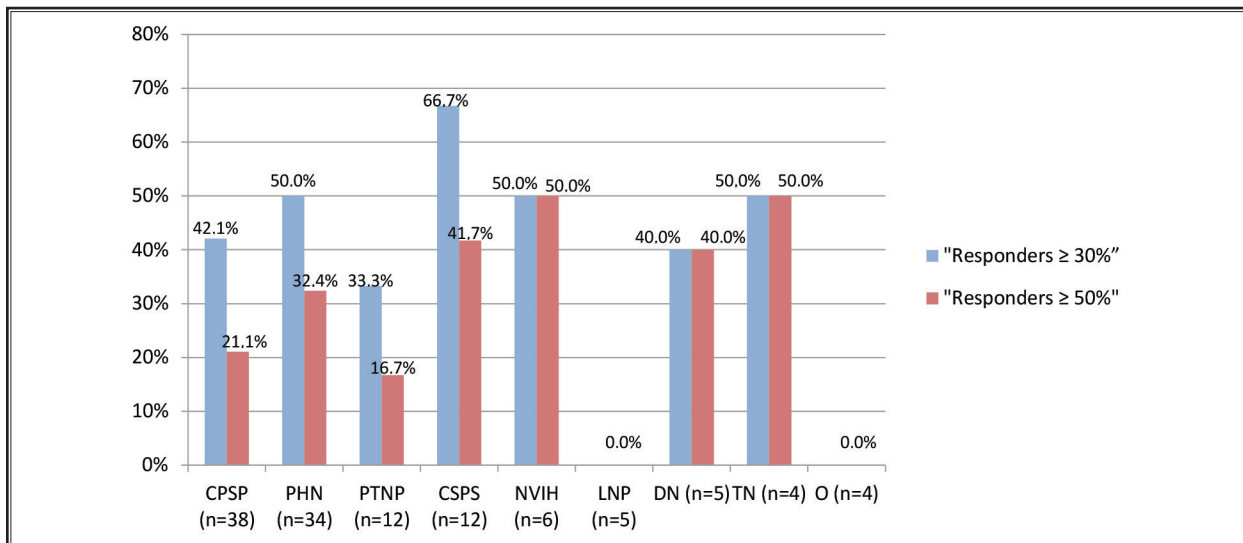


Fig. 3. Percentage of patients with decreases of $\geq 30\%$ and $\geq 50\%$ from baseline NRS-11 score 8 weeks after treatment.

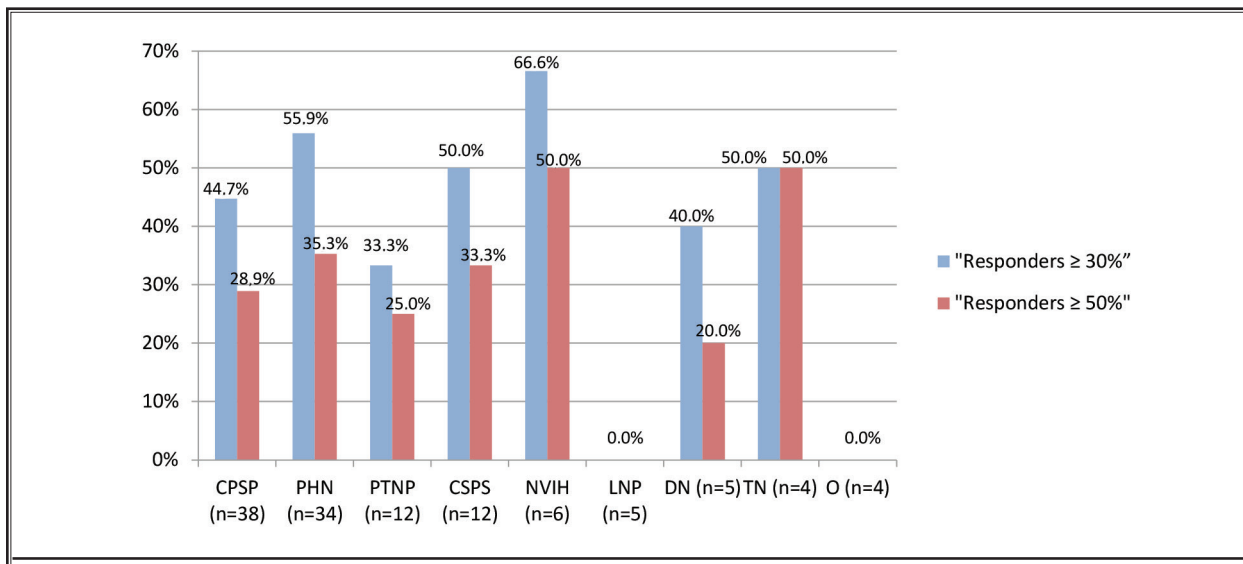


Fig. 4. Percentage of patients with decreases of $\geq 30\%$ and $\geq 50\%$ in baseline NRS-11 score 12 weeks after treatment.

Table 4. Response to treatment.

	Diagnosis									T (n = 120)
	CPSP	PHN	PTNP	CRPS I/II	HIVN	LNP	DN	TN	O	
	(n = 38)	(n = 34)	(n = 12)	(n = 12)	(n = 6)	(n = 5)	(n = 5)	(n = 4)	(n = 4)	
Decreased pain area, n (%)	16 (42.1%)	12 (35.3%)	5 (41.7%)	8 (66.7%)	2 (33.3%)	0	1 (20%)	0	0	44 (36.7%)
Reduction of systemic therapy, n (%)	6 (15.8%)	7 (20.6%)	3 (25%)	1 (8.3%)	3 (50%)	0	1 (20%)	1 (25%)	0	22 (18.3%)

that have been demonstrated in the literature (2,8-10).

It should be noted that this therapy has been shown to be highly effective in patients with TN (50% of patients with $\geq 50\%$ decrease in NRS-11 scores over 12 weeks of follow-up), although current recommendations restrict the application of the patch to the face. Similarly, although the literature is scarce regarding the safety and efficacy of this therapy in the pediatric population, 2 children were included in the sample with no reported incidents. In turn, there were no cases of LNP achieving a decrease in NRS-11 scores of $\geq 30\%$. Interestingly, in the ASCEND2 study there was a 30.9% reduction in NRS-11 scores after 8 weeks of treatment in patients with the same diagnosis (2). The results evidenced in our study can be explained by the large extension of the painful area in these patients, sometimes not completely covered by the capsaicin patch, in order to respect the maximum number of patches applied simultaneously (maximum of 4 patches simultaneously, according to the manufacturer's recommendations).

One of the objectives of this study was to evaluate whether treatment with the 8% capsaicin patch facilitated the reduction of chronic systemic therapy. Wagner et al (11) showed a 54% reduction in the average number of analgesic drugs for each patient.

In our sample, only 18.3% of patients were able to reduce their therapy (unquantified reduction) as a result of decreased pain intensity after treatment. Although the reduction of chronic analgesic therapy was possible in only a small number of patients, treatment with the 8% capsaicin patch allowed symptomatic relief in several patients, which otherwise might only have been achieved with higher doses of their chronic drugs or with the addition of new systemic drugs, considering all inherent potential risks.

The present study suggests that the 8% capsaicin patch may not only decrease pain intensity, but also the extent of the painful area. Pain area decreased in 36.7% of patients. It was also found that in patients with moderate baseline pain (NRS-11 scores of 4-6), this therapy was less effective. Future studies with a larger sample will be needed to validate this result.

Although the application of the 8% capsaicin skin patch has the potential to trigger pain due to the initial activation of TRPV-1 receptors and secondary inflammatory response (frequent erythema), it was tolerated by most patients, as has been shown in various pub-

lished clinical studies (12). One hour after patch application, 20.8% of patients showed a worsening of pain, but there was only one case of sustained severe pain requiring systemic analgesia to resolve the condition. There was only one case of early discontinuation of treatment due to intolerance (0.8%). The safety profile of the drug was confirmed, with no major adverse reactions to report.

Limitations

This study has limitations. As this was a retrospective study conducted at a pain unit, it was not possible to control all variables and to ensure the maintenance of the chronically prescribed analgesic medication over the 12 weeks, which may have influenced the results. Another limitation of this study was the small number of patients included in some diagnostic groups such as TN, LNP, or DN, which made the statistical analysis directed to some subgroups difficult. Note that, since diagnoses associated with episodes of irruptive pain such as TN or PHN were included, the assessment of pain intensity may have been influenced by pain memory. It would have been interesting to assess the impact of therapy on the frequency of pain episodes. Finally, although patients had follow-up for at least 6 months, we only studied a limited follow-up period (12 weeks), so it was not possible to assess whether the results obtained were consistent over time.

CONCLUSIONS

Treatment of several syndromes associated with chronic peripheral neuropathic pain with 8% capsaicin patch seem to be effective in the short and medium term, both in decreasing pain intensity and in reducing painful area. Being a topical therapy, it has several advantages regarding the risk of side effects and drug interaction, representing an important therapeutic option in at-risk populations (like older adults, patients with multiple coexisting diseases, or those on multiple medications). Despite the discomfort induced in some patients immediately after application, treatment with the 8% capsaicin patch is tolerated by most patients.

Acknowledgments

The authors would like to thank all professionals of the pain unit for their daily dedication to patients.

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