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A Retrospective Analysis of the efficacy of treatment of Neuropathic Peripheral Pain

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Abstract:

Introduction: Neuropathic pain is defined as pain arising from a direct consequence of lesion or disease affecting the somatosensory system. Although there are several guidelines for neuropathic pain managent and various effective drugs are accessible, neuropathic pain remains untreated or undertreated. The goal of this study was to evaluate retrospectively efficacy of combining topic capsaicin 8% with oral neuropathic pain therapy in peripheral neuropathic pain/localized neuropathic pain, by measuring pain intensity and pain treatment area reduction.

Methods: This retrospective study was conducted at the Chronic Pain Unit in the Hospitalar Center Tondela-Viseu, Portugal. Forty-three patients with either post-herpetic neuralgia or post-traumatic/post-surgical neuropathic pain with localized allodynia and submitted to a combined therapy with oral neuropathic pain medication (opioids, anticonvulsants, antidepressants) and topical capsaicin 8% were enrolled. Therapeutic efficacy was evaluated considering pain intensity and treatment area variables. Pain intensity was assessed at baseline and 7-14 days after each treatment, using the numerical pain rating scale (NPRS). Treatment pain area was assessed at baseline and after each treatment.

Results: The median percentage reduction in NPRS score was -40.0, [-50.0,-33.3] (95% CI, bootstrap) and the median percentage reduction in treatment pain area was -35.1 [-50.9, 3.4] (95% CI, bootstrap). There was no significant difference in efficacy between postherpetic and post-traumatic/postsurgical neuropathic pain. No differences were detected in pain intensity and pain treatment area reduction regardless the use of different concomitant oral pain medication.

Conclusion: This study evaluates clinical efficacy of combined topical capsaicin and oral neuropathic pain therapy in PNP/localized neuropathic pain by combining NPRS scores and treatment area assessment. This study newly demonstrates that combined medication significantly reduces both peripheral neuropathic pain and treatment pain area in localized neuropathic pain.

Key-Words: Capsaicin; Peripheral neuropathic pain; Localized Neuropathic Pain; Postherpetic Neuralgia; Post-traumatic neuropathic pain; Postsurgical Neuropathic pain; Allodynia; Pain Management.

1. Introduction

Neuropathic pain (NP) is defined as "pain caused by a lesion or disease affecting the somatosensory system" [1]. Neuropathic pain is a source of suffering, impaired quality of life and economic burden. Although its exact prevalence is unknown, studies report a prevalence of 7-8% in the European population [2].

NP can be originated in the central or peripheral nervous system. Peripheral neuropathic pain (PNP) is originated from damage to peripheral nerves, plexus, dorsal root ganglion or roots. Posttraumatic and postoperative nerve injuries represent a frequent cause of PNP, for example, inguinal hernia repair results in chronic neuropathic pain in 10% of patients [3]. Whereas in herpes zoster, 8% of patients present chronic neuropathic pain (postherpetic neuralgia; PHN) [4]. Other causes include diabetic neuropathy, HIV neuropathy, chemotherapy and cancer related neuropathic pain.

Localized neuropathic pain (LNP) is a type of neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain, associated with abnormal sensitivity of the skin and/or spontaneous symptoms characteristic of neuropathic pain [5]. These patients should be able to point the area of pain or abnormally sensitive skin. Especially patients with chronic pain after shingles (PHN) or chronic pain after surgery can be afflicted [6]. This LNP is often described by patients as shooting, burning, stabbing, or being like an electric shock. In addition, LPN physical examination reveals allodynia, hyperalgesia [7] and sensory abnormalities (hypoesthesia or hyperesthesia) as well as loss of noxious, mechanical, or thermal perception, within the painful area [5].

Neuropathic pain is often underdiagnosed and undertreated. In fact, due to its pathophysiology, neuropathic pain is difficult to treat. Non-pharmacologic, pharmacologic and interventional therapies are used. Although several guidelines for NP treatment have been published, they are not consistent and they have limited value, because they do not recognize LPN specifically. Also, the majority of randomized clinical trials in neuropathic pain, investigated patients with a specific etiology, such as PHN, painful diabetic peripheral neuropathy and HIV neuropathy.

On one hand, guidelines published by the Special Interest Group on Neuropathic Pain proposed, with strong recommendation, for first line treatment: tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors and calcium channel $\acute{\alpha}_2$-δ ligands. As second line, with weak recommendation: lidocaine or capsaicin patches and tramadol and as third line, with weak recommendation: strong opioids (oxycodone, morphine) and botulinum toxin-A [8].

On the oher hand, The European Federation of Neurological Societies Guideline for the Pharmacological Treatment of Neuropathic Pain, proposed capsaicin 8% patch has level A for efficacy in patients with PHN and HIV neuropathy [9].

It was recently developed a screening tool that enables patients with probable neuropathic pain/LNP to be identified quickly and easily [5]. In LNP patients, first-line treatment should be a topical analgesic agent, such as 5% lidocaine and capsaicin 8% patch (176 mg/patch), due to benefit/risk advantages over systemic agents.

Capsaicin, is an agonist of the transient receptor potential vanilloid 1 (TRPV1) channels. Continuous activation of TRPV1 causes nociceptor defunctionalization and reversible reduction in epidermal nerve fiber density, with inhibition of pain transmission [10]. This results in a prolonged (8-12 weeks) reversible, reduction in the symptoms of peripheral neuropathic pain. Topical application of capsaicin offers site-specific delivery with lower total systemic dose and avoidance of first-pass metabolism, reducing the risk of drug interactions and side effects.

Treatment of neuropathic pain is challenging, because many patients have refractory pain to existing therapies. Besides insufficient pain relief, patients also experience adverse side effects and are often unable to tolerate medication. Combination therapy is usually prescribed for neuropathic pain and may result in higher efficacy and better tolerability. Although there is insufficient trial of evidence comparing cost effectiveness and tolerability of different drug association [8].

In this regard, our main objective was to evaluate the efficacy of a combined therapy consisting in capsaicin 8% patch and oral medication (anticonvulsants, antidepressants and opioids) in patients with PNP/LNP. We, particularly, analyzed simultaneously pain intensity reduction, using the numerical pain rating scale, and treatment pain area changes in each capsaicin 8% patch application. This strategy is aligned with newly launched suggestions for LNP management.

2. Material and Methods

This retrospective study was conducted at the Chronic Pain Unit in the Hospitalar Center Tondela-Viseu, Portugal.Of all sixty-three patients with peripheral neuropathic/localized neuropathic pain submitted to a combined therapy with oral neuropathic pain medication and 8% topical capsaicin, followed in our Pain Unit between 2010 and 2015, forty-three patients were included in this study because they matched inclusion criteria.

2.1 *Ethics Statement*

The data was collected after receiving approval from the Ethical Committee of the Hospitalar Center Tondela-Viseu and informed written consent of patients diagnosed with PNP/LNP, treated with capsaicin 8% patch and oral NP medication.

2.2 Procedure

2.2.1 Exclusion criteria

Patients were excluded if they were under 18 years of age; pregnant; with neuropathic painful areas located on the face, above hairline of the scalp and/or in proximity of mucous membrane; painful diabetic neuropathy; had opioid medication greater or equal to 60 mg of morphine or equivalent; use of topically applied pain medication; hyper sensibility to capsaicin, local anesthetic or patch; unable to give consent and loss of follow-up data.

2.2.2 Outcome Measurements

Between 2010 and 2015, we collected the following information from patients submitted to 8% topical capsaicin and oral NP medication, in our Chronic Pain Unit: gender, age, duration of LNP, LNP etiology, classified as postherpetic neuralgia (PHN) or post-traumatic/postsurgical neuropathic pain (PostNP), baseline pain score, NP anatomical location, size of treatment area, number of treatments and baseline concomitant oral NP medication.

Numeric Pain Rate Scale

Pain intensity was assessed at baseline and 7-14 days after each capsaicin 8% patch application, using the Numeric Pain Rate Scale (NPRS) (Figure 1). This most common unidimensional pain instrument, consists of a horizontal line with a beginning point marked zero or "no pain" and the number ten at the opposite end, marked as "worst pain possible". When using this pain rating tool, the patient reports the number which best represents the pain he or she is feeling [11]. Generally, pain in the 1-3 category is ranked as mild pain, 4-6 as moderate pain and 7-10 as severe pain [11]. All NPRS assessment were for average pain in the last 24 hours. Following the initial treatment, visit to the pain clinic or telephone contacts were conducted after 7-14 days. Re-treatment with capsaicin 8% patch was scheduled approximately after 12 weeks according to significantly increased pain during the follow up evaluation.

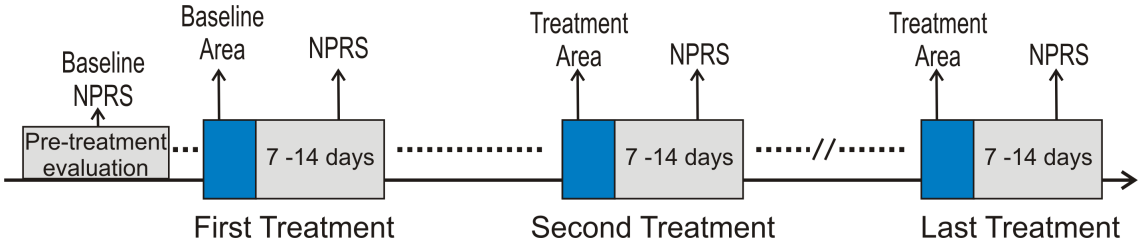

Figure 1. Graphical representation of patient´s treatment and follow-up time-line. The blue box represents the treatment day with pre-treatment pain area measurement.The gray box represents the post-treatment period with NPRS score evaluation after each treatment.

Treatment area

The painful area to be treated was identified through mechanical allodynia, using a brush and was marked on the patient's skin; the markings were used to match the size of the capsaicin 8% patch to the treatment area. In each treatment the area was recorded and determined, in cm^2, using image analysis software (Figure 2).
The decision to initiate capsaicin in our patients was made according to existing guidelines at the time of data collection (2010-2015). Only recently (2016), topical capsaicin 8% (176 mg/patch) was proposed as first line treatment in LPN [5].

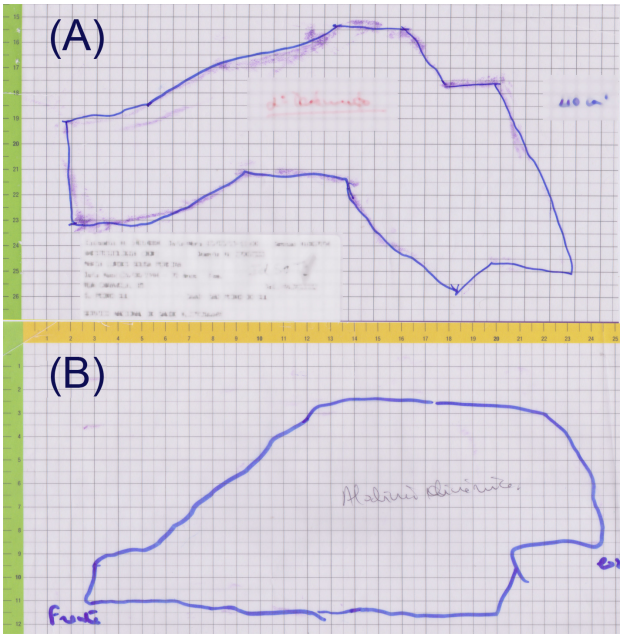

Figure 2. Example of two consecutive pain treatment areas (A and B) in the same patient. The areas were determined using mechanical allodynia and drawn on the patient´s skin, for capsaicin patch application.

The capsaicin 8% patch was applied for 30 minutes to the feet and for 60 minutes to all other areas of the body. After patch removal, the area was cleaned with cleansing gel and cool packs were placed on the treatment area to reduce discomfort. The duration of cooling was variable and patients were recommended to continue cooling measures at home, as needed.

Safety of topical capsaicin 8% was assessed by monitoring of vital signs (blood pressure, heart rate) during patch application, adverse effects and medication used for treatment-related discomfort, on the treatment day and on the following 48h. Patients were offered paracetamol and/or nonsteroidal anti-inflammatory drugs (NSAIDS) for mild pain , while for moderate pain, patients were offered tramadol.

2.2.3. Patient Demographics, clinical characteristics and baseline oral pain medication

Patients were grouped in five categories according to concomitant oral NP medication: patients meditated only with anticonvulsants (A), with anticonvulsants and opioids (AO), and patients that were taking anticonvulsants, antidepressants and opioids (AAO). Other two groups were created with patients that had other (Ot) medication combinations (anticonvulsants and antidepressants, antidepressants and opioids) and none medication (N) (see Table 1).

Demographics		
Gender	Male (%)	20 (47%)
	Female (%)	23 (53%)
Age (years)		65.0±13.9
Clinical Characteristics		
Duration of LNP (years)		2.9± 4.7
LNP etiology	PostNP (%)	28 (65%)
	NPH (%)	15 (35%)
Baseline pain (NPRS)		6.3± 1.8
Pain Anatomical Location		
Thorax		22 (51%)
Upper Limb		7 (16%)
Lower Limb		12 (28%)
Groin		2 (5%)
Baseline size of treatment area (cm^2)		207.7±155.8
Number of treatments		3.7± 2.6
Baseline oral pain medication		
Anticonvulsants		13 (30%)
Anticonvulsants and Opioids		11 (25%)
Anticonvulsants and Antidepressants and Opioids		9 (21%)
Other Combinations		5 (12%)
None		5 (12%)

Table 1. Patient demographics, clinical characteristics and baseline oral pain medication. Variables are expressed as mean ± sd and relative frequencies are expressed in percentage.

2.3 Statistical Analysis

First we wanted to evaluate the patient's treatment efficacy, considering pain intensity and treatment area variables. . In particular, we wanted to test if there was a reduction in any of these two measures from the baseline to the last treatment in the study period.

The efficacy was quantified by looking at absolute differences and percentage change from baseline in both NPRS score and Pain Area variables. As is standardly accepted [12-15], a clinically relevant response was considered if pain intensity score was reduced by at least 30% from baseline. Mean and median statistics, along with 95% confidence intervals, were calculated for percentage and absolute changes. The mean value was calculated mainly for comparison with others studies, as in our analysis we have used the median. All statistics are presented with their 95% confidence intervals, [95% CI].

We used bootstrapping to obtain a 95% confidence intervals for the mean and median. Specifically, we resampled (across subjects) 999 times with replacement from the test-set data to obtain a distribution over the performance metric of interest. The 2-sided 95% confidence interval bounds were then computed as the interval between 2.5 and 97.5 percentiles of this empirical distribution.
In both analyses a Wilcoxon signed-rank test was performed to assess the variables' changes. To access possible differences in Pain intensity and Pain treatment area changes considering Gender, Pain diagnosis and Baseline concomitant pain medication subgroups, a Mann-Whitney rank test or a Kruskal-Wallis H-test were used when appropriated [16].

3. Results

3.1 Changes in NPRS score

We started by analyzing the change in pain intensity between NPRS score at baseline and the NPRS score obtained after the first treatment (see Figure 1; refer to section 2.2.2 for NPRS score accessement methodology). Thirty-five patients (81%) presented a reduction in NPRS score after the first capsaicin 8% patch application. Five of those presented complete pain relief (NPRS score lower or equal to 1) and were discharged. Twenty–four patients (55, 8%) had a greater than 30% reduction in NPRS score. In fact, the median percentage reduction was of -33.3 [-42.7,-25.0], and there was evidence of an absolute and relative pain reduction ($P<0.001$, one-sided Wilcoxon signed-rank test).

After the first patch application, the mean time to re-treatment was 105.3 (±43.2) days and the number of patch applications varied between patients (mean number of treatments: 3.7±2.6 – table 1; Figure 3). Therefore, it was mandatory to evaluate pain score changes between the first and last treatments.

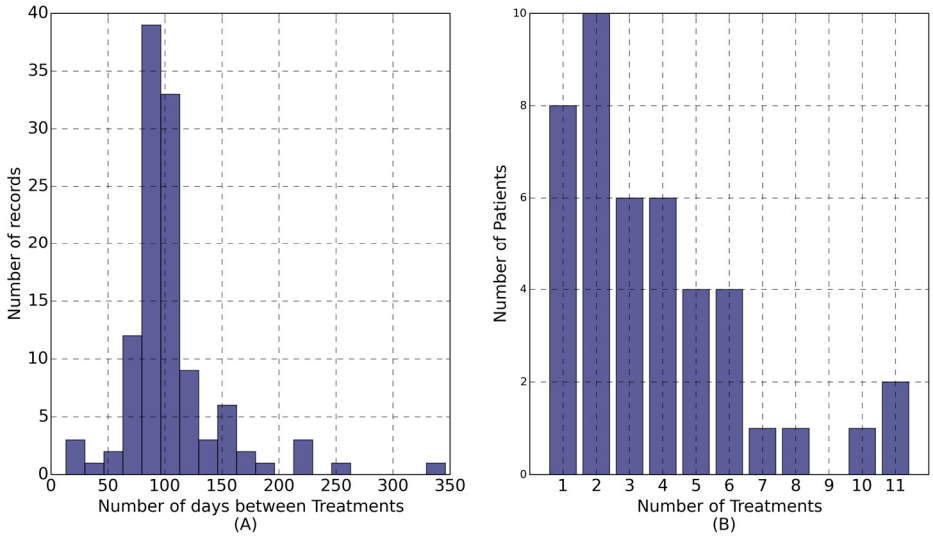

Figure 3. Histogram A: time between treatments, in days.Histogram B: number of treatments, per patient.

This was accessed by determining changes in NPRS scores comparing baseline with last treatment NPRS scores. In this framework, 28 patients registered a decrease of 30% or more, from baseline and 20 have a reduction of more than 2 points in NPRS. As we can see in Figure 4, the median baseline score was 6.0 [5.0, 7.0] was reduced to 4.0 [3.0, 4.0], corresponding to an absolute and percentage change of -2.0 [-3.0,-2.0] and -40.0% [-50.0,-33.3]) respectively, see Table 2.

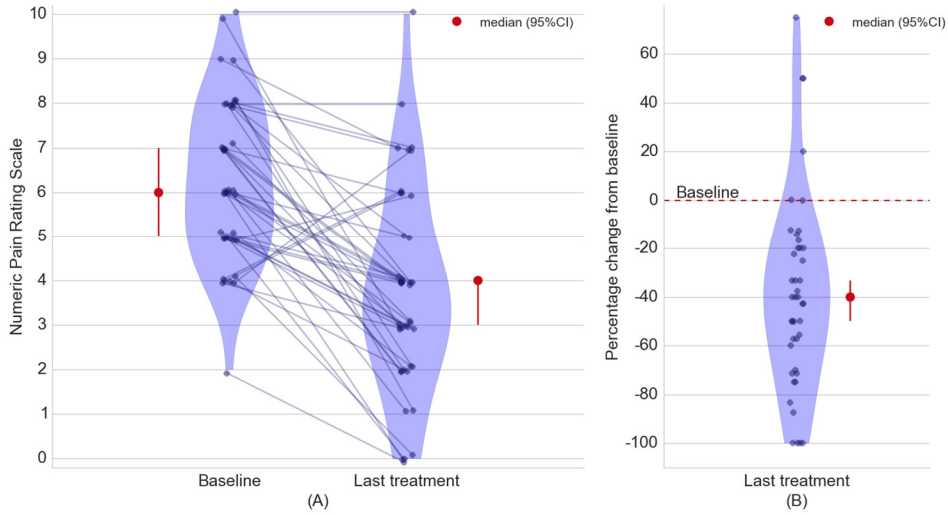

Figure 4. Patients Numeric Pain Rating Scale. (A) Individual patients' NPRS change, from baseline to the last treatment. Blue area of the violin plot is proportional to the number of patients that resgisted the correspondent score. The red dot indicates median values (95% CI). The individual patient's scores in both times were linked for a better visualization of the score change. (B) Distribution of percentage change of NPRS from baseline, and its corresponding median (95% CI). In both representation 95% confidence intervals were obtained with bootstrap across patients.

As we have register a bigger reduction between the baseline to the last treatment, comparatively to the reduction observed between the baseline and the first treatment, we wanted to analyse if a persistent reduction could also be observed between consecutive treatments. To this end, we compared NPRS score of between every pair of consecutive treatments, see Figure 5. As we can see, there is a noticeable regression toward the mean effect [17] between two consecutive treatment's NPRS score. That is, patients that did not improve in the previous treatment tend to register higher improvement in the next treatment, and on the other hand, patients with the best improvements in the former treatment tend to obtain worse scores in the next ones.

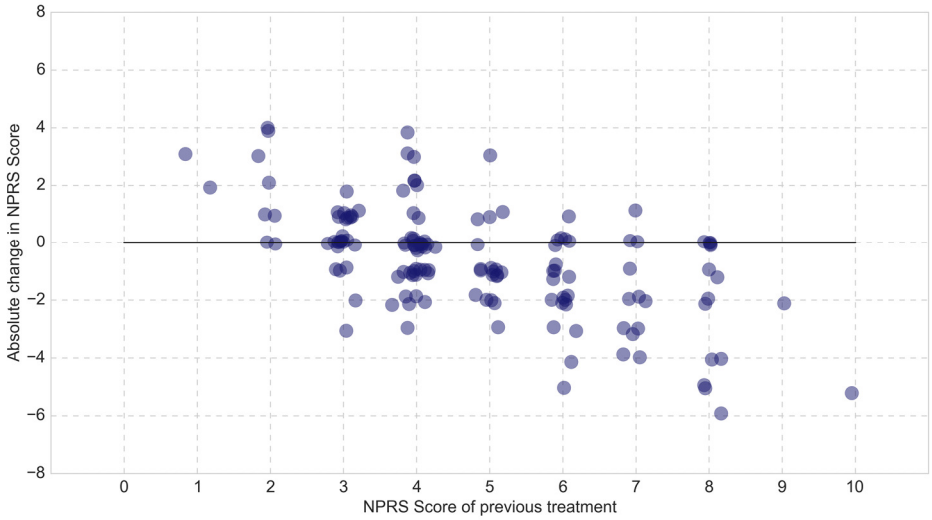

Figure 5. Scatter plot former treatment NPRS score versus absolute change in NPRS score. Every blue dot represents two consecutive treatments.

3.2 Pain treatment area

Regarding changes in the size of treatment area, we compared treatment area between the first treatment area and the treatment area recorded on the last treatment.

The median baseline pain area was of 193cm^2 [136.4, 276.2]. Before the last treatment the median pain area reduced to 131.1cm^2 [74.0, 191.8], corresponding to an absolute and percentage change of -59.0cm^2 [-123.9, 5.9] and -35.1% [-50.9, 3.4] respectively, see Table 2.

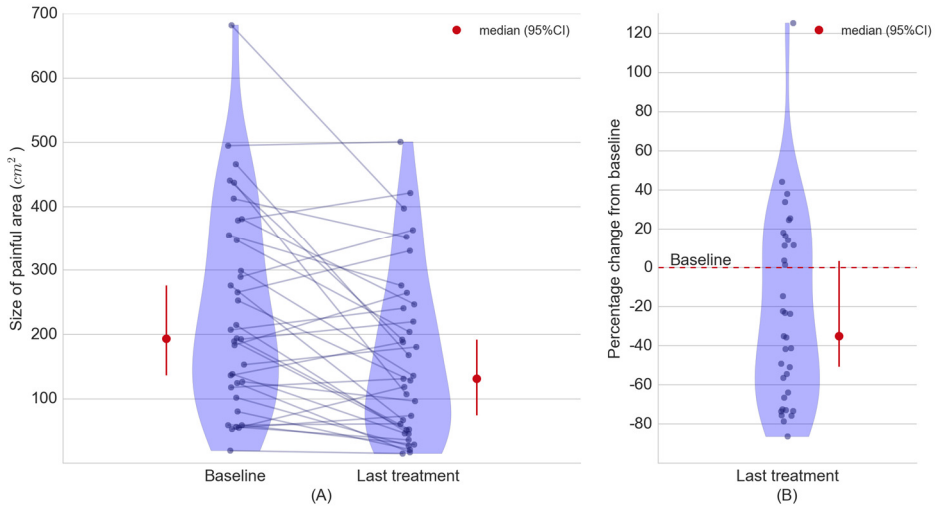

Figure 6. Size of treatment area. (A) Distributions and median (95% CI) of the size of treatment area (cm^2) for baseline and measured after the last patients treatment. The individual patients´ areas in both times were linked for a better visualization of the area change. (B) Distribution of percent change of the size of treatment area from baseline, and its corresponding mean (95% CI). In both, representation has some added noise for visualization purposes and the 95% confidence intervals were obtained with bootstrap across patients.

Results show a significant median reduction in both Pain Score and Treatment Area, see Table 2.

	Mean (95%CI)	**Median (95%CI)**	**P-value**
NPRS baseline	6.3 [5.72, 6.81]	6.0 [5.00 , 7.00]	--
Absolute Change in NPRS Score	-2.5 [-3.2, -1.9]	-2.0 [-3.0 , -2.0]	<0.001
Percentage Change in NPRS Score	-39.0 [-50.8 , -27.3]	-40.0 [-50.0 , -33.3]	<0.001
Treatment Area at Baseline	235.4 [187.9, 287.8]	193.6 [136.4 , 276.2]	--
Absolute Change in size of treatment area (cm^2)	-69.4 [-108.3, -32.3]	-59.0 [-123.5 , 5.9]	0.0013
Percentage Change in size of treatment area	-23.5 [-37.7, -6.3]	-35.1 [-50.9, 3.4]	0.0013

Table 2 – Summary of efficacy evaluation. Mean, Median and 95% confidence intervals (obtained by bootstrapping across patients) for NPRS Score and Treatment Area. The *P* values where computed with Wilcoxon signed-rank test. NPRS Score changes were evaluated between baseline and after the last treatment. Treatment Area changes were evaluated between baseline and the pain area the patient was treated for.

3.3 NPRS score and Pain treatment area changes within sub-Groups

Finally, we wanted to evaluate if there were significant differences between gender, LPN etiology and concomitant NP medication, regarding NPRS score changes and pain treatment area changes, from baseline to the last treatment. We obtained the results presented in Table 3.

		Pain Intensity (NPRS score)				*Pain Treatment Area*			
Sub-group		*Absolute Change*	*P*-value	*Percentage Change*	*P*-value	*Absolute Change*	*P*-value	*Percentage Change*	*P*-value
Gender	M	-2.0 [-3.5, -1.0]	0.356 (M)	-40.0 [-64.0, -20.0]	0.442 (M)	-44.5 [-139.4; 5.9]	0.493 (M)	-32.5 [-66.5, 3.4]	0.364 (M)
	F	-3.0 [-4.0, -2.0]		-43.0 [-56.0, -33.3]		-75.0 [-143.0 ; 18.7]		-35.9 [-56.5,11.4]	
LPN etiology	PostNP	-2.0 [-3.0, -1.0]	0.151 (M)	-36.0 [-53.0, -20.0]	0.241 (M)	-60.1 [-123.9 , 2.0]	0.361(M)	-41.2 [-64.0, 3.4]	0.266 (M)
	NPH	-3.0 [-4.0, -2.0]		-50.0 [-60.0, -33.3]		-25.2 [-153.1, 39.6]		-23.1 [-49.1, 14.1]	
Baseline concomitant pain medication	A	-3.0 [-4.0, -1.0]	0.981(K)	-50.0 [-72.0, -20.0]	0.931 (K)	-67.0 [-137.5, 39.2]	0.881(K)	-38.4 [-73.0, 18.0]	0. 541(K)
	AO	-3.0 [-4.0, -1.0]		-43.0 [-60.0, -13.0]		-20.2 [-92.0, 51.9]		-23.2 [-64.0, 38.1]	
	AAO	-2.0 [-5.0, -1.00]		-23.0 [-56.0, -17.0]		-68.6 [-483.0, 23.10]		-20.0 [-64.5, 25.9]	
	Ot	-2.0 [-6.0, -1.0]		-34.0 [-100.0, -15.0]		-107.5 [-248.7 - 42.8]		-50.8 [-86.4, 11.3]	
	N	-2.0 [-6.0, -1.0]		-34.0 [-100.0, -15.0]		-107.5 [-248.7 , 42.8]		-50.8 [-86.4, 11.3]	

Table 3 – Summary of efficacy evaluation within subgroups. We present the Median value and 95% confidence intervals [obtained by bootstrapping across patients] for NPRS Score and Size of Pain Area, changes from baseline to last treatment. The statistical tests used to compute the P values are indicated: [M] Mann-Whitney rank test, [K] Kruskal-Wallis H-test.

Safety

Capsaicin 8% patch was well tolerated. Adverse effects presented were minor application-site events, such as transient local skin erythema and application-site pain. The majority of patients received analgesia (paracetamol or NSAIDS), for mild application-related pain during the treatment. Twenty patients required oral tramadol for moderate application-related pain. Only one patient required intravenous tramadol for moderate to intense application-related pain during the treatment and didn´t wanted to repeat the patch application.

4. Discussion and Conclusion

This retrospective study describes a combined treatment, including oral NP medication and topical 8% capsaicin, in a routinely clinical setting.

To our knowledge this is the first analysis assessing clinical efficacy of combined NP therapy, using both the NPRS scores and treatment pain area, in patients with LNP. We consider the size of painful area an important clinical tool in assessing efficacy of topical NP treatment. Pain size area is a source of suffering and impairment in patients quality of life.

In the recent review [6], the definition of LNP was presented, (see section 1). Although the author's objective was to facilitate easier identification of patients who can potential benefit with topical treatments, the proposed definition presents some limitations, as it does not provide an upper size limit for the treatment pain area. As Allegri *et al* proposed, localized neuropathic pain, should be consistent and circumscribed within an area smaller than an A_4 sheet of paper [5], and so, incorporating the size of the painful area can improve LNP diagnosis.

Although at the time of data collection, the definition of LNP did not existed, one can presume that our patients match the definition criteria of localized neuropathic pain, according to the existing definition.

Previous studies with capsaicin 8% patch reported about one third of the patients with clinical significant response, in PNP [15]. The studies of Backonja *et al* [18] and Gordon et al [19], reported a mean percentage pain reductions, within two to eight weeks after the first treatment, of -25.4 [-31.0 , -19.8] and -26.9 [-31.5, -22.2], respectively. Our study presented a mean percentage reduction in the NPRS score after the first treatment of -33.0 [- 43.47, -22.38], consistent with the previous reported results.

Although, the pain intensity reduction after the first treatment is used in most studies to quantify treatment's efficacy, it is important to know what happens in the long-term. Concretely, it is essential to understand if more treatments lead to higher improvements and, consequently, better patient's satisfaction, or on the other hand if multiple treatments lead to an efficacy reduction. To the author's knowledge, only a few studies address this question [20].

In this study, data was collected in a long period of time in a standard clinical setting, which allowed us to access information from multiple treatments for the same patient, and therefore to evaluate treatment's efficacy in this setup. The mean number of patient's treatments was 3.7, see Table 1, with two patients receiving a maximum of eleven patch applications. In the study of Treede R.-D. *et al*, the authors reported that the best responder rates tend to increase with repeated applications [15]. In fact, our study shows a -40% [-50.0, -33.3] median reduction in NPRS score between the baseline and after the last treatment, comparatively to -33.3% [-42.7,-25.0] reduction from baseline to the first treatment.

Regarding to the baseline treatment area, that is, the pain area registered just before the first treatment, our patients presented a smaller area compared to other studies [18, 19, 21, 22], however these studies only included patients with PHN. The anatomical location of LNP varies among patients and different diagnosis. In PHN the pain area is located in the correspondent dermatoma, whereas in post-traumatic/postsurgical NP pain area is usually restricted to the primary lesion, such as scar pain.

Comparing the baseline pain area with the one registered just before the last treatment, we obtain a median percentage pain treatment area reduction of -35.9% [-56.7, 3.4], indicating that most of the patients tend to present, not only a reduction in pain intensity, but also a reduction of pain area.
Although there is a good evidence of the treatments efficacy, that is, both pain intensity and pain treatment area decreases, the two variables are not directly correlated. In fact, there is no evident relation between the percentage changes in the pain score and pain treatment area. This shows the need to further study in order to obtain a deeper understanding of the causes underlying Pain Intensity/Pain Area reduction.
To access the efficacy analysis in different sub-groups, we have found that there were no differences between efficacy in terms of both pain intensity and pain treatment area from baseline to the last treatment. Although differential responses to pain treatment for opioids and topical lidocaine have been described between genders [23], in our work did not verified differential responses to pain treatment between genders. Also, in our study there was no diference in response to treatment between the two diagnosis sub-type: PNH or post-traumatic /postsurgical NP, simmilary to the work of Treed *et al*, that reports good results with capsaicin 8% patch, in patients with both mononeuropathies (including post-traumatic NP) and PHN [15]. Putative response predictors to capsaicin include the underlying pathology and allodynia. Sensory profiling, including the combination of mechanical allodynia, pin prick and thermal threshold, is suggested to determine potential predictors of the response to capsaicin 8% patch [15] . In our study, painful treatment area was determined only through mechanical allodynia, because full sensory profile tests are difficult to implement in the clinical routine due to operative reasons (eg. time-consuming and resource constrains).

Regarding to concomitant NP medication, there was no diference in pain intensity and treatment pain area reductions regardless the use of different oral medication (anticonvulsants, antidepressants and opioids). Although, weak opioids (tramadol) represent the second line therapy for neuropathic pain [8], twenty-one patients were medicated with tramadol, one patient was medicated with codeine and another patient was medicated with transdermal buprenorphine. The use of opioids by our patients can be explained because similarly to other studies [18, 22, 24] our patients presented a moderate intensity pain at baseline, with a mean duration of approximately three years, refractory to treatment and difficult to control, leading to a scaled of combination therapy. Also, some patients (four) were medicated with opioids due to other pain syndromes such as low back pain or chronic osteoarticular pain. Besides that, tricyclic antidepressants recommended as first–line therapy are associated with systemic adverse events such as urinary retention, weight gain, constipation, sedation, myocardial infarction and cardiac arrhythmia particularly in elder patients [25]. Adverse events associated with anticonvulsants also limit their use in some patients. In fact, two patients didn´t tolerate the adverse effects of both anticonvulsants and antidepressants. Capsaicin 8% patch was well tolerated with only minor application-site events. Capsaicin has the advantage of site-specific delivery with lower total systemic dose and avoidance of first-pass metabolism, reducing the risk of drug interactions and adverse effects.

Our study caveat is twofold: 1-a small sample size and 2-the lack of a control group (eg. patients on oral medication and having a placebo patch).

As is known, the regression to the mean effect [17, 26] can lead to misleading conclusions concerning the effects of treatment efficacy in uncontrolled evaluation. Although, we have observed a regression to the mean effect (see Figure 5) in NPRS score measurements between consecutive treatments. However, in our main analysis, that is, evaluation of NPRS score and pain area between baseline and the last treatment, the reduction effect was observed across patients, and not only in patients with higher NPRS scores or higher areas, as would be expected if only regression to the mean was present.

The absence of a control group also raises an important issues as follows: one cannot ascertain the real contribution of capsaicin alone to the final pain outcomes. However, pain intensity and pain area reductions in patients not taking oral medication were smiliar from patients taking oral neuropathic medication and regardless of concomitant neuropathic pain combinations. This, suggests that pain reduction and treatment pain area reduction could be imputed to the peripheral target-mechanism of 8% topical capsaicin, providing an additive effect to the central acting neuropathic pain oral medication, with the advantage of reduce risk of adverse effects and drug interactions.

In conclusion, this analysis shows that combination of topical capsaicin 8% with oral neuropathic pain medication reduces localized neuropathic pain and treatment pain area in both postherpetic and pos-ttraumatic/postsurgical NP. This treatment approach is aligned with newly launched pharmacological treatment algorithm for LNP management.

Future prospective research is warranted for validating these results and confirming pain area reduction as a primary endpoint for responder analysis to capsaicin 8% patch in localized neuropathic pain.

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6. Conflict of Interests
Loureiro, M. C. participated as primary site investigator in the observational study ASCEND NIS QTZ-EC-0003, in 2012, sponsored by ASTELLAS Farma Europe Ltd.

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