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Lidocaine 700 mg medicated plaster for post-herpetic neuralgia: focus on Quality of Life, effectiveness and safety – a retrospective observational study

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Abstract. – OBJECTIVE: Postherpetic neuralgia (PHN) is a neuropathic pain syndrome following herpes zoster (HZ) infection, characterized by pain that persists for months to years after the resolution of the HZ rash. Therapeutic management remains challenging for every clinician.

We report the follow-up of patients diagnosed with PHN and treated with lidocaine 700 mg medicated plaster (LMP), focusing on effectiveness, safety, and Quality of Life (QoL).

MATERIALS AND METHODS: This study is a retrospective observational investigation of patients with PHN treated with LMP. Patients were regularly followed for pain intensity, co-analgesic consumption, adverse effects, QoL using the EQ-5D, and patient satisfaction for 8 weeks.

RESULTS: A total of 31 patients were evaluated. At enrollment, 18 patients (58.1%) were treated with at least one PHN concomitant medication, for which the number and dosing remained constant during the study. Patients had a mean average pain intensity of 6.5±1.0 at baseline, which decreased to 3.6±1.1 at week 4 and 2.8±0.9 at week 8. Four patients reported erythema, and one complained of vesicles eruption associated with pruritus. EQ-5D at weeks 4 and 8 of treatment showed persisting improvements in all domains except for the "anxiety/depression" domain. At week 8, <80% of patients reported to be satisfied or very satisfied.

CONCLUSIONS: This study adds further weight to the growing body of clinical and research evidence that LMP treatment is effective and well-tolerated in patients with PHN.

Key Words:
Herpes zoster, Postherpetic neuralgia, Lidocaine 700 mg medicated plaster, Versatis®.

Introduction

Herpes zoster (HZ) results from the reactivation of the latent varicella-zoster virus (VZV) acquired following primary varicella infection, also known as chickenpox[1]. HZ is characterized by a unilateral dermatomal rash and pain, lasting between 2 weeks and 1 month[1]. The incidence of HZ has been increasing in recent decades. In the USA, the overall incidence increased from 286.0 cases per 100,000 person-years in 1994 to 579.6 cases per 100,000 person-years in 2018[2]. In Italy, the annual incidence in 2010 was 6.3/1000 person-years, and 157,000 new cases of HZ are estimated to occur every year[3].

The most common complication of HZ is postherpetic neuralgia (PHN). PHN is a neuropathic pain syndrome that persists for months to years after resolving the HZ rash[4].

Injury of the peripheral nerves and altered central nervous system signal processing are the cause of the chronic pain associated with PHN, which is often described as shooting, stabbing or hot-burning; this happens since, after the injury, peripheral neurons discharge spontaneously at lower activation thresholds ("hyperalgesia"), and result in disproportionate pain following nonpainful stimuli ("allodynia")[4-10].

New knowledge on chronic pain and its reconsideration as a disease state highlighted its importance as a biological, psychological, and social problem[11], where related conditions, such as anxiety, discomfort, impaired functional status, often complicate the treatment of the painful condition and negatively impact patients' Quality of Life (QoL)[12].

There are several effective PHN treatments[13-15]. Current guidelines recommend anticonvulsants, such as gabapentin and pregabalin, tricyclic antidepressants, such as amitriptyline, nortriptyline, and desipramine. Recently, lidocaine 700 mg medicated plaster has been added to the first-line

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treatment options[16,17]. Opioids, such as tramadol and topical capsaicin patch or cream, are the second or third-line treatment choices.

The lidocaine 700 mg medicated plaster (*Versatis*®) was first registered in 1999 in the USA. In Italy, it has been approved and used to relieve neuropathic pain associated with PHN in adults. It exerts no local anesthesia but only analgesia[18]. It reversibly inhibits the conduction of neuronal impulses by blocking sodium channels and stabilizing neuronal membranes of abnormally excitable A-delta and C fibers, resulting in a reduction of ectopic discharges[7,19]. A reduced peripheral nerve input (counteracting the central sensitization) and a reduced nerve fiber density in the epidermis seem to play a key role in lidocaine 700 mg medicated plaster's long-term pain relief action[20]. Compared with first-line oral treatments, lidocaine patches have shown a very low systemic uptake (3%) associated with good short-term and long-term tolerability and minimal risk for pharmacological interactions or systemic adverse events, which are one of the main drawbacks of first-line oral treatments[7,21-23]. Since the majority of the PHN patients are elderly, and therefore, have frequent comorbidities and/or are taking several other medications, the favorable safety profile of lidocaine 700 mg medicated plaster (LMP) is of particular relevance in clinical practice; furthermore, treatment adherence may be enhanced with the use of plasters[15,24-26].

Although the clinical usefulness of LMP is well understood, there is still a need for more evidence regarding the role of topical lidocaine in the treatment of pain[27-29] and its impact on biopsychosocial factors, such as quality of life and patient satisfaction.

Therefore, the current study aimed at evaluating the impact of PHN and the subsequent treatment with Versatis® on patients' QoL in a clinical practice scenario and evaluate the effectiveness and safety of LMP for the treatment of neuropathic pain associated with a previous HZ infection.

Patients and Methods

The present study was a retrospective observational investigation of patients with PHN who had been treated with lidocaine 700 mg medicated plaster (Versatis®, Grünenthal GmbH, Germany)[30] in the "*Pain Unit*" of our hospital (University of Campania "Luigi Vanvitelli", Naples, Italy) in the period from 1 November 2019 to 31 October 2020.

The local Institutional Review Board approved this study, and it was in accordance with the Declaration of Helsinki. All patients signed informed consent to the use of their data for research purposes.

Eligibility Criteria

The inclusion criteria were: (1) first time PHN has been diagnosed; (2) treatment failure due to insufficient effectiveness or poor tolerability of previous therapy; (3) no previous treatment for PHN with lidocaine plaster; and (4) being older than 18 years. PHN was diagnosed by using the following diagnostic criteria[31]: (1) a history of HZ based on a unilateral dermatomal rash consisting of grouped vesicles or papules on an erythematous base; (2) pain in the affected dermatome or immediately adjacent dermatomes persisting for more than 4 months after HZ rash onset; (3) at least one positive sensory sign (e.g., dynamic mechanical allodynia) or one negative sensory sign (e.g., elevated von Frey thresholds) in the affected area; and 4) no other condition, such as radiculopathy, that could be the origin of pain in the affected dermatomes.

The exclusion criteria were: (1) inflamed or injured skin, such as active HZ lesions, atopic dermatitis, or wounds; (2) severe cardiac, renal, or hepatic impairment; (3) pregnancy; (4) allergy to lidocaine or any other excipients.

Procedures

We collected and examined 38 medical records of patients diagnosed with PHN and treated with LMP. The investigators collected data in November 2020. For each patient, we recorded: (1) demographic details; (2) clinical and diagnostic aspects of PHN, namely period of onset, duration, severity (assessed using a numerical rating scale [NRS]), concomitant symptoms (allodynia, sensory disorders), and previous analgesic treatments; (3) co-analgesic consumption, such as anticonvulsants drugs, analgesics (including nonsteroidal anti-inflammatory drugs [NSAIDs] and acetaminophen) and antidepressants; (4) pain intensity, using a NRS with values between 0 ('no pain') and 10 ('the most intense pain imaginable'); (5) adverse effects (AEs) considered by the investigators to be related to 700 mg LMP; (6) quality of Life (QoL), addressed using the EQ-5D questionnaire[32], which defines health in terms of "mobility", "self-care", "usual activities", "pain/discomfort" and "anxiety/depression", and divides each dimension into three levels ("no problems", "some or moderate problems" and "extreme prob-

Table I. Demographics and clinical characteristics (n=31).

	n (%)
Female/Male	21 (67.7) – 10 (32.3)
Age (years):	
- 30-39	2 (6.5)
- 40-49	3 (9.7)
- 50-59	7 (22.6)
- 60-69	9 (29.0)
- 70-79	9 (29.0)
- ≥80	1 (3.2)
Time since onset of HZ lesion:	
- <6 months	5 (16.1)
- 6 months to 1 year	4 (12.9)
- 1-3 years	10 (32.2)
- 3-5 years	3 (9.7)
- 5-10 years	3 (9.7)
- >10 years	2 (6.5)
Short-form McGill Pain Questionnaire:	
- Shooting	25 (80.6)
- Stabbing	28 (90.3)
- Hot-burning	26 (83.9)
- Aching	10 (32.2)

lems"); (7) patient's satisfaction, measured using a 5-point verbal rating scale (0 = "very dissatisfied", 1 = "dissatisfied", 2 = "neutral", 3 = "satisfied", 4 = "very satisfied") and (8) sensory dimensions of pain assessed with the short-form McGill Pain Questionnaire (SF-MPQ)[33].

Patients were systematically followed-up for 8 weeks after LMP initiated. Data were retrieved from the records based on assessments before LMP treatment initiation, and 4 and 8 weeks after treatment initiation.

A self-adhesive plaster was applied to intact, dry, non-irritated skin for a period of no longer than 12 hours. The subsequent plaster-free interval was at least 12 hours. The plaster could be applied during the day or the night. All patients were educated on the correct application of plaster.

Statistical Analyses

Data were analyzed using a standard computer program (MS Excel). Results are reported as mean ± standard deviation (SD). We tested the significance of our data between groups using the ANOVA test, as appropriate. To test for a significant difference in means within groups over time, a repeated-measures ANOVA was used. The level of statistical significance was <0.05. The percentage of patients with demonstrated successful treatment, which is defined as a more than 50% pain reduction from pre-treatment baseline on the NRS pain scale at 8 weeks, is reported.

Results

All patients who came to the pain unit of our hospital with a diagnosis of PHN were considered. A total of 31 out of 38 medical records of identified patients could be evaluated. The remaining seven dossiers were excluded because they contained insufficient information about diagnosis or the evaluation of effectiveness.

Patients' mean age was 62.0 ± 11.2 years (range 34-80); most were older than 50 years of age (83.9%) and 32.3% were older than 70 years of age. Table I summarizes patients' demographics and clinical characteristics, such as gender, age, time since onset of HZ lesion, and scores for the SF-MPQ reported as the number of subjects who used specific descriptors; out of the 15 descriptors available, only four were used by the patients.

Nearly one-third of patients (32.2%) presented with PHN from one to three years after the HZ outbreak. The time after the HZ outbreak responsible for pain was less than 1 year in 9 patients and more than 3 years in the remaining patients. Patients complained of pain for less than a year in 32.3% of cases, from 1 to 3 years in 41.9% of cases, and finally for more than 3 years in the remaining cases. Almost all patients reported allodynia (93.5%) and hyperalgesia (87.1%) at baseline. According to the short-form McGill Pain

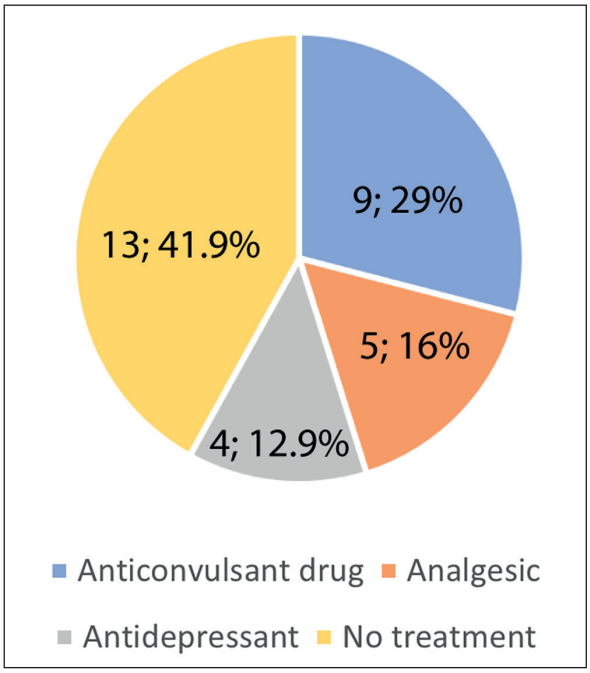

Figure 1. Co-analgesic consumption at enrolment. Number of patients; percentage of patients.

Table II. Pain intensity before and at week 4 and 8 after LMP application.

Age group (n)	T_0	T_4	T_8	*p*-value
30-39 (2)	7.0	4.0 ± 1.0	2.5 ± 0.5	<0.05
40-49 (3)	7.0 ± 0.8	3.3 ± 0.5	2.0	<0.05
50-59 (7)	6.1 ± 0.9	4.1 ± 0.7	2.9 ± 1.1	<0.05
60–69 (9)	6.2 ± 1.2	3.1 ± 0.9	1.8 ± 0.8	<0.05
70-79 (9)	6.7 ± 1.1	3.8 ± 1.4	2.0 ± 0.9	<0.05
≥80 (1)	7.0	3.0	1.0	<0.05
p-value (comparison between different age groups)	0.71	0.46	0.16	
Total	6.5 ± 1.0	3.6 ± 1.1	2.2 ± 0.9	<0.05

LMP: lidocaine 700 mg medicated plaster. T-0, T-4, T-8 : prior to treatment initiation with LMP, 4 and 8 weeks after treatment initiation with LMP, respectively.

Questionnaire (SF-MPQ), patients described the pain as "*shooting*" (80.6%), "*stabbing*" (90.3%) or "*hot-burning*" (83.9%) at enrollment.

At enrollment, 18 patients (58.1%) were treated with at least one concomitant medication for PHN. Figure 1 shows the proportion of patients on co-analgesic medication. The number and dosing of co-analgesic medicines taken by patients remained constant during the study.

A maximum of three or four plasters was applied for up to 12 hours within each 24-hour period in patients with PHN. LMPs were applied to the chest in the dermatomes (between T3 and L3) most often affected by the herpetic eruption, and then, the site of PHN.

Patients had a mean average pain intensity (11-point NRS) of 6.5 ± 1.0 at baseline, which decreased to 3.6 ± 1.1 at week 4 and 2.2 ± 0.9 at week 8. A significant improvement in pain intensity was reported in all age groups, while similar results were reported across age groups. Analysis between different age groups showed no statistical difference at any time point (Table II).

All enrolled patients experienced a 50% decrease in pain scores from baseline at weeks 4 and 8, representing substantial clinical improvement. Four patients (12.9%) presented local reactions: all reported erythema, and a patient complained of vesicles eruption associated with pruritus. No patient discontinued the treatment due to AEs.

The results of the EQ-5D questionnaire are shown in Table III. Data of two patients included in the study were not available at weeks 4 and 8.

All patients reported at least some or moderate problems for pain/discomfort, and 58% reported severe problems. Treatment with LMP resulted after 4 weeks in 14% of patients reporting severe problems and no patient reporting severe problems after 8 weeks. Moreover, only 31% reported some or moderate problems and most patients reported no problems.

For usual activities, most patients reported either severe (10%) or some or moderate problems prior (71%) to LMP treatment start. Improvement was already observed after 4 weeks (no patient reporting severe problems) and further increased

Table III. EQ-5D before and at week 4 and 8 after LMP application.

	Mobility			Self-care			Usual activities			Pain/Discomfort			Anxiety/Depression		
	1, n (%)	2, n (%)	3, n (%)	1, n (%)	2, n (%)	3, n (%)	1, n (%)	2, n (%)	3, n (%)	1, n (%)	2, n (%)	3, n (%)	1, n (%)	2, n (%)	3, n (%)
T_0 (31)	23 (74.2)	8 (25.8)	0	27 (87.1)	4 (12.9)	0	6 (19.3)	22 (71.0)	3 (9.7)	0	13 (41.9)	18 (58.1)	9 (29.0)	15 (48.4)	7 (22.6)
T_4 (29)	29 (93.5)	0	0	29 (93.5)	0	0	14 (48.3)	15 (51.7)	0	0	25 (86.2)	4 (13.8)	11 (37.9)	15 (51.7)	3 (10.3)
T_8 (29)	29 (93.5)	0	0	29 (93.5)	0	0	25 (86.2)	4 (13.8)	0	20 (69.0)	9 (31.0)	0	9 (31.0)	13 (44.8)	7 (24.2)

1 = "no problems"; 2 = "some or moderate problems"; 3 = "severe problems". LMP: lidocaine 700 mg medicated plaster. T-0, T-4, T-8: prior to treatment initiation with LMP, 4 and 8 weeks after treatment initiation with LMP, respectively.

after 8 weeks of treatment with LMP, with 86% reporting no problems.

Before treatment, no patients had severe problems for mobility and self-care, whereas 26% and 13% reported some or moderate problems. After 4 and 8 weeks of LMP treatment, none of the patients reported any problems in these dimensions.

Only for anxiety/depression, no changes over time in the proportion of patients across the three categories have been reported. At week 0 and week 8, >20% of patients reported extreme anxiety/depression.

Figures 2 shows, for each of the five domains, the number of patients who reported "No problems", "Some or moderate problems", and "Extreme problems" at baseline, and at week 4 and 8 after LMP application.

When patient satisfaction was measured at week 8, 35.5% of patients were satisfied and 51.6% were very satisfied (Table IV).

Table IV. Patient satisfaction at week 8.

Satisfaction level	No. (%)
Very dissatisfied	0 (0)
Dissatisfied	1 (3.2)
Neutral	3 (9.7)
Satisfied	11 (35.5)
Very Satisfied	16 (51.6)

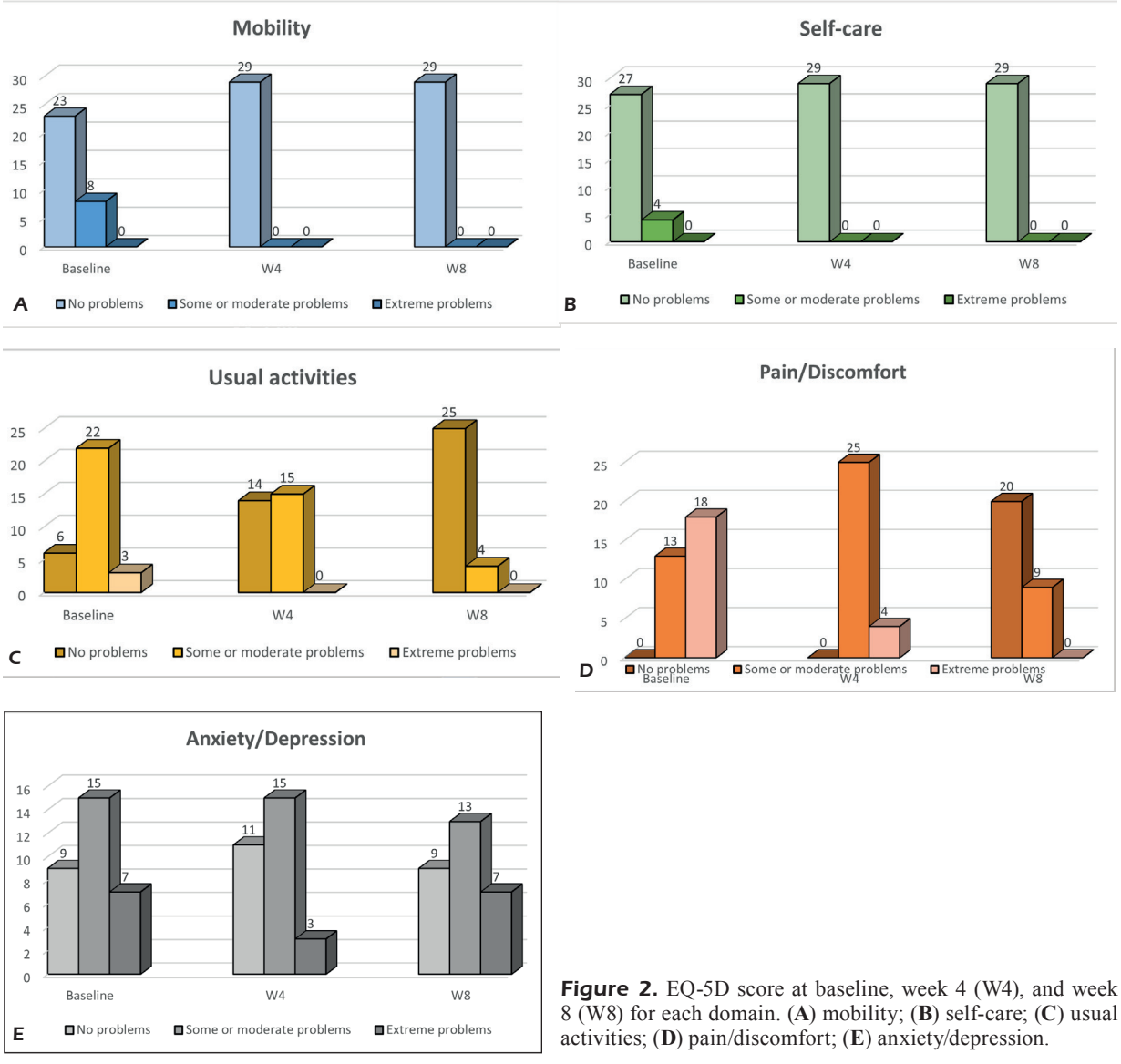

Figure 2. EQ-5D score at baseline, week 4 (W4), and week 8 (W8) for each domain. (**A**) mobility; (**B**) self-care; (**C**) usual activities; (**D**) pain/discomfort; (**E**) anxiety/depression.

Discussion

We report the follow-up of patients diagnosed with PHN and treated in our "Pain Unit" with LMP. The study was retrospective in nature; nevertheless, the use of well-defined selection criteria made it possible to increase the robustness of the study, which allowed to evaluate the impact of LMP on PHN patients' QoL. Furthermore, it also focused on the treatment's effectiveness and safety.

The characteristics of patients enrolled in this study were typical for PHN and consistent with epidemiological data for patients with PHN.

PHN can have a devastating effect on the QoL, with patients experiencing fatigue, anorexia, weight loss, reduced mobility, physical inactivity, sleep disturbance (especially insomnia) and reductions in overall health[12]. In the present study, EQ-5D was used to measure various aspects of QoL in patients treated with lidocaine 700 mg medicated plaster. At all visits after baseline, mean scores for the "mobility", "self-care", "usual activities", and "pain/discomfort" categories increased, showing that treatment with LMP produced patient-assessed improvements in QoL. An overall reduction in pain or discomfort was reported at the end of treatment. Only a few reported some or moderate problems at week 8. A general improvement was reported in the performance of daily activities, and no problems were found regarding mobility and self-care. Almost all patients reported a significant level of satisfaction.

The "anxiety/depression" domain was the only one that did not improve after 8 weeks of LMP treatment. Importantly, 71% of patients reported at least some problems. It is well known that anxiety and depression can further exacerbate pain and sleep disturbance[34]. While the other EQ-5D domains are strongly correlated with the sensation of pain, anxiety and depression can exist independently. The co-existence of depression/anxiety and pain is well known[35]. In the last years, a growing number of studies have tried to investigate the molecular basis of the comorbidity of mood disorders and chronic pain and whether they share similar neural mechanisms, such as imbalance of inhibitory and excitatory neurotransmission or pro-inflammatory and anti-inflammatory cytokines, and polymorphisms of the serotonin transporter[36]. A potential hypothesis could be that anxiety/depression remains unaltered by topical treatment with LMP because chronic pain can cause persistent brain alterations that remain in place even if the pain has disappeared. In this scenario, breaking the circle of chronification of pain with early interventions would be of utmost importance[12]. Given that pain chronification typically results from peripheral and central sensitization, earlier treatment with topical treatments could effectively prevent it[37,38]. Anyway, there is a strong need for further preclinical and clinical studies that address comorbidity between chronic pain and mood disorders and shed light on this association[36].

Our study also showed that the lidocaine 700 mg medicated plaster resulted in consistent and sustained pain relief after 8 weeks of treatment. The decrease in NRS pain scores reflected a statistically significant and clinically important reduction in pain intensity and relevant pain relief was already achieved at week 4. Additional, smaller reductions in pain symptoms occurred during the following weeks. All enrolled patients experienced a pain reduction of at least 50%, representing substantial clinical improvement, irrespective of the age of the patients. 40% of patients in the present study were treated for PHN with analgesic treatment that was insufficiently effective or poorly tolerated before receiving topical treatment.

Moreover, most patients had suffered from neuropathic pain for more than a year before being treated with LMP. A relatively refractory population of patients was thus treated in this trial. Nevertheless, all patients experienced benefits

Moreover, LMP has a good safety and tolerability profile resulting in minimal systemic absorption of lidocaine after topical administration of the plaster[39]. In our study, AEs related to plaster treatment were limited to localized skin reactions occurring in only 12.9% of patients. No patient discontinued the treatment due to these AEs. The number and dosing of co-analgesic medications taken by patients remained stable during the trial.

Limitations

This study has several limitations. It was a retrospective observational study with no control group, conducted on a low number of patients, possibly chosen under a selection bias, of whom compliance was not measured. Lidocaine 700 mg medicated plaster treatment was added to other previous analgesic treatments in 54.8% of patients. It is impossible to appreciate the contribution of each treatment to the observed pain relief and the contribution of the natural course of the conditions. Moreover, there has been no "wash-out" of pre-treatment analgesics, meaning that pain intensity at baseline could thus not be judged without bias, and concomitant medications other than analgesics were

not captured, which may underlie the reasons for lidocaine patch prescriptions. However, it must be considered that none of the patients obtained satisfactory results with previous analgesic therapy and that the number and dosing of co-analgesic medications remained stable during the trial. Last, the 8-week treatment duration is relatively short for this indication, and patients' outcomes beyond 8 weeks were not addressed.

Conclusions

This study shows that lidocaine 700 mg medicated plaster treatment positively impacts PHN patients' pain and QoL already at 8 weeks with a high level of satisfaction, even though anxiety and depression levels remained unchanged in most cases. Anxiety and depression are the results of many biopsychosocial factors, of which pain can be one. Pain relief with LMP was achieved with minimal adverse effects of mainly localized skin reactions of mild to moderate intensity, which never led to treatment withdrawal. This work adds further weight to the growing body of clinical and research evidence concerning the positive benefit-risk profile of LMP for treating PHN.

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Conflicts of Interest
The authors declare no conflicts of interest.

Availability of data and materials
Data will be provided upon reasonable request.

Authors' contributions
Study conception and design: LGG, CA, PS; collection and interpretation of data: LGG, CA, PS; statistical analysis: FC, VP; manuscript drafting: MCP, MBP; manuscript editing: LGG, PS; approval to submit: LGG, CA, FC, MBP, MCP, VP, PS.

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