

# Treatment of localized post-traumatic neuropathic pain in scars with 5% lidocaine medicated plaster

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**Objective:** To evaluate the use of 5% lidocaine medicated plaster (LMP) for treating painful scars resulting from burns or skin degloving.

**Patients and methods:** This was a prospective, observational case series study in individuals with painful scars <70 cm<sup>2</sup> in area, caused by burns or skin degloving. The study included a structured questionnaire incorporating demographic variables, pain evaluation using the numeric rating scale (NRS), the DN4 questionnaire, and measurement of the painful surface area. Patients with open wounds in the painful skin or with severe psychiatric disease were excluded.

**Results:** Twenty-one men and eight women were studied, aged (mean ± standard deviation) 41.4 ± 11.0 years, with painful scars located in the upper extremity (n = 9), lower extremity (n = 19), or trunk (n = 1). Eleven patients (37.9%) had an associated peripheral nerve lesion. The scars were caused by burns (n = 13), degloving (n = 7), and/or orthopedic surgery (n = 9). The duration of pain before starting treatment with lidocaine plaster was 9.7 ± 10.0 (median 6) months. The initial NRS was 6.66 ± 1.84 points, average painful area 23.0 ± 18.6 (median 15) cm<sup>2</sup>, and DN4 score 4.7 ± 2.3 points. The duration of treatment with LMP was 13.9 ± 10.2 (median 11) weeks. After treatment, the NRS was reduced by 58.2% ± 27.8% to 2.72 ± 1.65. The average painful area was reduced by 72.4% ± 24.7% to 6.5 ± 8.6 (median 5) cm<sup>2</sup>. Nineteen patients (69%) showed functional improvement following treatment.

**Conclusion:** LMP was useful for treating painful scars with a neuropathic component, producing meaningful reductions in the intensity of pain and painful surface area. This is the first time that a decrease in the painful area has been demonstrated in neuropathic pain using topical therapy, and may reflect the disease-modifying potential of LMP.

**Keywords:** chronic postsurgical pain, chronic post-traumatic pain, lidocaine medicated plaster, neuropathic pain

## Introduction

Neuropathic pain arises as a direct consequence of injury or disease affecting the somatosensory system.<sup>1</sup> Neuropathic pain may occur as a manifestation of various conditions that cause nerve damage, such as viral infections (postherpetic neuralgia), metabolic disorders (diabetes mellitus), drug-induced toxicity, inflammation, cancer, trauma, and postsurgical complications.<sup>2</sup>

Lidocaine is a local anesthetic that produces nonselective blockade of both open and inactive voltage-dependent sodium channels (NaV 1.7, NaV 1.8, and NaV 1.9) in excitatory membranes responsible for nerve conduction in C and A-δ primary afferent fibers, suppressing the spontaneous and evoked abnormal activity that initiates and sustains neuropathic pain.<sup>3,4</sup> 5% lidocaine medicated plaster (LMP, Versatis®, Grünenthal, Germany), acts peripherally as a noninvasive topical analgesic, combining efficacy

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with minimal systemic absorption, a low risk of interaction with other medicinal products, and an excellent safety and tolerability profile. Several studies have provided evidence for the use of LMP in treating the neuropathic pain associated with postherpetic neuralgia.<sup>5–8</sup> LMP has been included as the first-line treatment for localized peripheral neuropathic pain in many treatment recommendations for the US,<sup>9</sup> Europe,<sup>10</sup> and Latin America.<sup>11</sup> Two years ago, LMP was approved by the Hospital del Trabajador de Santiago Pharmacy Committee for use in patients with post-traumatic pain.

LMP is applied to the most painful area for 12 hours each day and then removed for 12 hours, with no need for titration. The 12-hour dosage interval is based on the results of clinical trials demonstrating that a patch-free interval reduces skin exposure and prevents unwanted local effects induced by continuous occlusion of the affected skin, but provides continuous analgesia for 24 hours.<sup>12,13</sup>

The aim of this study was to evaluate the effectiveness of LMP in patients with painful scars of the post-traumatic/post-surgical neuropathic type, caused by burns, degloving injuries, and surgical incisions.

## Methods

An observational, open-label, clinical case series study was conducted in patients who had occupational diseases or had suffered accidents at work and were seen at the Hospital del Trabajador de Santiago in Chile from October 2008 to September 2009. Inclusion criteria were patients who had scars with a painful area measuring less than 70 cm<sup>2</sup>. Patients with open wounds or severe psychiatric illness were excluded.

A structured protocol was used, addressing demographic variables, diagnoses, causes of pain, and mental health. The DN4 questionnaire<sup>14,15</sup> was used in all patients. This defines neuropathic pain as having a score of 4/10 or above. The painful area was evaluated by measuring the width and length of the region in which the patient felt pain at the time of examination, and a photographic record of the affected area was obtained. In all suspected cases of peripheral nerve injury, a neurophysiologic study was carried out.

The initial dose (number of plasters) of LMP, use of co-analgesics, and concomitant drugs were recorded. In all patients, hypoallergenic adhesive tape (Micropore®, 3M, St Paul, MN) was used to attach the plaster securely to the skin. The results of therapy were expressed as absolute and percentage changes in numerical rating scale (NRS), painful area, sleep quality, regained function, and return to work. Patients were checked monthly, and the protocol described above was used at each consultation. LMP therapy was

considered effective if there was a reduction in NRS score of  $\geq 3$  points or  $\geq 50\%$ , and/or the painful area decreased by  $\geq 50\%$  compared with the start of therapy.

Each LMP contains 700 mg of lidocaine. The amount of lidocaine systemically absorbed is very low ( $3\% \pm 2\%$  of the topical dose applied) and is directly related to the duration of application and the area of skin in direct contact with the LMP. Peak serum levels with a dose of four plasters for 12 or 24 hours, ie, in excess of the recommended dose and duration, are 225 ng/mL and 186 ng/mL, respectively, which is approximately one-seventh the concentration required for an antiarrhythmic effect (1500 ng/mL)<sup>16–18</sup> and 25 times less than the toxic dose (5000 ng/mL).<sup>17,19,20</sup> LMP has been used in patients with heart disease and painful scars with no reports of significant side effects.<sup>21</sup> All adverse reactions have been of mild to moderate intensity. Fewer than 5% of these led to discontinuation of treatment. Patients were informed of this risk and told that, in the event of occurrence, they should discontinue use.

All patients were suitably informed about the characteristics of the medicinal product and its side effects before starting the study, and gave their consent before being included. Side effects and treatment adherence were solicited by direct questioning at each interview. The study was approved by the Hospital del Trabajador de Santiago Ethics Committee.

The analysis of quantitative variables employed the mean, standard deviation, and maximum and minimum values. Qualitative variables were summarized in terms of absolute and percentage relative frequencies. The paired Student's *t*-test was used to compare mean values from the same patients examined at two time points during the investigation.

## Results

### Demographics

The study population consisted of 29 patients (21 men and 8 women) with a mean age of  $41.4 \pm 11.0$  (range 23–62) years. The traumatic injuries were located on the lower limb in 19 cases (65.5%), the upper limb in nine cases (31%), and the trunk in one case. The underlying cause was diagnosed as burns in 13 cases (44.8%), post-surgical scarring in nine cases (31%), and crush and degloving injury of the extremity in seven cases (24.1%).

### Pain evaluation

Involvement of peripheral nerves was observed in 11 patients (37.9%), ie, the superficial radial nerve in three patients, the peroneal nerve in two, the sural nerve in two, and the medial antebrachial cutaneous nerve, the palmar branch of the median nerve, the collateral palmar nerves, and the saphenous

nerve in one patient each. Pain intensity (NRS) at the start of the study was  $6.66 \pm 1.84$  (median 7, range 4–10 points). Fifteen patients (51.7%) had pain scores of  $\geq 7$ . The duration of pain prior to starting LMP treatment was  $9.7 \pm 10.0$  months (median six months, range one month to 2.8 years). In seven patients (24.1%) the duration of pain was less than three months, in 15 (51.7%) it was 3–12 months, and in 7 (24.1%) it was more than 12 months.

### Painful area and doses employed

At the start of the study, the mean size of the painful area was 23 cm<sup>2</sup> (median 15 cm<sup>2</sup>, range 8–70 cm<sup>2</sup>). In all patients, the plaster was applied to the painful area. Five patients used half a plaster and the other 24 used a quarter of a plaster daily.

### Presence of neuropathic pain

Using the DN4 questionnaire, the mean score for the study population was  $4.7 \pm 2.3$  points. Twenty-one patients had a score of  $\geq 4$ , including the 11 patients with a peripheral nerve lesion.

### Comorbidity

Twenty-one patients (72.4%) required treatment for accident-related psychiatric illness. The diagnoses were adjustment, anxiety, depressive, or mixed disorder in 13 cases,

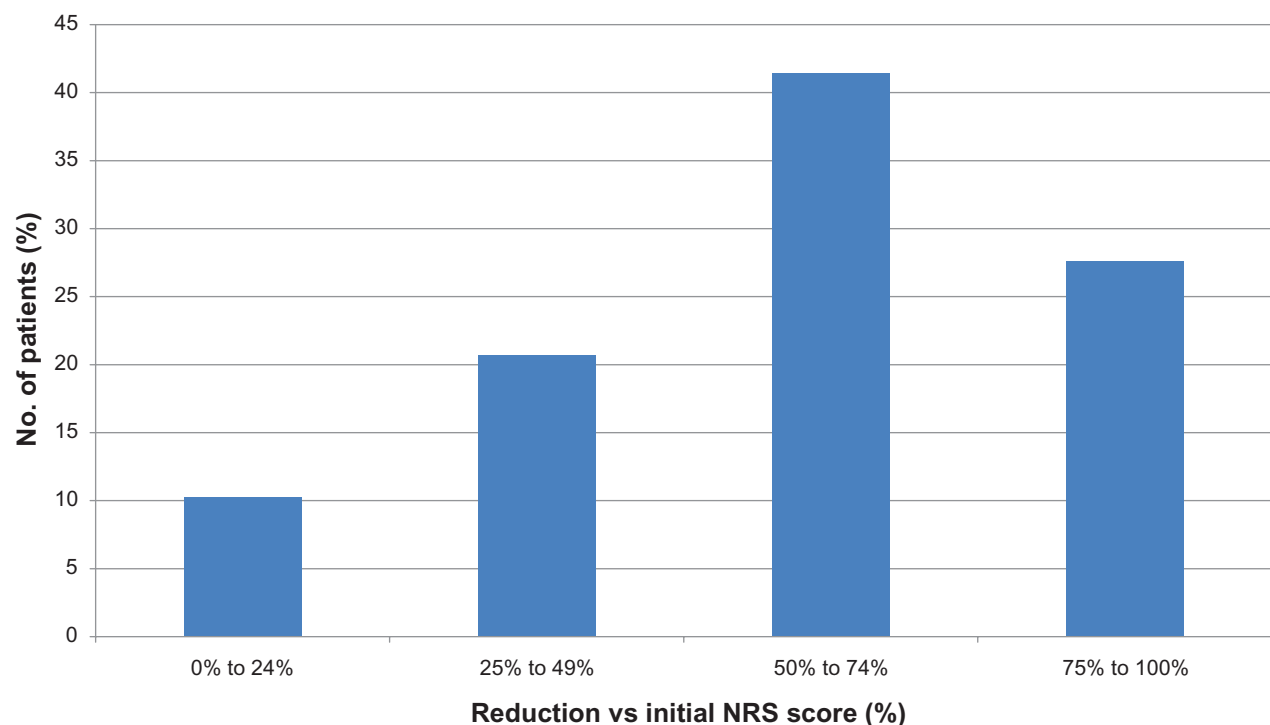
post-traumatic stress disorder in four cases, and major depression in four cases.

### Change in pain

After  $13.9 \pm 10.2$  weeks of treatment (median 11 weeks, range 4–45 weeks), the mean reduction in NRS was  $2.72 \pm 1.64$  points (median 3 points, range 0–5 points). This is equivalent to a reduction of  $58.2\% \pm 27.8\%$  compared with baseline pain intensity (see Figure 1). In 22 patients (75.9%) the NRS score fell by  $\geq 3$  points; in 20 patients (69%), the NRS score was reduced by  $\geq 50\%$  after LMP treatment (see Table 1), and no patient still had an NRS score of  $\geq 7$ . The painful area decreased by  $16.5 \pm 13.7$  cm<sup>2</sup> (median 11 cm<sup>2</sup>, statistically significant by the paired Student *t*-test,  $P < 0.0005$ ). This is equivalent to a mean reduction of  $72.4\% \pm 24.7\%$  (see Figure 2). In 25 patients (86.2%), the painful area was reduced by  $\geq 50\%$  (see Table 1). Three patients (10.3%) noticed a significant improvement in sleep quality, and 17 patients (58.6%) reported significant functional recovery during LMP use (see Table 2).

### Comparison of patients with nociceptive and neuropathic pain

This study relates to painful scars, not postsurgical neuropathic pain, and it is difficult to document a nerve lesion in neuropathic pain associated with a scar. However, the DN4



**Figure 1** Percentage reduction in pain score (NRS) in patients treated with 5% lidocaine medicated plaster (LMP).

**Table 1** Percentage reductions in pain score and painful area in patients treated with 5% lidocaine medicated plaster

Reduction versus initial NRS score (%)	Patients (n, %)	Reduction versus initial painful area (%)	Patients (n, %)
75–100	8 (27.6)	75–100	15 (51.7)
50–74	12 (41.4)	50–74	10 (34.5)
25–49	6 (20.7)	25–49	3 (10.3)
0–24	3 (10.3)	0–24	1 (3.5)
Total	29 (100)	Total	29 (100)

**Abbreviation:** NRS, numeric rating scale.

questionnaire is an adequate clinical tool for differentiating between nociceptive and neuropathic pain. The eight patients (27.6%) with nociceptive pain according to the DN4 questionnaire (score < 4) had moderate to severe pain (NRS = 6) and intense stabbing pain, in one case associated with allodynia.

Before starting treatment with LMP, the duration of pain was shorter in the nociceptive pain group than in the neuropathic pain group (median three months versus seven months), and the painful area was smaller (median 10.8 cm<sup>2</sup> versus 18.0 cm<sup>2</sup>). The NRS scores were similar. The length of treatment until maximum pain relief was shorter in the nociceptive pain group (median 9.2 weeks versus 12 weeks). After LMP treatment, the NRS scores were similar in both groups, as were the percentage of patients that reduced their

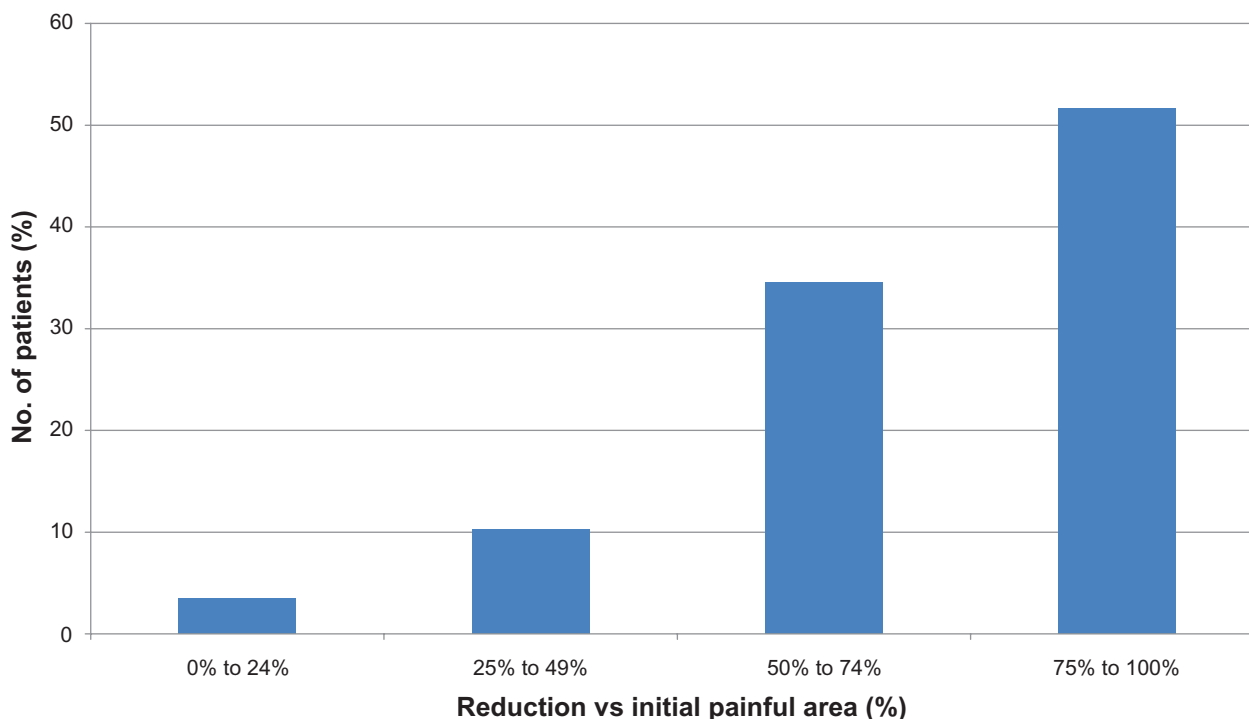
NRS by  $\geq 3$  points, the average size of the painful area, the percentage reduction in size of the painful area, and the percentage of patients with a reduction of  $\geq 50\%$  in the size of the painful area. It can be concluded that there were few differences between the two groups in their response to LMP treatment, and none was significant.

### Occupational impact

Before the pain-related accident, all the patients were in active employment. Twenty-seven patients (93%) returned to work after the accident. In patients who started LMP therapy after going back to work, functional improvement with an impact on occupational performance was observed in 12/15 cases (80%, see Table 3).

### Change in concomitant analgesic medication

Fourteen patients (48.3%) were using oral analgesics, including paracetamol and tramadol, when they began treatment with LMP. No other medication was added after this point. The oral analgesics were progressively withdrawn as the patients achieved pain relief, and by the end of the study 18 patients (62%) were using LMP therapy alone. Given that oral analgesics had been taken previously for at least three months with limited benefit, the improvement in pain relief was considered to be due to LMP therapy. Two patients were



**Figure 2** Percentage reduction in painful area in patients treated with 5% lidocaine medicated plaster (LMP).

**Table 2** Functional improvement in patients treated with 5% lidocaine medicated plaster

Functional aspect showing improvement	Patients (n, %)
Ability to walk	8 (27.6)
Daily life activities	5 (17.2)
Increased tolerance of standing	3 (10.3)
Sleep quality	3 (10.3)
Increased tolerance of upper limb prosthesis use	2 (6.9)
Increased tolerance of trunk flexion	1 (3.5)

taking pregabalin (150 mg/day) when they started LMP; one discontinued its use during the study while the other continued taking it throughout.

## Tolerability

None of the patients in the case series suffered any local or systemic adverse reactions to LMP use.

## Treatment adherence

Patients' adherence to treatment was excellent in all cases.

## Discussion

The presence of chronic pain following trauma or surgery is a common event. The exact frequency, prevalence, and natural history of these painful neuropathies are not yet known.<sup>21</sup> According to Hans et al<sup>21</sup> postoperative/post-traumatic neuropathic chronic cutaneous pain may follow any surgical incision. It is associated with touch-evoked allodynia,

hyperalgesia, and paroxysms of spontaneous (nonevoked) pain that significantly impair the patient's quality of life, and often tends to become chronic.

The analgesic efficacy of LMP has previously been demonstrated in acute and chronic forms of peripheral neuropathy, such as postherpetic neuralgia<sup>22</sup> and diabetic polyneuropathy.<sup>23</sup> To date, two studies have been published on the use of LMP in post-traumatic pain.<sup>21,24</sup> The first<sup>24</sup> reported five cases of severe localized neuropathic scar pain, all of more than one year's duration. After 12–16 weeks, pain intensity was reduced to mild in two cases, and pain ceased completely in another two cases. In one case, pain remained at the same intensity and then ceased spontaneously.<sup>24</sup> The second study<sup>21</sup> evaluated the use of LMP in 40 patients with severe chronic post-traumatic cutaneous pain of surgical and nonsurgical origin. A significant reduction in pain intensity was observed at four and 12 weeks.<sup>21</sup>

The prospective study by Hans et al<sup>21</sup> strongly suggests that LMP offers a novel therapy for postsurgical and post-traumatic localized neuropathic pain syndromes. The authors stressed that the analgesic response developed over a long period. In our study, LMP was effective in managing localized postsurgical and post-traumatic neuropathic pain. The pain relief provided by LMP improved occupational performance in two-thirds of our patients after their return to work. A high level of patient satisfaction was observed, because of ease of use and lack of side effects. Published analyses have shown

**Table 3** Occupational impact of 5% lidocaine medicated plaster in active patients

Case	Time from returning to work to starting LMP (months)	Functional improvement with occupational impact	Previous job	Current job
1	41.6	Working with mouth	Construction worker	Mouth artist <sup>a</sup>
2	39.2	Ability to walk and stand	Telephone line installer	Telephone line installer
3	21.0	Increased functionality of nondominant hand	Advertisement hoarding erector	Advertisement hoarding erector
4	18.9	Increased functionality of nondominant hand	Telephone line repairman	Gardener <sup>b</sup>
5	12.0	Working with percussion tools	Maintenance mechanic	Maintenance mechanic
6	3.3	Sleep quality	Boiler worker	Boiler worker
7	1.9	Ability to walk	Foundry worker	Foundry worker
8	9.7	Increased functionality of dominant hand	Garment presser	Garment presser
9	5.2	Resumption of prosthesis use <sup>c</sup>	Shoe factory worker	Shoe factory worker
10	5.7	Improved tolerance of standing, squatting, going up/down stairs	Senior electrician	Senior electrician
11	6.1	Improved tolerance of standing	Restaurant chef	Restaurant chef
12	2.9	Heavy work with the dominant limb	Transformer factory worker	Transformer factory worker

<sup>a</sup>Amputations at both shoulders, prevented from working in a new job by painful dorsolumbar scar; <sup>b</sup>job changed for reasons unrelated to pain; <sup>c</sup>Wrist disarticulation, unable to use prosthesis because of pain in superficial radial nerve region, underwent surgery three times without success.

**Abbreviation:** LMP, 5% lidocaine medicated plaster.

LMP to be a cost-effective method for treating localized neuropathic pain relative to pregabalin or gabapentin.<sup>25,26</sup> However, further studies are needed to evaluate the impact of LMP and oral therapies in these patients, by comparing savings in the time taken as sick leave.

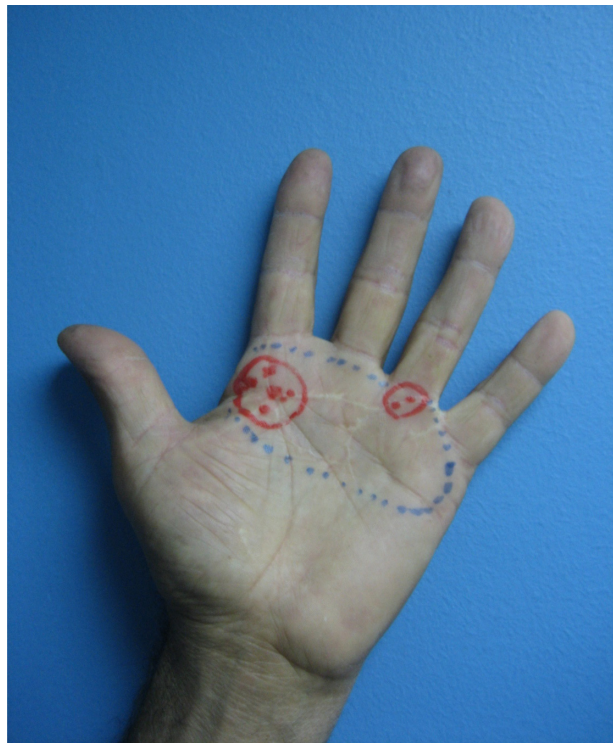
Our series differs from that of Hans et al<sup>21</sup> because our patients had localized post-traumatic pain and were 15 years younger on average. Pain relief was higher in our study, with a 58.2% reduction in pain intensity, rather than 36%. Our study also measured the painful area, which was significantly reduced in patients receiving LMP therapy. LMP has been shown to decrease the area of hyperalgesia induced by capsaicin or sunburn in healthy volunteers,<sup>27</sup> and oral adenosine,<sup>28</sup> mexiletine,<sup>29</sup> and rofecoxib<sup>30</sup> can reduce the painful area, but this is the first time the effect has been demonstrated in patients with neuropathic pain using topical therapy. Such an effect has important functional implications, especially if the painful area is located on the palm of the hand or sole of the foot. LMP may directly affect peripheral sensitization and modulate the impact of neuropathic pain. This could possibly indicate disease-modifying potential, but further investigative studies are needed.

## Conclusion

In conclusion, LMP was shown to be a safe, effective treatment for localised post-traumatic or postsurgical neuropathic pain. Our results also suggest that LMP significantly improves patients' functional level, and is associated with an improvement in occupational performance. However, the study is limited by the small number of patients, a nonrandomized and open design, and lack of a placebo group, so a degree of caution should be exercised when extrapolating from these results.

## Case study

This patient is a 58-year-old male, a mechanic, who suffered a high-voltage burn (12,000 volts) to his left hand which affected the collateral nerves. This trauma produced severe (NRS 8/10), persistent, neuropathic pain (DN4 9/10) in the palm of his hand, accompanied by intense allodynia. The painful surface area (outlined in blue in Figure 3) extended over 21 cm<sup>2</sup>. Pain interrupted his sleep and interfered with his work, preventing him from manipulating the tools that he had used prior to his accident. Over a period of two years and three months, the pain proved resistant to analgesic treatment. A range of analgesic drugs and schemes were tried, both singly and in various combinations, which



**Figure 3** Painful surface area before (blue area) and after (red areas) treatment with 5% lidocaine medicated plaster (LMP).

**Abbreviations:** NRS, numerical rating scale; LMP, 5% lidocaine medicated plaster.

included gabapentin 400 mg/day, tramadol 200 mg/day, meloxicam 15 mg/day, ketoprofen 50 mg/day, and topical diclofenac. The dosage of gabapentin could not be increased owing to intolerance.

At this point, treatment with LMP was started. Five months later, pain intensity had reduced by 63% and the painful surface area had reduced to 4.5 cm<sup>2</sup> overall (areas outlined in red in Figure 3). The red dots indicate discomfort rather than pain (NRS 3/10 or below) and the cross indicates pain with an NRS of 4/10 or above. Allodynia had disappeared, his quality of sleep had improved significantly, and he could now manipulate tools at work without difficulty.

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## Disclosure

The authors report no conflict of interest in this work.

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