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Efficacy and safety of 5% lidocaine-medicated plasters in localized pain with neuropathic and/or inflammatory characteristics: an observational, real-world study

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Abstract. – OBJECTIVE: Based on clinical study results, 5% lidocaine-medicated plaster (5% LMP) is currently recommended for the treatment of localized peripheral neuropathic pain, such as post-herpetic neuralgia (PHN). However, its effective action, as well as the high safety, have indeed led to its use in clinical practice for pain conditions with similar pathophysiological mechanisms. In this study, the efficacy and safety of 5% LMP were investigated in patients with localized pain with neuropathic and/or inflammatory characteristics, such as PHN, post-traumatic/surgical or musculoskeletal pain.

PATIENTS AND METHODS: 503 patients with localized pain treated with 5% LMP were evaluated at baseline (T0), after 30 days (T30) and after 60 days (T60). The primary endpoint was number and proportion of 30% responders at T60, whereas secondary endpoints included number and proportion of 30% responders at T30, mean pain intensity, mean extension of the painful area, dynamic mechanical allodynia and quality of sleep. Evaluations were assessed in all patients and subgroups based on different clinical entities. Concomitant treatments and adverse reactions were also recorded.

RESULTS: 72% and 90% of all patients responded to 5% LMP treatment at T30 and T60, respectively. Comparable results were also obtained in subgroups such as PHN patients (72% and 68% at T30 and T60, respectively), and musculoskeletal pain (73% and 83% at T30 and T60, respectively). The mean pain intensity, as well as the extension of the painful area, significantly decreased during the study, in all patients and each subgroup. In addition, secondary endpoints significantly improved at each time-point compared with baseline, in all groups.

CONCLUSIONS: The effectiveness and safety of 5% LMP were shown in localized pain conditions such as neuropathic and, importantly, in musculoskeletal pain, a condition never investigated with this product. This field-practice study suggests that topical pain-reducing strategies such as 5% LMP could be effective in neuropathic and/or inflammatory, localized pain conditions.

Key Words
Localized neuropathic pain, Inflammatory pain, 5% lidocaine-medicated plaster.

Introduction

Pain represents a major healthcare burden[1]. Basically, pain could be classified in nociceptive pain (occurring as a consequence of damaged tissue or disease, in the presence of a functionally intact nervous system), neuropathic pain, caused by a somatosensory system disease or damage, and mixed pain, characterized by a coexistence of nociceptive and neuropathic pain[2]. From 6% to 8% of the general population experience chronic pain with neuropathic characteristics[3]. The most common pain descriptors reported by patients included lancinating (75.6%), burning (68.3%), pins-and-needles (65.9%), electric shock (64.6%), numbness (65.9%) and tingling (59.8%)[4]. Several peripheral or central neuropathic conditions could

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lead to neuropathic pain, including posttraumatic neuralgia, post-herpetic neuralgia (PHN), diabetic peripheral neuropathy (PDN), spinal cord injury, multiple sclerosis, stroke, chronic low back pain[5]. According to the etiology, the distribution on the body areas of the neuropathic pain can greatly vary. In most neuropathic pain conditions (around 60%), pain is clearly localized in a circumscribed area of the body (localized neuropathic pain)[6]. In order to support physicians, a definition of localized neuropathic pain (LNP) was proposed in 2012, based on the International Association for the Study of Pain (IASP) definition of neuropathic pain and on 13 reference articles, stating it as 'a type of neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain'[6].

Since the majority of chronic pain patients are managed and treated by primary care physicians and non-pain specialists[7], this definition could help identify patients who may benefit from topical treatment. Particularly in LNP patients with a superficial pain generator (such as post-traumatic neuralgia and PHN), the topical administration offers advantages over the systemic administration, reducing the risk of systemic adverse reactions, drug-drug interactions, and overdose[8,9]. Furthermore, chronic, localized pain characterized by peripheral inflammation and/or somatosensory system damages, with a superficial pain generator [such as musculoskeletal (MSK) pain], could also benefit from treatment with topical local anesthetics[10].

Among different treatment options, topical 5% lidocaine-medicated plaster (5% LMP; Verasatis®, Grunenthal Ltd, Uxbridge, UK) is currently recommended as a first-line treatment for localized (or focal) peripheral neuropathic pain[11]. To date, 5% LMP has been registered in approximately 50 countries worldwide for the symptomatic relief of neuropathic pain caused by PHN; in 11 of these countries, it is also approved for the treatment of LNP[12]. Although there is strong scientific evidence supporting 5% LMP in the treatment of LNP and in clinical practice it is also largely used to treat inflammatory pain characterized by a superficial pain generator, further evidence on its effects in these pain conditions appears advocated.

In this observational, prospective study, we evaluated the efficacy and safety of 5% LMP in patients with localized pain, including musculoskeletal (MSK) pain, a condition never investigated with this product.

Patients and Methods

This prospective, descriptive observational study was conducted at 10 Italian centers specialized in the treatment of pain conditions, on adult subjects with localized pain conditions including MSK pain. Patients were treated with 5% LMP.

All participants gave written informed consent before enrolment in this study. All procedures, performed in accordance with the Good Clinical Practice, received local Ethics Committee approval according with the latest version of the Declaration of Helsinki.

Each enrolled patient was subjected to clinical examinations, at the following time-points: at the beginning of the treatment with 5% LMP (T0), after 30 days (T30) and after 60 days (T60) from the first application.

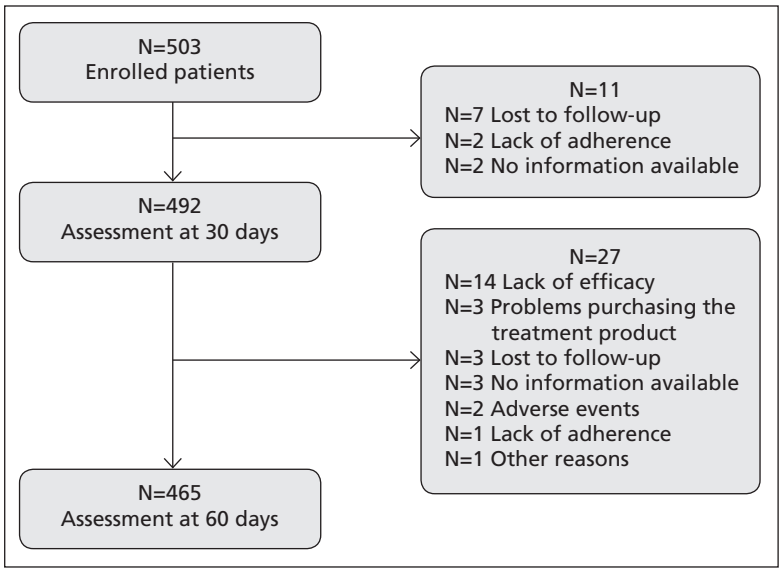
The primary endpoint was the number and proportion of subjects (responders) whose pain intensity assessed by a Numerical Rating *Scale* of pain (*NRS*) decreased of at least 30% at the end of the study (T60) compared with baseline (T0). NRS for pain is a patient-rated 11-point numeric scale with 0 representing "no pain" and 10 representing "worst pain imaginable".

The secondary endpoints were:

— Number and proportion of subjects (responders) whose pain intensity assessed by a *NRS* decreased of at least 30% at T30 compared to baseline (T0);
— Mean pain intensity as measured by NRS for pain at each time-point;
— Mean extension of the painful area (in cm^2) at each time-point;
— Number and proportion of patients with *dynamic mechanical allodynia* at each time-point;
— Number and proportion of patients with a poor quality of sleep at each time-point;
— Number and proportion of patients with a Douleur Neuropathique 4 (DN4) questionnaire score ≥4;
— Clinical Global Impression of Improvement (CGI-I);
— Use of analgesic concomitant treatments.

Primary and secondary endpoints were evaluated in all patients and subgroups of patients with specific clinical entities. In particular, three subgroups were analyzed: PHN patients, subjects with post-traumatic/surgical neuralgia and individuals with superficial MSK pain. Adverse reactions were also recorded.

Figure 1. Study design.



Statistical Analysis

Descriptive statistics were used to summarize basal characteristics. Comparisons of numerical data were performed by ANOVA test for repeated measures, with a post-hoc Bonferroni's correction. Categorical data differences were evaluated by McNemar test. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.4 software.

Results

In total, 503 patients were enrolled (Figure 1). Their baseline characteristics are depicted in Table I.

The most common site of pain was chest (n = 164, 33%), followed by lower limb (n = 101, 20%) and craniofacial area (n = 60, 12%). Overall, 13 sites of pain were reported (Table II). The majority of patients experienced a pain lasting 6-24 months (n = 229, 46%), 65 patients (13%) suffered from pain from > 24 months and 98 patients suffered from pain lasting lower than 3 months (19.5%). At each time-point, most of patients used a range of 1-2 5% LMP and nobody used more than 3 5% LMP during the study.

The numbers and proportions of responders in the whole study population and in each clinical entity subgroups are summarized in Figure 2. In

Table I. Study population details.

	Study population (n=503)
Age (years), mean (SD)	67.6 (13.7)
Range	17-93
Females, n (%)	316 (62.8)
Etiology of pain, n (%)	
Post-herpetic neuralgia	208 (41.4)
Post-traumatic/surgical neuralgia	159 (31.6)
Musculoskeletal pain (rhizarthrosis, back pain, gonarthrosis)	31 (6.2)
Cancer pain	29 (5.8)
Trigeminal neuralgia	22 (4.4)
Diabetic peripheral neuropathy	18 (3.6)
Others localized neuropathic pain (entrapment neuropathy, Morton's syndrome, cervical radiculopathy, intercostal neuralgia)	36 (7.2)

SD: standard deviation.

Table II. Pain sites.

Pain sites	N	%
Abdominal area	16	3.2
Abdominal-Pelvic area	30	6.0
Anogenital area	2	0.4
Lower limb	101	20.1
Upper limb	46	9.2
Neck-Shoulder – Upper limb	39	7.8
Neck-Shoulder – Upper limb-Thorax	2	0.4
Craniofacial area	60	11.9
Lumbar area	7	1.4
Lumbosacral area	22	4.4
Lumbosacral area – Lower limb	11	2.2
Thoracic area	164	32.6
Thoracic-Abdominal area	3	0.6
Total	**503**	**100**

particular, at the end of the study (T60), 442 out of 494 (90%) patients resulted responders to 5% LMP treatment (95% IC: 86% – 92%).

The mean pain intensity significantly decreased during the study, in all patients and in each subgroups (Figure 3). Compared to baseline values, the mean intensity decreased of 43%, 41%, 44%, 36% at T30 and of 60%, 59%, 58%, 48% at T60 in all patients, PHN patients, subjects with post-traumatic/surgical neuralgia and MSK pain patients, respectively. The extension of the painful area also significantly decreased during the study, in all group evaluated, with minor extension in patients suffering from MSK pain (Figure 4). All secondary endpoints, such as patients with dynamic mechanical allodynia, quality of sleep and patients with DN4 questionnaire score ≥ 4, significantly improved at each time-point compared with baseline, in all groups (Table III). Of note, at baseline, 92.3%, of patients resulted positive for neuropathic pain (assessed by the DN4 questionnaire); on the other hand, in the subgroup of patients suffering from MSK pain this percentage was significantly lower (66.7%) (p <0.01). The physician's global impression of improvement (CGI-I) was positive for 91% of patients at T30, and for 92% of patients at T60.

At each time-point, most patients reported to use 1-2 concomitant analgesic treatments. The median number of concomitant medications used decreased from 1.4 at T0 to 1.0 at T60. Consequently, the number of patients who did not need further concomitant treatment to control pain increased from 15% to 40%. Table IV shows the concomitant analgesic medication used in this study.

Overall, 38 patients prematurely discontinued treatment; the most common reason for treatment discontinuation was lack of efficacy (37%), 2 drops out occurred for adverse reactions (skin rush to the application site). During the study, 24 out of 503 (5%) patients experienced adverse events. Among 33 adverse events reported, the most frequent was sleepiness (45%), probably due to the concomitant treatment with gabapentinoids, followed by burning (12%) and itching (9%).

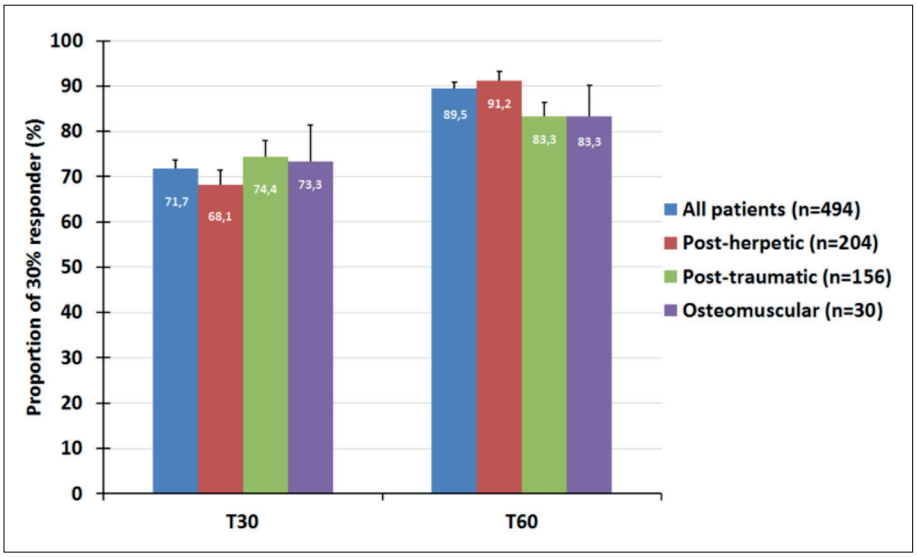


Figure 2. Number and proportion of subjects (responders) whose pain intensity decreased of at least 30% compared to baseline, in all study population and by clinical entity.

Table III. Treatment outcomes for the overall study population and by clinical entity.

	Time-points		
	T0	T30	T60
All patients (n=494)			
– Dynamic mechanical allodynia, n (%)	360 (72.8)	168 (34.0)**	61 (12.4)**
– Poor quality of sleep, n (%)	353 (71.3)	114 (23.1)**	41 (8.3)**
– DN4 questionnaire score ≥ 4, n (%)	456 (92.3)	254 (51.4)**	79 (16.0)**
Post-herpetic neuralgia (n=204)			
– Dynamic mechanical allodynia, n (%)	168 (82.4)	89 (43.6)**	37 (18.1)**
– Poor quality of sleep, n (%)	138 (67.6)	53 (26.0)**	22 (10.8)**
– DN4 questionnaire score ≥ 4, n (%)	194 (95.1)	117 (57.4)**	34 (16.7)**
Post-traumatic/surgical neuralgia (n=156)			
– Dynamic mechanical allodynia, n (%)	96 (61.5)	34 (21.8)**	16 (10.3)**
– Poor quality of sleep, n (%)	109 (69.9)	33 (21.2)**	10 (6.4)**
– DN4 questionnaire score ≥ 4, n (%)	145 (93.0)	86 (55.1)**	30 (19.2)**
Musculoskeletal pain (n=30)			
– Dynamic mechanical allodynia, n (%)	18 (60.0)	7 (23.3)**	1 (3.3)**
– Poor quality of sleep, n (%)	21 (70.0)	6 (20.0)**	2 (6.7)**
– DN4 questionnaire score ≥ 4, n (%)	20 (66.7)	2 (6.7)**	1 (3.3)**

Table IV. Concomitant analgesic treatments.

Concomitant analgesic treatment	T0		T30		T60	
	N	%	N	%	N	%
Antidepressants	51	10.2	73	14.6	67	13.4
Corticosteroids	9	1.8	5	1.0	8	1.6
NSAIDs	56	11.1	17	3.4	6	1.2
Gabapentinoids	203	40.4	175	34.8	154	30.6
Opioids	298	59.3	276	54.8	202	40.3
Paracetamol	104	20.7	83	16.5	65	12.9

NSAID: nonsteroidal anti-inflammatory drugs

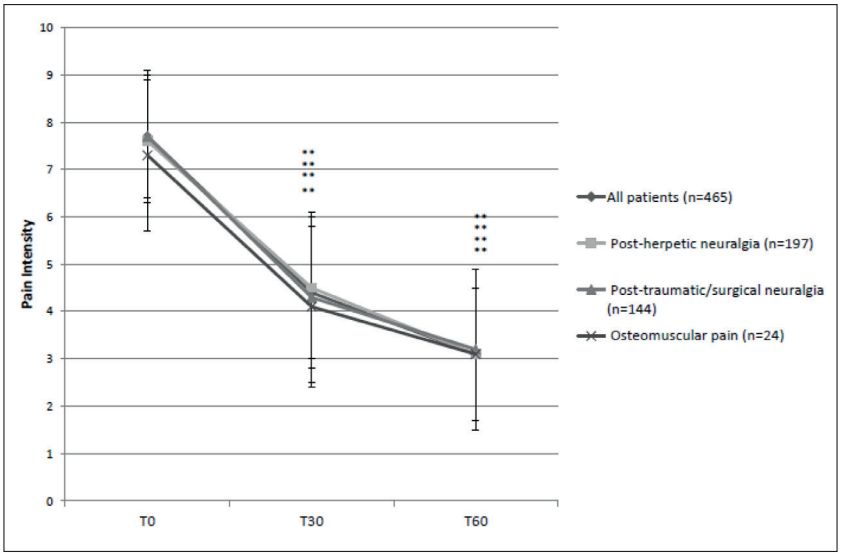


Figure 3. Changes of pain intensity in overall population and by clinical entity. ** $p<0.01$.

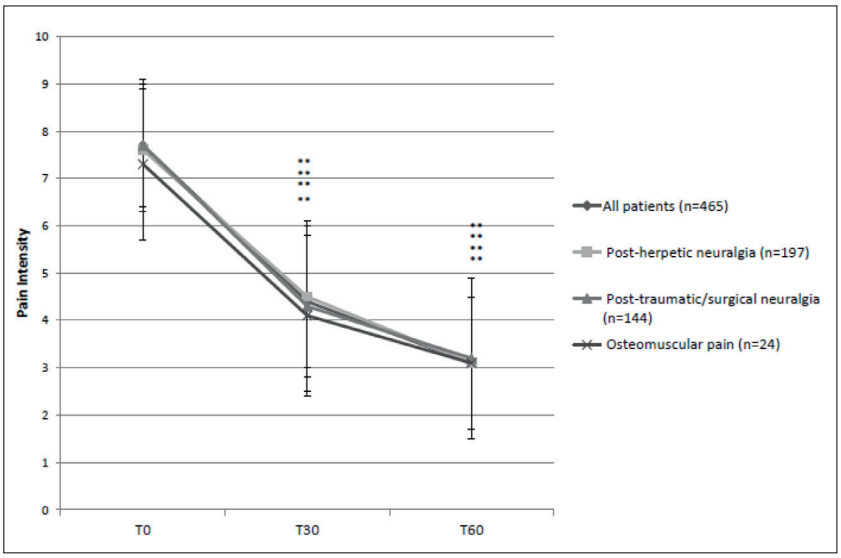


Figure 4. Changes of painful area extension in overall population and by clinical entity. ** $p<0.01$; *$p<0.05$.

Discussion

Neuropathic pain conditions can severely impair physical functioning and daily activities[13], leading to loss of autonomy and depression. They represent a social burden that markedly impact on patients' quality of life and that is likely to increase with aging population in the future[14].

In addition, patients suffering from neuropathic pain are often poorly responsive or undertreated with appropriate pharmacotherapy, and as a consequence many patients are not satisfied with their treatment[15]. Given the heterogeneity among different neuropathic pain conditions and the numerous mechanisms underlying pain generation[16,17], the management of neuropathic pain requires a complex and multidimensional approach. In clinical practice, non-responsive pain conditions are usually managed with medication known to be effective for other pain conditions with similar pathophysiological mechanisms.

Although 5% LMP is only licensed for the treatment of neuropathic pain symptoms associated with previous PHN, its effective action as well as the high safety have indeed led to a large use in clinical practice as first-line therapy in LNP, supported by international guidelines and recommendations[7,12,18,19]. In this study, the efficacy and safety of 5% LMP were investigated in patients with localized pain with neuropathic and/or inflammatory characteristics. Overall, the percentage of patients who experienced at least 30% improvement in pain intensity (30% responders) was 72% and 68% in all patients and in PHN patients, respectively, after 30 days of treatment; at the end of treatment (T60) it reached 90% and 91% respectively. These data strongly suggest that despite significant results are reachable after only 30 days of treatment, continued therapy for at least 60 days, consolidates and improves patient outcome. Comparable results were also obtained in subgroups of patients suffering from other LNP and also in localized inflammatory MSK pain, (73% and 83% at T30 and T60, respectively). Accordingly to previous studies on LNP patients[20-22], we observed that treatment with 5% LMP significantly reduced the painful area in patients with localized pain conditions with neuropathic features. Similar changes, although much less evident, were also detected in patients with MSK pain. The mean pain intensity similarly decreased in all subgroups, at each time-points. Furthermore, the decrease in pain intensity was also translated into improvements in functioning (namely quality of sleep) for all patients and subgroups analyzed. Of note, at baseline 66.7% of MSK patients reported a DN4 questionnaire score ≥ 4; these data suggested that in our study population the MSK pain is mainly a mixed pain including nociceptive and neuropathic components. Management of MSK pain with 5% LMP significantly decreased the number of patients with a positive DN4 questionnaire score, indicating that this topical treatment is effective also in alleviating pain conditions with mixed origin.

In fact, lidocaine is a voltage-gated sodium channel inhibitor that acts by targeting sodium channel isoforms, namely Nav1.7 and Nav1.8, responsible for the ectopic hyper-excitability of small impaired peripheral nerve fibers (A delta and C fibers), resulting in abnormal sensory phenome-

na such as pain[23,24]. Recent studies indicated that ion channel overexpression and hypersensitization are underlying mechanisms of both inflammatory and neuropathic pain conditions , suggesting that pain-reducing strategies based on channel modulation (such as lidocaine) could also be effective in mixed pain[10,25]. In addition, lidocaine has been shown to exert immunoregulatory effects on T cells[26] as well as to inhibit nitric oxide production by activated macrophages[27]; therefore this drug could also suppress mediators of inflammatory pain. Another potential mechanism of peripheral action of lidocaine is the desensitization of TRPV1 and TRPA1 channels that could be likely associated with the analgesic, non-anesthetic effect of this drug[28,5].

The promising results here obtained by lidocaine plasters in MSK pain confirms the potential inhibition of mixed pain with inflammation-related features[29,30]. However, further investigations and controlled studies using active comparators are needed to better characterize the effects of these topical medications in MSK pain conditions.

Conclusions

Here we confirmed the effectiveness and safety of 5% LMP in numerous LNP conditions such as PHN and post-traumatic/surgical neuralgia. Of note, we showed that this medication exerted beneficial effects also in MSK pain with values comparable to those obtained in others localized pain conditions with superficial pain generator.

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Conflict of Interests

CLP has served as consultant for MUNDIPHARMA, TEVA, Kiowa Kirin and Molteni. The other Authors declare no conflicts of interest.

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