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Efficacy and tolerance of Lidocaine 5% patches in neuropathic pain and pain related to vaso-occlusive sickle-cell crises in children: a prospective multicenter clinical study

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Abstract

Background: The management of neuropathic pain and pain related to bone vaso-occlusive crises in sickle-cell disease remains challenging in children. Lidocaine 5% patches are recommended in adults for neuropathic pain treatment, but they are not recommended in children. The purpose of this study was to assess the efficacy and tolerance of lidocaine 5% patches in pediatric inpatients.

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Methods: This prospective multicenter single-arm phase II aimed to assess the use of lidocaine 5% patches in 6 to 21 years old pediatric patients suffering from neuropathic pain or superficial bone vaso-occlusive crises. Patches were applied on the painful area for 12 hours a day. The primary endpoint was the proportion of inpatients with significant pain relief defined as a decrease of at least two points on the Visual Analogue pain Scale measured at 12 hours after patch placement (12h-VAS) during at least two consecutive days.

Results: The 12h-VAS score decreased by at least two points (≥2p-decrease) during two consecutive days in 48.6% of patients (95%CI [33.8%;-[). Only 7.7% of patients experienced grade 1 or grade 2 toxicities.

Conclusion: Although lidocaine 5% patches decreased pain's intensity in nearly half of enrolled patients with an excellent tolerance, the efficacy endpoint was not reached. Further studies should consider a more refined selection of the experimental population to assess lidocaine 5% patches efficacy in the pediatric population.

Keywords: Lidocaine; Neuropathic pain; Vaso-occlusive sickle-cell crisis pain; Pediatrics.

INTRODUCTION

Neuropathic pain defined as a pain initiated or caused by a primary lesion or dysfunction in the nervous system, is frequently associated with and/or related to anti-cancer treatments.[1,2] Neuropathic pain is particularly described in the aftermath of a cancer treatment and may be a sequel of chemotherapy, radiotherapy and/or surgery.[3] Neuropathic pain can impair quality of life through suffering and reduced ability to perform activities of daily living.[4-6] Neuropathic pain have rarely been examined in children and the management of pain in pediatrics is usually extrapolated from adults. Anti-epileptics (gabapentin) or tricyclic antidepressants (amitriptyline) are commonly used in children either associated or not with level II or III analgesics, although no rigorous assessment of these therapies has been done so far in pediatrics.[7,8] Fearing significant risks and side-effects of drug interactions, especially in pediatric oncology, neuropathic pain is often undertreated in children.

The French Society for Pain Evaluation and Treatment recommends lidocaine 5% patches (700 mg/patch) as initial treatment of neuropathic post-herpetic pain in adults.[9,10] This treatment is known to be efficient against such specific pain and well-tolerated.[11-13] Lidocaine acts on the peripheral nerve through a selective blockade of sodium channels (allosteric coupling of lidocaine to the voltage sensors) along A and C nerve fibers known to be the main fibers disseminating pain. The effect of lidocaïne on sodium channels results in a stabilization of neuronal membranes inducing a pain relief.[14,15] Moreover, lidocaine might inhibit the local nitric oxide

production and reduce the inflammation of suffering tissues in the area of patch application.[16] Recent publications assumed the existence of a neuropathic component in pain induced by superficial bone vaso-occlusive crises in sickle-cell disease. Molecular and neurobiological mechanisms leading to and maintaining neuropathic pain in this illness have been reported.[17,18] We consequently hypothesize a potential efficacy of lidocaine 5% patches in patients with superficial bone vaso-occlusive crises through nerve ending stabilization around the periosteum and alleviation of the associated inflammation.

Lidocaine 5% patches are not labelled in pediatric population and no recommendation exists regarding their use in patients younger than 18 years. Nayak and colleagues reported their utilization in five adolescents with chronic localized neuropathic pain ; symptoms were thoroughly evicted in four patients with good clinical tolerance.[19] A prospective study conducted in fourteen pediatric patients suffering from burn sequelae showed a significant efficacy in 11 of the 12 patients, through a decrease in the mean pain intensity on FACES scale from 6.8 to 0, and a decrease in the mean Neuropathic Pain score in 4 questions (DN4) from 6 to 2.3, without any adverse reactions.[20]

This study aims to evaluate the proportion of patient with significant pain relief after 12 hours of lidocaine 5% patch application during two consecutive days, in a pediatric population suffering from localized neuropathic pain or superficial sickle-cell vaso-occlusive crises.

METHODS

Study design

This study was a prospective, multicenter, single-arm phase II trial evaluating the efficacy and safety of lidocaine 5% patches in pediatric inpatients suffering from neuropathic pain or superficial sickle-cell vaso-occlusive crises.

The protocol was approved by Ethics Committee Lyon Sud-Est IV and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation on Good Clinical Practices guidelines (GCPs). All children and their parents provided suitable written informed consent (one for parents, one for children less than 12 years old, and one for teenagers and young adults) before enrollment. The clinical trial was registered with ClinicalTrials.gov, NCT01314300.

Eligibility criteria

Children and young adults aged from 6 to 21 years old suffering from either neuropathic pain in an oncologic setting, or localized and superficial pain due to vaso-occlusive bone crises in sickle-cell patients, insufficiently relieved by the commonly used treatments (level II or III analgesics, and/or anti-epileptics, and/or neuroleptics) were eligible. The DN4 score had to be ≥4.[21] Exclusion criteria were Glasgow score <12, clinical conditions not allowing Visual Analogue Score (VAS) self-assessment, a wide painful area regarding to body surface area (i.e. greater than the recommended surface of one patch for a body surface area <1m², of two patches for a body surface between 1 and 1.5m², or of three patches for a body surface area >1.5m²), and any contraindication for the use of lidocaine 5% patch as defined in summary of product characteristics.

Interventions

The lidocaine 5% patches (Versatis®, Grünenthal GmbH, Aachen, Germany) for cutaneous application consists of a hydrogel base stuck to a polyethylene terephthalate support covered with a protective film of polyethylene terephthalate.[22] Each plaster, supplied in 10 by 14cm size and containing 700 mg of lidocaine, was applied to the painful area (the most painful one in case of several painful areas) for 12 hours per day (12 hours application then 12 hours without patch), and for at least three consecutive days. The patch was applied on intact skin, not irritated, not injured, to more thoroughly cover the painful area with the number of patches defined according to the size of the painful area and the patient's body surface (one patch maximum for a body surface area <1m², two patches for a body surface between 1 and 1.5m², and three patches for a body surface area >1.5m²). If necessary, the patch could be cut to fit the painful area before removing the protective film. The pain score was assessed by a 100 mm-Visual Analogue Score (VAS) self-assessment graduated from 0 (no pain) to 10 (maximal pain) at patch application (t0), at 6 hours (t6), and at 12 hours (t12) post application during three consecutive days. The analgesic treatments prescribed before the inclusion was not changed during the three days of evaluation unless absolutely required. In case of significant increase in pain during the three days (i.e. at least two points increasing in VAS score), the use of additional level II or level III analgesics, antiepileptics, or antidepressants was allowed and collected.

Outcomes measures

The primary outcome was the proportion of patients with a significant pain score decrease i.e. difference in VAS pain score of at least two points between t0 and t12 (12h-VAS ≥2p-decrease) during at least two out of the three consecutive days of treatment.

The secondary outcomes were the proportion of patients with VAS pain score decrease of at least two points between t0 and t6 hours (6h-VAS ≥2p-decrease) in at least two consecutive days out of the three days of treatment, and tolerance. Adverse events (AEs) were graded according to the National Cancer Institute-Common Terminology Criteria of Adverse Events (NCI-CTCAE) version 4.0.

To note, the VAS pain scores equal to 0 or 1 at t0 for the Day 2 (D2) or the Day 3 (D3) with no VAS increase at t6 or t12 were considered as a success on that day.

Statistical analysis

The sample size was calculated using the Fleming-A'hern single-stage design[23] assuming that the proportion of patients with a 12h-VAS ≥2p-decrease during at least two of the three consecutive days following patch application should result in at least 60%. A rate of 60% or less would mean that the benefit in pain relief is not confirmed. This assumption was based on a retrospective study conducted in 2009-2010 in a pediatric, adolescent, and young adult population of 14 patients (personal communication) suffering from localized neuropathic pain and superficial sickle-cell vaso-occlusive crises in the Institute of Pediatric Hematologic and Oncology, Lyon, France. The threshold of two points was used in agreement with a pediatric study published by Mc Conahay.[24] Assuming a 5% one-sided alpha and 85% power, 39 patients had to be enrolled. A minimum of 29 successes was required to consider the lidocaine 5% patches as promising. Results were expressed as a proportion of patients with its confidence interval (CI). To conform to study design, primary endpoint was associated with a unilateral 95%CI, while bilateral 95%CI was used for the other parameters. In case of hospital discharge prior to D3, the cause of discharge was collected. In the complete lack of reported pain, we assumed that all subsequent VAS pain scores after discharge were 0. Adverse event rates were reported with a 95%CI.

Additional exploratory analyses using VAS scores on D1 were performed. Box-plots were used to explore VAS scores changes between t0 and t6, and between t0 and t12, and the Wilcoxon signed rank test was used to test if these differences were significant. Proportions (95%CI) of patients with a VAS ≥2p-decrease, or with a pain intensity decrease greater than 20%, between t0 and t6, and t0 and t12, were also computed. The association between the absolute variations in VAS score (t0-t6 and t0-t12) with the type of pain (sickle-cell vaso-occlusive crises pain and neuropathic pain) were tested with the Mann–Whitney U test. In order to explore a potential relationship between VAS decrease and another additional analgesic treatment, the association of a VAS score ≥2p-decrease between t0 and t6, and between t0 and t12, with another additional medication's use was tested with a Fisher's exact test.

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Between July 2011 and July 2014, 40 patients were enrolled in four authorized pediatric French centers and 39 patients were evaluable (all pain assessment data missing for one patient). Demographic and clinical characteristics are detailed in Table 1. The mean age was 12.7 ±3.5 years, and 18 (46%) patients were male. The most common type of pain was sickle-cell vaso-occlusive crises pain observed in 23 (59%) patients. The number of painful areas extended from one (n=23, 61%) to six areas (n=1, 3%). Pain was localized in the thighs in 10 (27%) patients, in vertebrae in 10 (26%), and in the legs in 9 (24%) patients. Pain characteristics are detailed in Table 2. At inclusion, 19 (51%) patients were treated with level I analgesics, 19 (50%) with level II, and 16 (42%) with level III. Antiepileptics were used in 16 (42%) patients, and antidepressants in 2 (5%) patients.

Treatment

The mean duration of treatment was 5 ±4 days. Thirteen (33%) patients had a patch application for two to 11 additional days. The mean duration of patch application was 12.7 ±2.1 hours on the first day (D1), 12.9 ±2.7 hours on D2, and 11.5 ±3.1 on D3. The duration of patch application (12h a day) was not strictly respected in seven patients for "respect of the child's sleep" (n=4), "oversight" (n=2). The median (min-max) number of concomitant treatments for pain management was 3 (2-6). Thirty-five (89.7%) patients received analgesics: 14 (35.9%) received level III analgesics, 17 (43.6%) level II, and 4 (10.3%) level I. Fifteen (38.5%) patients received antiepileptics, and 3 (7.7%) patients were treated with antidepressants. Eight (20%) patients received additional analgesics at D1 and 11 (28.2%) patients received additional analgesics at least once during the three days.

Ten (26%) patients were prematurely discharged from the hospital before D3, including 8 (21%) early discharges due to complete pain relief. To note, one patient returned home on family request with his patch and no data was subsequently collected, and one patient with no patch applied on D3 due to an oversight by the healthcare team.

Efficacy and Safety

In the 39 evaluable patients, 35 patients were evaluable for primary endpoint (missing data, n=4), and 32 for secondary outcome in term of efficacy (missing data, n=7). A 12h-VAS ≥2p-decrease was observed in 48.6% (95%CI [33.8%,-[) of patients during two consecutive days.

As secondary endpoint, a 6h-VAS ≥2p-decrease was observed in 46.9% (95%CI [29.1%-65.3%]) of patients during two consecutive days (Table 3). A 12h-VAS ≥2p-decrease was observed in 59% of patients at Day 1, 54% on Day 2, and 67% on Day 3.

Three (7.7%, 95%CI [1.6%-20.9%]) patients experienced at least one grade 1 or 2 adverse event with only two events possibly related to the patch application (one localized erythema and one pruritus at the application site). One generalized skin eruption was recorded but assessed as unlikely related to treatment. No serious adverse event was observed (Table 4).

Exploratory analyses were performed on Day 1. The median (min-max) VAS pain score was 5 (2-10) at t0, 4 (0-8) at t6, and 4 (0-9) at t12 (Figure 1). VAS pain scores were significantly reduced between t0 and t6 (p=0.0001), and between t0 and t12 (p=0.0001). Nineteen (57.6%, 95%CI [39.2%-74.5%]) patients had 6h-VAS ≥2p-decrease, and 23 (59.0%, 95%CI [42.1%-74.4%]) patients had a 12h-VAS ≥2p-decrease (Table 3). To note, 25 patients (64.1%; 95%CI [47.2%-78.8%]) had a 12h-VAS score decrease of greater than 20%, and 20 patients (60.6%; 95%CI [42.1%-77.1%]) had a 6h-VAS score decrease of greater than 20%. The VAS score absolute variation between t0 and t6 and between t0 and t12 was not significantly related to the type of pain (p=0.2721 and p=0.5986 respectively). Moreover, 6h-VAS and 12h-VAS-≥2p-decrease was not significantly associated with additional medication's use (p=0.3631 and p=0.2349 respectively).

DISCUSSION AND CONCLUSION

Our study shows that the application of lidocaine patches during three consecutive days in children suffering from neuropathic pain or pain induced by sickle cell disease allows a decrease of at least two points in VAS score 12 hours after patch application (12h-VAS ≥2p-decrease) in 59% of patients at Day 1, 54% on Day 2, and 67% on Day 3. The proportion of patients experiencing 12h-VAS ≥2p-decrease during two consecutive days is reduced to 48.6% which prevent us to conclude to the positivity of the study. To note, 64.1% and 60.6% of patients experienced respectively a 6h- and a 12h-VAS score reduction greater than 20% on the first day. Since

the patch can be used more than three days, a potential cumulative effect in pain relief cannot be excluded. However, this question still need to be explored.

Neuropathic pain in children is usually observed as pain associated in the context of complex clinical situation, especially severe neurological disorders and diseases or cancer.[2,25] Only few studies explored the management of neuropathic pain in children and poor evidence of efficacy of the available treatments is provided.[4,26] Current guidelines are derived from recommendations for adults and advocate the use of tricyclic antidepressants and some anticonvulsants as a first-line treatment even if the side-effects of the current treatments are poorly tolerated .[7,9,10] Moreover, no trial described the safety or the efficacy of antiepileptic drugs for "off-label" indications in the pediatric population.[27] The lidocaine patches was first applied in adult patients suffering from post-herpetic neuropathic pain in 1995.[13,28] Several studies subsequently confirmed the efficacy of lidocaine patches in the treatment of post-herpetic neuropathic pain both as a single agent or in combination with conventional treatments.[29-36] Lidocaine 5%-medicated plasters were authorized in Europe in 2007 to alleviate neuropathic pain symptoms associated with herpes zoster infection in adults. This treatment was further tested in different therapeutic area such as diabetic neuropathy, post-operative pain, low-back pain, post-traumatic neuralgia, neuropathic pain related to cancer or algodystrophy.[37-47] In 2009, Garnock et al. also emphasize the reduced systemic exposure from lidocaine 5% patches, leading to an excellent tolerance and limiting drug-drug interactions risks in heavily treated patients.[12]

In sickle-cell disease, the obstruction of bone micro-capillaries might induce a local inflammation consequently stimulating the pain-related nerves at the periosteum level. Vasoconstriction might also be induced by the disruption of nitric oxide metabolism.[16] Recurrent vaso-occlusive pain crises are the clinical hallmark of sickle-cell disease either in children and adults, and pain is often inadequately addressed and unsatisfactory treatment responses are observed.[47] Recent publications reported the potential physiopathological relationship between neuropathic pain and pain related to sickle-cell vaso-occlusive crises.[17-18,47-50] Smith and Scherer suggested the existence of a neuropathic component in teenagers and adults.[50] However, no study confirmed or refuted these hypotheses in children. Moreover, a possible inhibition of nitric oxide production previously reported with topical lidocaine might reduce the inflammation of suffering tissues.[16] We consequently hypothesized that lidocaine patches may act through nerve ending stabilization around the periosteum and allow alleviation of the associated inflammation in patients with superficial bone vaso-occlusive crises. We thus started to use topical

lidocaine as adjuvant analgesic treatment for painful vaso-occlusive crisis in our pediatric oncology unit in 2009. In a series of six children hospitalized for vaso-occlusive crisis, and treated with lidocaine 5% patches to improve insufficient analgesic treatment relief, we reported for all patients a VAS ≥2p-decrease 24 hours after patch placement, with no local nor systemic adverse event observed.[51]

In the present study, the pain score was expected to decrease within the first hours following the patch application. With a significant decrease observed within the six first hours, our results are consistent with reported lidocaine efficacy within the first few hours post-application with residual pain relief until patch removal at the 12th hour (half-life of 7.6 hours). The variation in 6h-VAS, and 12h-VAS score on Day 1 was not significantly related to the type of pain, patients with sickle-cell vaso-occlusive pain responded as well as patients with neuropathic pain suggesting that the treatment might be suitable in both cases. This finding is consistent with our hypotheses and assumptions underlying the involvement of a neuropathic pain component in sickle-cell vaso-occlusive crises, recently taken over by Brandow in a review of the literature.[48] The systemic passage of topical lidocaine being of 3±2% of the recommended doses (maximum three plasters simultaneously applied for 12 hours),[22] the analgesia may most likely be driven by the local rather than a systemic effect.

Data from analgesic studies are often difficult to interpret because of the heterogeneity of endpoints used. We would draw attention on the importance of criteria definition and cut-off assumptions on which assessment of the proportion of patients with clinically significant pain relief should be based. The "percentage of pain intensity difference" (PID%) and the "absolute pain intensity difference" (PID) are shown to be relevant and reliable primary outcomes in clinical trials in the field of pain therapy.[52] The 12h-VAS score decrease in the absolute pain intensity difference and the cut-off of 20% in percentage of pain intensity difference were explored in the present study for the clinically meaningful response they provide for patients and clinicians. Recent pediatric analgesic trials in the field of chronic pain also used these endpoints.[24,53]

Despite a 12h-VAS ≥2p-decrease during two consecutive days was reached in 48.6% (95%CI [33.8%;-]) of patients, and a 6h-VAS ≥2p-decrease in 46.9% (95%CI [31.5%-62.7%]), results are below the pre-specified rate of 60% to conclude efficacy. Since our assumptions were based on historical estimations and not from a contemporaneous control group, differences between the study population and the historical control group can't be excluded. The statistical assumptions were challenging to define since no methodology is recommended to

evaluate lidocaine patches in prolonged neuropathic pain and no clinical trial designs are tailored to pediatric analgesics.[54] A 12h-VAS ≥2p-decrease during two consecutive days was probably a too restrictive criterion and 60% of efficacy a too optimistic endpoint. Indeed, neuropathic pain and pain induced by vaso-occlusive crisis are known to be difficult to treat.[26,47] Despite an increasing number of clinical trials and the development of new drugs, the responses to neuropathic pain treatment remain weak with numbers needed to treat (NNT) ranging from 4 to 10 across most positive trials for 50% pain relief.[26] A meta-analysis of 123 randomized trials evaluating pharmacologic treatments for adult neuropathic pain shows that only 46% of patients assigned to active medication reported a 50% or greater pain decrease.[55]

Considering the results published after this study was designed, our hypotheses might have been too strong. With a clinically significant pain relief observed in more than 50% of patients, we would actually find regrettable to rule out the lidocaine patches. Indeed, standard treatments for neuropathic pain requires multiple drugs with different mutually reinforcing mechanisms of action to produce analgesia, and lidocaine patch would represent an interesting complement to conventional treatment options.

Moreover lidocaine 5% patch was a well-tolerated treatment since only three (7.7%) patients presented side-effects with low to moderate intensity in the present population. This corroborates lidocaine safety profile describing rare local side-effects at the application site such as erythema, rash, purpura, pruritus, dermatitis, vesicle, skin irritation, and burning sensation.[29-36] Compared to most painkillers inducing many side-effects and often poorly tolerated, we consider that maintaining this treatment as an alternative or a complementary therapeutic option remains relevant.

We must acknowledge the limitation of this study, performed as a non-randomized trial. Indeed, only a randomized placebo-controlled design would have allowed a higher quality of proof, but placebo controlled pediatric analgesic trial may be ethically and practically difficult to achieve. The FDA sponsored a scientific workshop in 2012 in order to reach a consensus on pediatric analgesic clinical trial design.[54] One of their conclusion is that no recommended design is available to assess efficacy of local anesthetics in subacute or chronic pain.[54] Other designs like quasi randomized design could have been choosen and would have probably provided better estimates of the efficacy. But the sample size needed for such designs was not realistic in a few institution. Methods including analgesic sparing as primary efficacy endpoint or rescue-analgesic designs have

been proposed in order to overcome these issues, but once again larger sample size difficult to reach in pediatric neuropathic pain setting would have been required.

Cross-over designs with intra-patient comparison might have also been proposed. However, neuropathic pain is not necessarily a recurrent event especially in oncology setting and this option was consequently not retained. Moreover, no recommended designs are available to assess efficacy of local anesthetics in subacute or chronic pain.[54] We consequently opted for a single-arm phase II study to explore the efficacy and safety of lidocaine patches in this specific population. We are nevertheless aware that such a design is open to criticism and does not allow to clearly distinguish the efficacy of the treatment from the potential placebo effect of the patch or the natural course of the pain. Since the present population is generally not sufficiently relieved by conventional therapies and faced to a pain score rapidly decreasing in some patients would make spontaneous resolution of pain unlikely. We would encourage the use of lidocaine plasters, although the relief might be partially linked to a placebo effect, to ensure improvement in the comfort of these children. Indeed, patient enrolled in this trial were receiving one or more analgesics with non-optimal efficacy, and only 11 (28%) patients received additional medication at least once in the first three days of the study period.

Based on a success rate of 60%, our results failed to confirm the efficacy of lidocaine 5% patches in neuropathic pain and in pain related to vaso-occlusive sickle-cell crises in children and young adults. Nevertheless, considering the moderate efficacy and common side-effects of most usual treatments, a clinically significant reduction of pain scores and a good tolerance in more than half of the patients in these indications are substantial and this treatment deserve to be evaluated in a larger trial with an adapted design and more suitable hypotheses.

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AUTHORS' CONTRIBUTIONS

VR, SC, and PMB designed the study and developed the methodology. VR, CA, VL, ST, BT, PMB collected the data, VR performed data capture, and quality controls management. MM and SC performed the statistical

analysis, VR, SM, MM, SC, PMB drafted the initial manuscript and SD contributed to the improvement of the manuscript. All the authors approved the final manuscript.

CONFLICT-OF-INTEREST DISCLOSURE

The authors have no conflict of interest to declare.

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Table 1. Baseline characteristics (n=39)

Parameters	
Age, years	
Mean (SD)	12.7 (3.5)
Median (min-max)	12.6 (7.4-20.7)
Gender, n (%)	
Male	18 (46.2%)
Female	21 (53.8%)
Height, m	
Mean (SD)	1.48 (0.17)
Median (min-max)	1.52 (1.03-1.80)
Body weight, kg	
Mean (SD)	42.0 (15.2)
Median (min-max)	42.0 (20.0-84.0)
ECOG Performance Status, n (%)	
0	3 (7.7%)
1	22 (56.4%)
2	14 (35.9%)

Table 2. Pain characteristics (n=39)

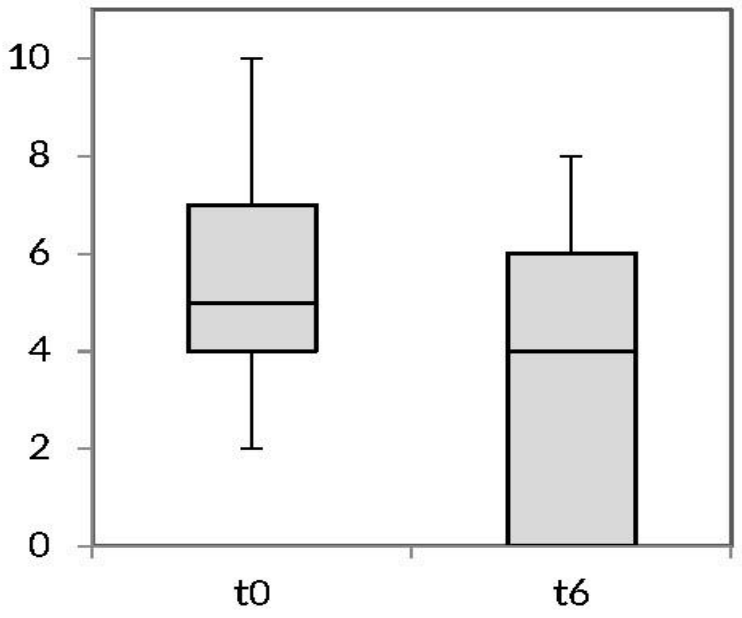
Variables	
Type of pain, n (%)	
Pure neuropathic pain	11 (28.2%)
Mixed neuropathic pain	5 (12.8%)
Sickle-cell vaso-occlusive crises pain	23 (59.0%)
Pathology, n (%)	
Sickle-celldisease	23 (59.0%)
Solid tumor	13 (33.3%)
Leukemia	2 (5.1%)
Sciatica	1 (2.6%)
Delay from diagnosis to inclusion, (years)	
Mean (SD)	6.9 (5.9)
Median (min-max)	8.5 (0-15.5)
Surgeryrelated pain, n (%)	
Yes	5 (12.8%)
No	34 (87.2%)
Radiotherapyrelated pain, n (%)	
Yes	0 (0%)
No	39 (100%)
Chemotherapy related pain, n (%)	
Yes	3 (7.7%)
No	36 (92.3%)

Table 3. Effect of lidocaine 5% patches on self-assessment pain scores measured with the Visual Analog Scale (VAS) on Day 1, 2 and 3, and during at least two consecutive days. Data are n (%). Decrease of at least two points in the VAS pain score: VAS ≥2p-decrease.

	Between t0 and t6	Between t0 and t12
At Day 1		
VAS ≥2p-decrease	19 (57.58%)	23 (59.97%)
At least 1 point VAS increase	7 (21.21%)	7 (17.94%)
No change	5 (15.15%)	4 (10.26%)
At Day 2		
VAS ≥2p-decrease	19 (55.9%)	20 (54.1%)
At Day 3		
VAS ≥2p-decrease	20 (64.3%)	20 (67.5%)
VAS ≥2p-decrease during at least two consecutive days	15 (46.9%)	17 (48.6%)

Table 4. List of adverse events (AEs). National Cancer Institute-Common Terminology Criteria of Adverse Events (NCI-CTCAE), Day 1, Day 2 (D1, D2).

Adverse event	NCI-CTCAE grade	Imputability	Early removal of the patch(es)	Local and/or general
Transient local erythema	grade 1	Possibly related	no	Local side-effects on D1
Generalized skin rashes	grade 2	Not related	no	General side-effects on D1
Pruritus	grade 1	Possibly related	no	Local side-effects on D2



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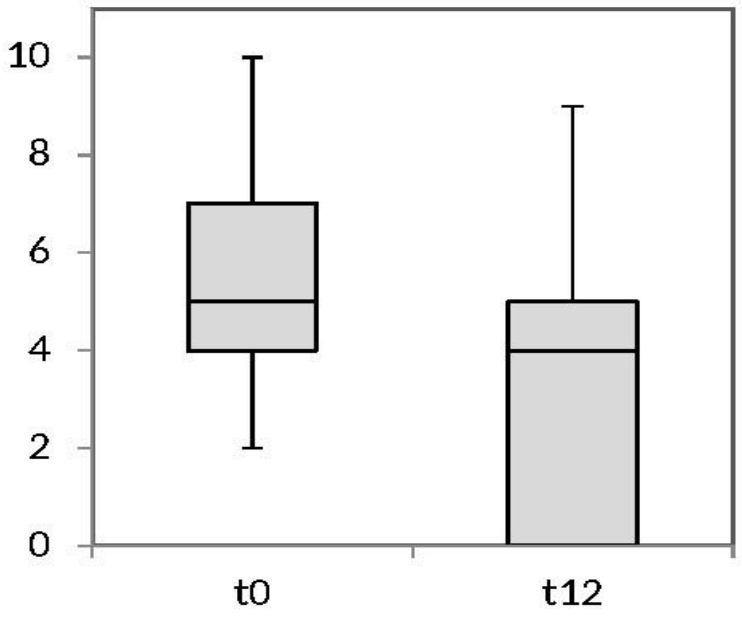

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