5% Lidocaine Hydrochloride Cream for Wound Pain Relief: A Multicentre Observational Study

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ABSTRACT

Background: Lidocaine hydrochloride is frequently used for management of painful wounds. This prospective, multicentre study examined the effects of 5% lidocaine cream on wound pain relief.  
Material and methods: The study included 78 patients with painful wounds treated with 5% Lidocaine cream for two weeks in two Italian Hospitals. Patients’ perception of pain was recorded by, using the 5-point Visual Rate Scale and the 11-point Numerical Pain Rating Scale. All medications and adverse events were evaluated in a daily diary. The primary outcome of the study was establishing the wound pain relief based on the results of 5-VRS and pain intensity based on the 11-NPRS testing from baseline to the end of treatment. Clinical aspects and adverse events were also collected.  
Results: Seventy-eight patients had a median age of 67.5 years (range 18-96 years). 62.8% were women. The wounds included traumatic wounds (n = 39), venous ulcers (n = 25), post-surgical wounds (n = 6) pyoderma gangrenosum (n = 6), vasculitis (n = 1) and pressure ulcer (n = 1). The intensity of pain significantly decreased from the baseline level established at the beginning of treatment (mean score 6.7 – 1.90) - to the level at end of treatment (3.0 – 2.23; p < 0.0001). 9 patients prematurely stopped the treatment for healing (n = 4), wound improvement (n = 2) and adverse events related to the treatment (n = 3). 13 patients presented a total of 25 adverse events, 4 of them were related to the treatment.  
Conclusion: The treatment of painful wounds with 5% Lidocaine Cream for 14 days resulted in reduced pain intensity, and showed high safety and tolerability.

KEYWORDS

Lidocaine; wound healing; acute pain; chronic pain; topical anesthetic

Introduction

In patients with chronic wounds, untreated pain is a major problem that should be addressed promptly and managed effectively [1–3]. Besides improving patients’ comfort, pain therapy can reduce harmful physiological and psychological consequences of untreated pain. Wound pain can cause depression and constant tiredness and, therefore, it should be handled, together with defining its cause as one of the two main priorities in wound management [1].

For painful wound management, oral analgesic, conductive anaesthesia, and topical analgesics are possible therapeutic options [4]. Topical anaesthetic drugs have a favourable safety profile since they can relieve local pain with minimal systemic effects [5]. Local anaesthetic drugs act mainly by inhibiting sodium influx through sodium-specific ion channels (the voltage-gated sodium channels) in the neuronal cell membrane. The binding occurs more readily to sodium channels when activated, and the onset of neuronal blockade is faster in rapidly firing neurons [6].

Lidocaine hydrochloride is frequently used to manage wound pain in many pathological conditions, including herpetic infection, systemic sclerosis, and venous leg ulcers [7,8] since it is available as cream, spray, and/or patches.

In this prospective observational study, the effects of 5% lidocaine cream on wound pain relief and wound healing were investigated. As secondary outcome, information about its safety were collected. Despite of the high safety profile of the drug and rare adverse effects with 5% lidocaine cream, the incidence of adverse effects is directly proportional to the total dose of the drug administered. For this reason, the side effects should be carefully monitored [9].

Material and methods

Study design

This prospective, observational, multicentre study included patients with painful wounds who were treated with 5% Lidocaine cream (Orotdermina®) in two Italian Hospitals. The inclusion criteria were: age ≥18 years, painful wounds
>1 cm² (painful ulcers and pressure ulcers of grade II, as per National Pressure Ulcer Advisory Panel (NPUAP) classification). The exclusion criteria were infected, discolored and odorous, ulcers, grade I, III, or IV pressure ulcers per NPUAP classification, diabetic foot ulcers, known contraindication to one/more drug’s components, severe allergies, vascular disorders and arteriopathies, pregnancy or lactation.

The study was approved by the local Ethics Committees (Approval n. 29/10/2015) and all patients were asked to sign an informed consent to participate to the study (NCT03720119).

**Treatment**

Wounds were treated with 5% Lidocaine Cream once a day for 14 days, according to the leaflet and to hospital standards of care. A single application of 5% Lidocaine Cream did not exceed 5 g of ointment. During the study, other medications containing lidocaine were not allowed and any other treatment prescribed for the wound, either ongoing prior to enrollment or initiated during the study, was reported in the clinical report form. Patients were screened and supplied with 5% Lidocaine Cream during the first visit (visit 1, baseline). Control visits were performed after one (visit 2) and two weeks of treatment (visit 3).

**Data collection**

At visit 1, demographic details and information on medications performed during previous 2 weeks, concomitant medications, and wound characteristics were collected. To assess the wound size, the clinicians from Pisa Hospital utilized a laser scanner system (Silhouette Star®, Aranz Medical) and the clinicians from Trieste Hospital utilized an informatic program (Image J). During this visit, patients received a daily diary and were instructed to record their perception of pain, using the 5-point Visual Rate Scale (5-VRS) [9] and the 11-point Numerical Pain Rating Scale (11-NPRS) [10]. All medications and adverse events were reported in the diary. During visit 2 and visit 3, information on allowed concomitant medications, wound size measurement, 5-VRS and 11-NPRS scores, and adverse events were recorded. At visit 3, the diary was revised by the investigator for completeness and accuracy and withdrawn.

**Outcomes**

The primary outcome was the evaluation of wound pain relief using the 5-VRS (where 0 meant no improvement and 4 meant total relief) and pain intensity based on the 11-NPRS -efficacy analysis-. The wound pain relief from baseline (visit 1) to the end of treatment (visit 3) was analyzed with a one-sample t-test, assuming a reference value equal to 0 (no relief) at baseline. The improvement in the pain relief was described when the VRS score at the end of treatment was significantly greater than 0; the difference was compared with a two-paired samples t-test. The improvement in pain intensity was defined as a decrease in the NPRS score measured at the end of treatment compared to that measured at baseline. The secondary endpoint was the overall incidence of adverse events during the study. All patients who received at least one dose of treatment and had a safety assessment performed at baseline were included in this analysis.

**Statistical analysis**

Limited to the hypothesis tests that were run on pain relief and pain intensity, sample population was sized by assuming a standardized effect size equal to 0.35, for a one-tailed test with a 5% significance level and a power equal to 90% [11]. Therefore, a minimum of 70 patients was required. Expecting a 10% of screening failure, 78 patients were recruited. Continuous data were described as median, mean, standard deviation, minimum, maximum; categorical variables were described as frequency tables. Analyses were performed using PSPP (psppire.exe 0.8.3-g5f5d6s, a program for the analysis of sampled data, Free Software Foundation, [http://www.gnu.org/software/pspp/](http://www.gnu.org/software/pspp/)) and Excel for presentation of data and results.

**Results**

78 patients participated in the study. The median age was 67.5 years (range 18-96 years). 49 (62.8%) of the patients were women. Before the beginning of treatment, 4 patients had one/more concomitant diseases (depression, heart failure and hypertension, road-related multiple trauma, and asthma). The wounds were traumatic wounds (n = 39), venous ulcers (n = 25), post-surgical (n = 6) pyoderma gangrenosum (n = 6), vasculitis (n = 1) and pressure ulcer (n = 1). At baseline, all wounds were evaluated for odor, edges, presence of exude, as summarized in Table 1. The mean wound dimensions were 2.99 mm (SD 2.973) in depth.
patients (16.6%); 4 were considered related to the treatment, 1 possibly related, 1 unlikely-related and 19 (76%) were considered as not related to the study treatment. Non adherent dressings or foams with silicone layer were used to cover the cream, and compressive therapies in case of venous leg ulcers. Patients with inflammatory ulcers (pyoderma gangrenosum and vasculitis) needed concomitant analgesics drugs, including oxycodone, tramadol, ibuprofen, ketoprofen, diclofenac, paracetamol, and methylprednisolone.

**Discussion**

This prospective, observational, multicentric study found a beneficial effect of 5% Lidocaine Cream treatment in pain management of patients with painful wounds. After 14 days of treatment, wound dimensions decreased, and the intensity and perception of pain consistently improved. The treatment was well-tolerated. Only 3 patients discontinued the treatment for adverse effects.

In the efficacy analysis, 5% Lidocaine Cream significantly reduced pain intensity and pain perception compared to baseline in all time points considered. These results were consistent with the changes of wound characteristics assessed during the control visits, indicating a clinical improvement. The high compliance to treatment supported its tolerability; 88% of patients completed the protocol, 9 patients prematurely ended, 4 of them for wound healing.

Our results with the use of 5% Lidocaine Cream confirmed the effectiveness of lidocaine as anesthetic for wound-related pain, as previously demonstrated with different formulations containing the drug [12]. 5% Lidocaine patches can be used to reduce acute herpetic pain intensity, once the lesions are healed [5]. In patients with leg venous ulcers, a spray solution of 10% lidocaine reduced the timing of debridement and dressing changes, improving the outpatient management and patient's compliance [13]. In patients with systemic sclerosis, topical application of 4% lidocaine had significantly reduced pain, allowing a safe debridement and an improved management of digital ulcers [14]. The main advantage of Lidocaine cream is the maintaining of adequate levels of analgesic over the lesions, guaranteeing a durable anesthetic effect.
The main limitations of the study are the lack of control group and the short-term duration of the treatment, only two weeks in which most of wounds improved but did not completely heal. Long-term treatments should be considered to allow complete tissue repair and further studies should be warranted to evaluate their effectiveness and monitor potential side effects.

Conclusion
The 14-day treatment with 5% Lidocaine Cream showed a clinical and statistically significant positive effect in reducing pain intensity and perception. Clinical improvement matched with the reduction of wound parameters over time. The benefit of treatment was achieved without safety and tolerability concerns. Further studies with a control group are needed in the future.

Disclosure statement
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