

Repeated Treatment with Lidocaine/Prilocaine Cream (EMLA^(R)) as a Topical Anaesthetic for the Cleansing of Venous Leg Ulcers

A Controlled Study

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Repeated topical analgesia with EMLA^(R) 5% cream prior to the cleansing of venous leg ulcers was studied. Patients were randomly allocated to a series of 8 treatments with EMLA^(R) ($n = 22$) or to a control group ($n = 21$). A thick layer of the cream was applied to the ulcers for 30 min. At each of the 8 treatments, local reactions were assessed on a 4-point scale and pain from ulcer cleansing on a visual analogue scale. At the first and the last treatment the area of the ulcer was determined by mapping, a sample for a bacterial culture was taken and the amount of dead tissue, slough and granulation tissue present was assessed. Treatment with EMLA^(R) for 30 min significantly decreased the pain from cleansing of the leg ulcers and the frequency of post-cleansing pain. The analgesic effect remained unchanged with successive treatments. Repeated treatment with EMLA^(R) in leg ulcers would appear to be safe, as indicated by the absence of any serious untoward events. No statistically significant differences in local reactions or adverse effects on granulation tissue, ulcer area or bacterial flora were observed in the EMLA^(R)-treated patients compared with the control patients. **Key words:** Pain; Analgesic effect; Anaesthetic cream.

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Ambulatory venous hypertension, the cause of venous leg ulcers, is counteracted by elevation of the leg and by support bandages (1). Another important factor in ulcer healing is the removal of dead tissue and slough, in order to enable granulation tissue to form and to promote epithelialization (2–4). The cleansing procedure can be very painful (5–8).

EMLA^(R) cream, a eutectic mixture of the local anaesthetics lidocaine and prilocaine, has mainly been used for percutaneous analgesia prior to venepuncture (9, 10). It also provides satisfactory anaesthesia for the curettage of molluscum contagiosum (11, 12), split-skin grafting (13) and skin biopsies (14). Anaesthesia for the cauterization (15) or laser treatment (16) of vulval condylomata is achieved after application for 5–10 min to the mucous membranes.

EMLA^(R) cream has recently (5) been shown to give satisfactory pain reduction, significantly more effective than that provided by placebo, when applied for 30 min before the debridement of leg ulcers. The present study was performed to determine whether the repeated treatment of leg ulcers with EMLA^(R) cream would cause any adverse reactions or affect healing or the bacterial flora, and also to evaluate the analgesic effect of EMLA^(R) cream for the repeated cleansing of leg ulcers.

PATIENTS AND METHODS

Forty-three patients with venous leg ulcers from the Departments of Dermatology ($n = 33$) and Surgery ($n = 10$) were included. All the patients had a clinical diagnosis of venous ulcer and a systolic ankle pressure above 80 mmHg (to enable the use of compression bandages). Exclusion criteria were ulcers smaller than 1 cm² or larger than 50 cm², a history of sensitivity to local anaesthetics of the amide type, treatment with EMLA^(R) cream during the previous month, and ongoing local antibiotic or proteolytic enzyme treatment.

The study had an open randomized parallel-group design with a control group, which did not receive either topical anaesthesia or vehicle. A sealed envelope individual to each patient, containing information about allocation to EMLA^(R) treatment or control, was opened immediately before the first treatment. 5% sterile EMLA^(R) cream, containing 25 mg lidocaine and prilocaine per gram, was applied at 8 consecutive visits separated by an interval of 2–9 days. The control patients were similarly monitored for 8 consecutive treatments. The cream was applied to the ulcer in a thick layer, a maximum of 5 g for each patient, and covered with plastic film (Glad TM, First Brands, Germany) for 30 min to form an occlusive dressing. The cleansing was performed with a curette, scissors or a swab. In the group randomized to EMLA^(R) treatment, cleansing was started within 10 min after removal of the cream. In the same group, the ulcer was examined (before the start of cleansing, but after removal of the cream) for oedema, redness and paleness or any other local reaction. The patient was asked about local sensations such as burning or itching. Their severity was rated as none, slight, moderate or severe.

The pain intensity from the cleansing of the ulcer was rated by the patient on a visual analogue scale (VAS), consisting of a 100-mm ungraded, horizontal line with the ends marked "no pain" (0 mm) and "worst possible pain" (100 mm) (17). Prior to the first treatment, the patient was given instructions on how to use the VAS. The occurrence of post-cleansing pain within 4 h was recorded ("yes" or "no"). At the 1st and 8th visit, a sample was taken for a bacterial culture and the area of the ulcer was measured. The ulcer was also assessed for the presence of dead tissue (eschar or slough) and granulation tissue, rated as the percentage of ulcer size present (none, 1–33%, 34–66% or 67–100%).

The outline of the ulcer was mapped onto transparent film of known weight, a single batch of film being used. The accuracy of the measurements was estimated from the weight of 10 duplicates of the ulcer map cut out of 10 separate sheets of transparency film. The coefficient of variation was 1% (ulcer area 60 cm²) to 3% (ulcer area 3 cm²).

In accordance with the recommendations of the Declaration of Helsinki, all the patients gave their informed consent to participation. The study protocol was approved by the Local Ethical Committee at Sahlgrenska sjukhuset.

Statistical analysis

To provide an overall comparison of analgesic effect and local reactions, the mean response scores over time were calculated for each patient. To obtain a measure of the change over time, the regression coefficients for each patient were calculated for pain score and local reactions. Analysis of variance was used to test the differences between the two groups (i.e. EMLA^(R) and control). A stepwise regression method was used to find those variables capable of influencing the ulcer area (18). After the relevant variables had been found, the

Table I. Forty-three venous leg ulcer patients were randomly allocated to a series of 8 treatments with EMLA^(R) cream ($n = 22$) or to a control group ($n = 21$).

	EMLA ^(R)	Control
Patients	22	21
Men/women	11/11	8/13
Median age in years (min-max)	67.5 (42-88)	68 (43-90)
Initial ulcer area in cm ² (min-max)	8.1 (1.6-54.2)	7.1 (1.1-59.7)
Median ulcer age in months (min-max)	9.5 (1-168)	5 (1-504)

differences in intercepts and slopes between the groups were tested by means of a weighted regression analysis.

The change in amount of dead tissue (eschar and slough) and granulation tissue before and after the 8 treatments was analysed by a stratified Wilcoxon's rank sum test. In all the statistical tests performed, a two-tailed value of p less than 0.05 was considered to be statistically significant.

RESULTS

Patient age, sex and initial ulcer area were similar in the two groups, although the median ulcer age was higher in the EMLA^(R) group (see Table I).

The ulcers were located medially in 63% of the EMLA^(R) patients and in 45% of the controls; laterally in 26% of the EMLA^(R) patients and in 20% of the controls; in the front in 5% of the EMLA^(R) patients and in 20% of the controls. There was one patient with diabetes in each group. Three patients (2 in the EMLA^(R) group) were on systemic antibiotics at the start of the study and throughout the study.

Two patients in the EMLA^(R) group and one in the control group withdrew from the study after 1 or 2 treatments.

The duration of the cleansing was comparable between the groups (EMLA^(R) group: median = 3, range 1-17 min; control group: median = 4, range 1-25 min).

The VAS pain scores from ulcer cleansing were significantly lower in the EMLA^(R) group than in the control group, the medians being 4 and 33 respectively ($p = 0.0008$). Altogether 162 treatments were performed in the EMLA^(R) group and 156 in the control group. The mean number of visits with post-cleansing pain was significantly lower in the EMLA^(R) group, both immediately ($p = 0.0017$) and within 4 h of cleansing ($p = 0.021$). Overall, at 20 out of 161 visits (12%, with one missing observation) with EMLA^(R) treatment and at 96 out of 156 visits (62%) without analgesic treatment, the patients experienced pain immediately after cleansing. The corresponding figures for pain within 4 h were 49/161 (30%) for EMLA^(R) and 102/153 (67%) for the control. The pain scores and frequency of post-cleansing pain did not change over time, as measured by the regression coefficients, and did not differ significantly between the EMLA^(R) group and the control group. No serious local reaction or sign of sensitization was observed. The percentage of patients reporting burning or itching at or between treatments was no higher in the

EMLA^(R) group than in the control group. Most of the local reactions were of mild or moderate severity. The frequency and severity of local reactions did not change with successive treatments. The mean coefficient for the severity scores over time did not differ significantly between the groups ($p > 0.05$). In one EMLA^(R)-treated patient and in 5 controls the ulcer healed during the study period (Fisher's exact test: $p = 0.095$, n.s.). One of the controls whose ulcer healed attended the clinic only once a month after the 2nd visit and was, therefore, studied for up to 140 days, compared to a median of 38-46 days in the EMLA^(R) group and the control group respectively.

The median decrease in ulcer area was 2.0 cm² in the EMLA^(R) group and 2.2 cm² in the control group (n.s.). The ulcer area at the last visit was related to the initial ulcer area ($p = 0.0001$) and the ulcer age ($p = 0.066$), according to the stepwise regression. A weighted regression analysis including group, initial ulcer area, age of ulcer and interaction between group and initial ulcer area showed that the 2 groups were not significantly different (difference in slopes of initial ulcer area between groups: $p = 0.49$, and difference in intercepts between groups: $p = 0.68$).

Dead tissue (eschar) was present in one control patient at the first visit. No patient had any eschar tissue at the last visit.

The amount of slough initially present was comparable in the EMLA^(R) group and the control group. In all but 3 patients (2 EMLA^(R), 1 control) the amount of slough decreased or was unchanged from the first to the last treatment ($p = 0.55$).

The amount of granulation tissue was comparable at the first treatment and increased during the study in 12 patients in each group ($p = 0.60$). In 2 patients from each group, the amount of granulation tissue decreased.

Similar bacterial strains were found in the EMLA^(R) group and the control group. The most common isolate was *Staphylococcus aureus*, which was present in 52% of the samples and in 67% of the patients at any time. The bacterial flora of 9 EMLA^(R) patients and one control patient was the same at the first and the last visit.

DISCUSSION

The aim of the present randomized prospective study was to see whether EMLA^(R) cream had any adverse effects on leg ulcer healing. The healing rate was similar in the two groups, but the EMLA^(R)-treated patients had less pain. The treatment time was too short to allow ulcer healing to be achieved in a substantial number of cases, and this is a probable explanation of the numerically, but not significantly, larger number of ulcers which healed in the control group.

Treatment with EMLA^(R) cream 5% for 30 min has been shown to significantly decrease the pain from debridement for arterial and venous leg ulcers (5). This study, which is the first controlled trial of repeated treatments of venous leg ulcers with EMLA^(R), confirmed the analgesic effect. In addition, EMLA^(R) was found to significantly reduce the post-cleansing pain. As observed by Wanger et al. in an open study (6), the analgesia remained effective with successive treatments. The pain scores from ulcer cleansing in the control group (median = 33) were lower than those reported by Holm et al. (5) in

placebo-treated patients (median = 84), probably due to the fact that in their study arterial (ischemic) ulcers were included.

No serious adverse reaction or sign of sensitization has been observed after the repeated application of EMLA^(R) cream either in this study or previously (6). Redness was observed in both the EMLA^(R) group and the control group. Around some of the ulcers in the EMLA^(R) group the redness was found to be present after the 30 min of application of the cream, but not before. This may be due to vasodilatation caused by the direct effects of lidocaine and prilocaine on vascular smooth muscles (19–22). The amount of granulation tissue increased in more than half of the EMLA^(R)-treated patients, as in the control group. Similarly, the amount of slough as well as the bacterial flora did not differ between the groups. The finding that *S. aureus* was the most common species is in accordance with studies where EMLA^(R) cream was not used (4).

The maximum dose used on the leg ulcers, 5 g EMLA^(R) 5% cream, applied for 30 min, results in plasma levels of lidocaine and prilocaine far below those associated with initial signs of CNS toxicity (5). After a 24-hour application of 5–10 g EMLA^(R) 5% cream to leg ulcers, there were no or only minimal levels of the local anaesthetics remaining in the blood at the end of the application period (23). In the present study, in which a thick layer of cream was applied, a large part of the local anaesthetic dose was removed when the remaining cream was wiped away after 30 min.

In conclusion, no serious local reactions or signs were observed after the repeated application of EMLA^(R) cream. No significant local reactions or adverse effects on granulation tissue, ulcer area or bacterial flora were detected compared to control patients. Treatment with EMLA^(R) cream for 30 min significantly decreased the pain from the cleansing of venous leg ulcers and the frequency of post-cleansing pain.

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