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Regional Variations in Analgesic Efficacy of EMLA® Cream

Quantitatively Evaluated by Argon Laser Stimulation

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The effect of EMLA cream (a eutectic mixture of local analgesics) applied for 30, 60, 90 and 120 min on the forehead, cheek, back, cubital fossa, and dorsum of the hand was studied. Analgesic onset, efficacy and duration were evaluated by sensory and pain thresholds to laser stimulation measured before, and 5, 60, 120, and 180 min after the cream was removed from the skin. Cutaneous blood flow was measured and found to be 4–5 times as high on the face as on the other locations. On the forehead the analgesic efficacy decreased with increased application time. For all other locations, efficacy increased with increasing application time. On the back, onset was rapid and sufficient analgesia could be obtained, but analgesias began to wane immediately after removal of the cream. In the cubital fossa and on the hand, onset was tardy, and efficacy continued to increase for 60 min after cream removal, followed by a slow decline. Blood flow, epidermal and dermal thickness are important factors affecting onset, efficacy and duration of EMLA analgesia. ***Key words: Analgesia; Blood flow; Pain threshold; Onset, Duration.***

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Various dermatological applications of EMLA cream (a eutectic mixture of local anaesthetics) have been suggested since the appearance of the first clinical reports (1,2). The application time needed to provide sufficient analgesia for venepuncture is suggested to be 60 min (3); for split skin grafts 60 to 90 min is required (4), and for curettage of molluscum contagiosum 60 min is suggested (5). For genital application, 5–10 min is sufficient to afford adequate analgesia (6). The effect of EMLA has been shown less efficient on the face than on the arm, probably due to higher vascular uptake on the face (7). The effect of EMLA is dependent on the application time (3,8,9), but the influence of both the anatomical location and application time is not clear.

The purpose of the present study was to use argon laser stimulation (10) for quantitative assessment of onset, efficacy and duration of analgesia for various EMLA application times and anatomical locations. If individual EMLA application times are used for different regions, more standardized and adequate analgesia can probably be obtained. This could be of importance, for instance, for curettage of molluscum contagiosum from different locations. Recently Rosdahl et al. (5) found that 36% experienced slight or moderate pain when molluscs were removed from different locations, with EMLA analgesia.

METHODS AND MATERIALS

Volunteers

Ten healthy volunteers, 4 females (mean age 22 years, range 19–23 years) and 6 males (mean age 24 years, range 20–26 years) participated in this study. All volunteers gave their informed consent according to the Helsinki Declaration. The study was approved by the Local Medical Ethics Committee.

Determination of sensory and pain thresholds to laser stimuli

The output from an argon laser (Model 168, Spectra Physics, USA) was transmitted to the skin via a quartz fibre. Output power could be adjusted from 50 mW to 3.5 W. The argon laser wavelengths were 488 nm (blue) and 515 nm (green). An external laser power meter was used to measure the dissipated output power at the skin level. A continuous, low-energy beam (50 mW) from the laser was used to visualize the stimulation site.

The laser stimulus had a duration of 200 ms and the laser beam diameter was kept constant at 3 mm (0.07 cm^2). During the experiments, all persons in the room wore protective goggles. The cutaneous sensory and pain thresholds were calculated as the mean of 5 ascending and 5 descending series of argon laser stimulations. The sensory threshold was defined as warmth, and the pain threshold was defined as a sharp, distinct pin prick (10). The highest laser intensity applied to the skin was 3 W, because intensities above this level could cause minor, superficial burn lesions.

Table I. *Cutaneous blood flow (flux of red cells), epidermal thickness, and dermal thickness measured on five locations*

Means and standard deviations (SD) are given.

Location	Mean blood flow (arbitrary units ± SD)	Epidermis[a] (μm ± SD)	Dermis[b] (mm ± SD)
Forehead	6.25±1.60	50.3±20.2	1.8±0.4
Cheek	5.00±1.55	38.8±9.70	2.0±0.5
Back	1.27±0.30	43.4±12.8	3.6±0.5
Cubital fossa	1.20±0.35	60.9±20.0	1.5±0.3
Hand (dorsum)	1.31±0.43	67.0±18.2	1.4±0.3

[a] Data from Whitton & Everall (11). [b] Data from Fornage & Deshayes (12).

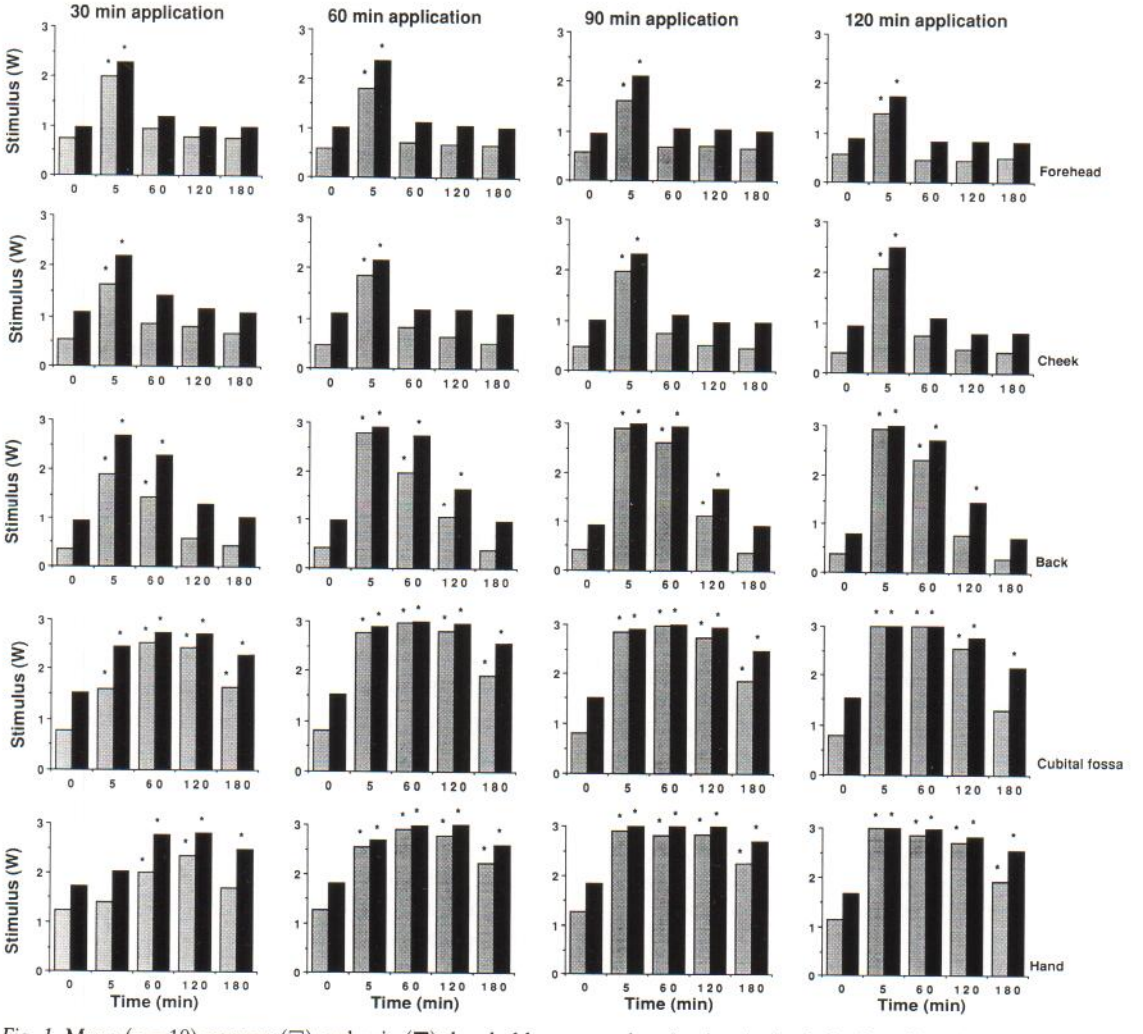

Fig. 1. Mean ($n = 10$) sensory (□) and pain (■) thresholds measured on forehead, cheek, back, cubital fossa, and dorsum of the hand before and after (5, 60, 120, 180 min) application of EMLA for 30, 60, 90, and 120 min. Asterisks (*) indicate significant ($p < 0.05$) changes compared with the thresholds before analgesia.

Table II. *Onset rate of analgesia, defined as the difference in thresholds before and after a 30-min EMLA application*

Decline rate of analgesia defined as the difference in thresholds, measured immediately after a 120-min application and 60 min later. The values given are the mean changes.

Location	Onset rate		Decline rate	
	Sensory (%)	Pain (%)	Sensory (%)	Pain (%)
Forehead	+235	+143	−66	−56
Cheek	+230	+124	−64	−55
Back	+380	+193	−21	−10
Cubital fossa	+100	+62	0	0
Hand (dorsum)	+13	+12	−1	0

EMLA cream application

The EMLA® cream (Astra, Sweden) is an oil-in-water emulsion. The oily phase consists of an eutectic mixture of lignocaine (25 mg/ml) and prilocaine base (25 mg/ml). Two and a half grams of EMLA cream was applied on encircled (12 cm^2) test areas on the forehead, right cheek, lower back, cubital fossa, and dorsum of the right hand. The cream was applied under an impermeable plastic occlusion (Tegaderm®, 3M, UK) for either 30, 60, 90, or 120 min.

Blood flow measurement

Laser doppler flowmetry (Periflux®, Perimed, Sweden) was used to determine the blood flow (flux of red cells) in the superficial layer (<1.5 mm) of the skin (11). The blood flow was given in arbitrary units between 0 and 10. The blood flow was determined at the five locations under investigation before application of the EMLA cream.

Statistics

Wilcoxon's test was used for statistical analysis, and $p < 0.05$ was regarded as significant.

Protocol

Each volunteer was tested four times in a randomized cross-over design. The four tests corresponded to the four application times of 30, 60, 90, and 120 min. One week elapsed between trials. The application time was randomized between the four trials. Sensory and pain thresholds were measured before application, 5 (immediately after), 60, 120, and 180 min after removal of the cream. Attempts were made to measure skin-fold thickness with calipers, but reliable measurements could not be obtained on all locations due to tight binding of the skin to underlying connective tissue. No medication or alcohol was allowed 48 h prior to each experimental series of investigation.

RESULTS

Blood flow

The cutaneous blood flow (flux) was significantly higher on the forehead and cheek, than on the back, cubital fossa and dorsum of the hand (Table I). As a control we monitored the blood flow on the hand and back following 10 stimuli (2W) given repeatedly at time 0, 5, 60, 120 and 180 min. No detectable changes in cutaneous blood flow were found throughout the experiment.

Laser thresholds before and after EMLA application

30 min application. Immediately after removal of the cream the sensory and pain thresholds were significantly ($p < 0.01$) elevated at all locations except on the hand (Fig. 1). Sixty min later the thresholds were normalized on the forehead and cheek; the thresholds on the back declined, whereas those on hand and in cubital fossa steadily increased. After 180 min thresholds on the back were normalized, whereas the thresholds on the hand and arm remained elevated.

60–120 min application. All thresholds were elevated significantly immediately after removing the cream (Fig. 1). The development of analgesia on the different sites followed the same patterns as for the 30-min application. Total analgesia (both sensory and pain thresholds were above 3 W) was obtained for all volunteers 60 min after a 60- and 90-min application in the cubital fossa, and immediately and 60 min after a 120-min application (Fig. 1). On the hand, total analgesia was obtained immediately after a 120-min application.

Onset and decline rates of analgesia for different application times on the 5 anatomical regions

The onset rate of analgesia was quantified by the proportional increase in threshold measured before

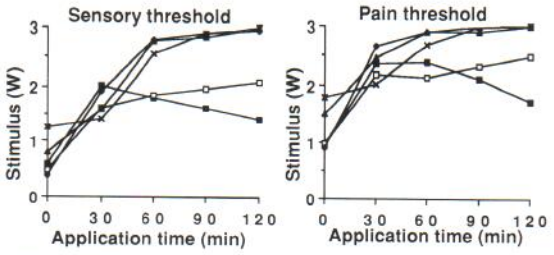

Fig. 2. Mean ($n = 10$) sensory (*left*) and pain thresholds (*right*) before and 5, 30, 60, 90 and 120 min of EMLA application on forehead (■), cheek (□), back (◆), cubital fossa (▲), and dorsum of the hand (×). The efficacy on the face was not improved by prolonging the application time.

and immediately after a 30-min application (Table II). The decline rate of analgesia was quantified as decline in thresholds between the determination immediately after a 120 min application and the determination 60 min later (Table II). The fastest onset rate was found on the back and the slowest on the hand. The epidermal thickness on the hand is 24 μm thicker than on the back (12), whereas the flow in the two regions is very similar. The fastest decline rate was found in the face, and the slowest in cubital fossa. This corresponded to the regions with the highest and the lowest blood flow, respectively (Table II). The decline rate on the back differed from the rates in the face and on the arm and hand. The dermal thickness on the back has been found (13) to be substantially greater than on the other locations (Table II).

Interestingly, both thresholds decreased with prolonged application on the forehead, whereas on all other sites the thresholds increased with increasing application time (Fig. 2). None of the volunteers was fully pain alleviated on either forehead or check. EMLA cannot be recommended for facial application when total analgesia is required.

DISCUSSION

Analgesic onset

The very slow onset rate of analgesia on the hand may have been due to the thick epidermis. The onset rate was lower on the cheek than on the back, although epidermis is thinnest on the cheek. High blood flow might therefore be of importance and prolong the onset time. On genital-, lip- and oral mucosa where the stratum corneum barrier is absent, the onset of analgesia is rapid (5–30 min), but the duration short (1,6). Rapid onset can be obtained on locations with low blood flow and thin barrier (absence of stratum corneum or thin epidermis).

Analgesic efficacy

On the forehead the efficacy decreased with increasing application time. Recently, we have shown (14) that the vasoconstriction (blanching) caused by EMLA was maximal for applications below 90 min. After a 120-min application the blanching effect vanished, and was eventually replaced by erythema. During a period of blanching the vascular uptake may be reduced, which explains why shorter applications on the forehead gave slightly better results than longer application times.

Juhlin et al. (7) have shown that the rate of vascular absorption is crucial for the efficacy and duration of EMLA analgesia. Sites with high cutaneous blood flow, e.g. the face, psoriatic plaques and atopic dermatitis, exhibit faster vascular uptake of analgesics, with consequent insufficient analgesia. This was confirmed in the present study where both the efficacy and duration of EMLA analgesia in the face were reduced compared with the other sites. This finding can be explained by the location of the main portion of the cutaneous free nerve endings at the dermal–epidermal junction close to the papillary capillaries. If the vascular uptake is high, the dose of analgesics in the microenvironment around the nerve endings will remain low, and cause inadequate analgesia.

Analgesic duration

On the hand and cubital fossa we found a delayed maximum of analgesia with respect to cream removal. Previously, this effect has been shown quantitatively by laser stimulation on the hand (15), and by controlled needle insertion on the arm (16). The delayed effect may indicate that a reservoir of analgesics is located and stored in the skin during application. After the cream has been removed from the skin surface, the diffusion of analgesic from the reservoir continues, giving improved analgesia. The long duration of analgesia might be an advantage in relation to surgical or other procedures that produce local release of inflammatory mediators in the skin, because the immediate Type I response is gradually inhibited for increased cutaneous analgesia (17). If the blood flow in the superficial vascular plexus is high, the rate of vascular uptake might be comparable to the influx of analgesics through the skin surface. In this case no reservoir can be obtained,

and the analgesic efficacy starts to decline immediately after removal of the cream.

The thick epidermis on hand and arm, together with low blood flow seem to be responsible for the delayed and long-lasting effect. The decline rate of analgesia on the back showed a different pattern than on other locations which were characterized by low blood flow or thin epidermis. The thick dermis on this location might be able to absorb and redistribute a larger volume of analgesics. The amount of EMLA applied to the skin (2.5 g) could be insufficient for this large absorbent, resulting in short analgesic duration. Especially for a 120-min application on the back, the opaque emulsion droplets coalesced and left the cream as a transparent residue under the film.

In conclusion the time-efficacy response to various EMLA cream application times on different anatomical regions varies markedly. High cutaneous blood flow may reduce efficacy and duration of analgesia. Thick epidermis may prolong onset of analgesia and result in delayed peak effect, and hence long duration of analgesia. For regions with thick dermis, longer-lasting analgesia might be obtained by applying a larger amount (or higher concentration) of EMLA. These findings suggest that adequae and homogeneous EMLA analgesia can be obtained by using individualized application times and doses for different locations.

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