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DEPTH AND DURATION OF SKIN ANALGESIA TO NEEDLE INSERTION AFTER TOPICAL APPLICATION OF EMLA CREAM

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SUMMARY

We have determined the depth and duration of analgesia to needle insertion after topical application of EMLA cream (Eutectic Mixture of Local Analgesics). EMLA was applied for 30, 60, 90 and 120 min and the sensory and pain threshold depths were determined before analgesia (1.0 and 1.9 mm, respectively) and up to 4 h after the cream was removed from the skin. The maximal depth of analgesia (approx. 5 mm) was observed 30 min after a 90-min application and during the 60-min period after a 120-min application of EMLA cream, for both sensory and pain thresholds. For application times shorter than 120 min, the depth of analgesia increased during the period after removal of the cream. This suggests new guidelines for the use of this topical analgesic.

KEY WORDS

Anaesthesia local: topical lignocaine/prilocaine. Anaesthesia: duration.

Discomfort or pain induced by insertion of needles for venepuncture may be alleviated by topical application of EMLA cream (Eutectic Mixture of Local Analgesics) [1]. Additional clinical applications include donor site analgesia for split skin grafting, removal of molluscum contagiosum, tattoos, and warts [2–4]. Juhlin, Evers and Broberg [2] reported that pain was felt when skin biopsies were obtained with EMLA analgesia, whereas superficial cutting could be performed without pain. Because EMLA provides analgesia for venous cannulation [5, 6] it follows that analgesia must extend as deep as the subcutaneous vessels. In the present study we have determined the depth of analgesia to controlled needle insertions after different times of application of EMLA.

Recently, Arendt-Nielsen and Bjerring [7] used an argon laser for cutaneous pain stimulation before and after EMLA analgesia. A period of 2 h of EMLA application was comparable to lignocaine infiltration in abolishing laser induced pain. After the cream had been applied for 15, 30, 60 and 80 min, maximal alleviation of the laser-induced pain occurred 30–60 min after removal. Similar observations were made by Evers and colleagues [8], who found that pain alleviation to pinprick increased 30–60 min after removal of the cream. This delayed analgesic effect was examined also in this study to see if it also affected depth of analgesia.

SUBJECTS AND METHODS

Volunteers

Twelve healthy volunteers (seven female) aged 24–28 yr (mean 25.7 yr) participated in this study. All volunteers gave informed consent according to the Helsinki Declaration.

Application of EMLA cream

EMLA cream 5 g (Astra, Södertälje, Sweden) was applied on four encircled (12 cm^2) test areas on the dorsal side of the middle part of both forearms (hairy skin) under an impermeable plastic occlusion dressing (Tegaderm). Application time was 30, 60, 90 or 120 min. Additionally, two test areas were selected, one for application of placebo cream and one for control

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(Tegaderm only). The test sites were selected randomly on each forearm and separated by 5 cm. The investigator was blinded with respect to application times and individual test areas.

Sensory and pain threshold depth determination

Immediately after removal of the occlusive bandages and creams, an i.v. needle (18-gauge) was inserted perpendicularly through the anaesthetized skin until a perception of pressure or touch was felt. This depth was defined as the sensory threshold depth. The needle was inserted further until pain was perceived (the pain threshold depth). For all test areas, needle insertions were made at 30-min intervals up to 4 h after cream removal. For each insertion, a new site was chosen inside the test area. Also, threshold depths were measured in non-treated adjacent control areas. The threshold depths are given as percentage increase of the adjacent, non-treated control area.

Needle depth measurement

The needle insertion depth was measured by a micrometer gauge with a resolution of 0.1 mm. The fixed part of the micrometer gauge was attached to a circular plastic plate (3 cm in diameter), which was resting with standardized pressure (200 g) on the skin surface. A sterile disposable 18-gauge needle for i.v. cannulation was attached to the moving end of the gauge. The needle was inserted slowly (approximately 0.5 mm s^{-1}) and perpendicular to the skin surface through a hole in the centre of the plate, and protrusion into the skin was monitored continuously with the gauge.

Skin thickness

Skin fold thickness was measured by a calliper. The skin thickness was calculated as 50% of skinfold thickness. All measurements were performed before analgesia. The mean of four measurements was calculated.

Statistics

Data were analysed by Wilcoxon's test. A probability of less than 5% was considered significant.

RESULTS

Skin thickness

The skin thickness was found to be slightly thicker (mean 3.35 (SD 0.70) mm) for the proximal areas than for the intermediate (mean 3.15 (0.62) mm) and the distal (mean 2.98 (0.55) mm) test areas (ns). Any possible differences in absorption characteristics of analgesics because of these differences were minimized by randomization of the application sites (table I).

Changes in sensory and pain threshold depths in relation to thresholds before EMLA application

The mean depths of sensory and pain thresholds for the placebo areas were 1.00 (0.20) mm, and 1.88 (0.60) mm, respectively (table I). The mean depths of sensory and pain thresholds for the non-treated control areas were 0.98 (0.24) mm and 1.82 (0.60) mm, respectively (table I). These depths represent a combination of the needle's indentation of the skin surface because of mech-

TABLE I. *Sensory and pain thresholds (mean (SD)) in the control, placebo and EMLA test sites, together with the skin thickness. The depths are measured immediately after removal of the cream. For EMLA cream the values are given for 30, 60, 90 and 120 min of application. Only at 90 and 120 min, the pain threshold exceeded the mean skin thickness* (*). n = *12 volunteers*

	Thresholds		Skin thickness (mm)
	Sensory (mm)	Pain (mm)	
Control	0.98 (0.24)	1.82 (0.60)	3.15 (0.65)
Placebo	1.00 (0.20)	1.88 (0.60)	3.03 (0.70)
EMLA 30	1.30 (0.53)	2.30 (0.82)	3.20 (0.55)
EMLA 60	1.88 (0.48)	3.11 (0.73)	3.30 (0.60)
EMLA 90	2.18 (0.87)	4.15 (1.40)*	3.20 (0.66)
EMLA 120	3.08 (0.69)	5.25 (1.50)*	3.24 (0.50)

anical pressure and the depth of needle penetration into the epidermis before any sensory or pain receptors are activated. The thresholds did not vary after different application times. The sensory and pain threshold depths measured immediately after removal of EMLA increased linearly for increasing application time (30, 60, 90 and 120 min) (fig. 1, table I). High correlation coefficients ($r > 0.9$) were obtained between threshold depths and application time.

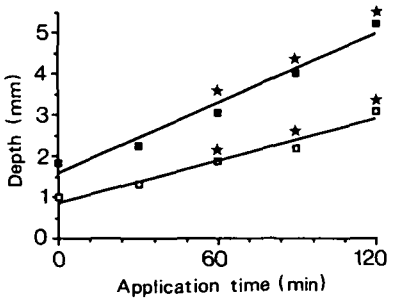

FIG. 1. Changes in depth of sensory (□) and pain (■) thresholds immediately after removal of EMLA cream following different application times. The thresholds before application of EMLA cream are shown on the ordinate (mean values for 12 volunteers). *Statistically different from the initial values.

After 90 and 120 min of EMLA application, the mean pain threshold depth exceeded the mean skin thickness (table I). After EMLA application for 30 min a significant increase in sensory threshold depth occurred 60 min after removal of EMLA. The mean pain threshold depth was increased significantly 30 min after cream removal, and reached maximal depth 90 min after removal. Both sensory and pain threshold depths were increased significantly up to 180 min after EMLA cream removal (fig. 2).

After application of EMLA for 60 min, the sensory and pain threshold depths increased significantly immediately after removal of cream. The maximal threshold depths occurred 30 min after cream removal. The sensory and pain threshold depths were significantly increased for 210 min and 240 min after cream removal.

After the 90-min application, the depth thresholds were increased significantly immediately after cream removal. This was maintained until 240 min after cream removal. Maximal depth of thresholds occurred 30 min after the cream was removed from the skin.

After a 120-min application period, the mean pain threshold depth exceeded the skin thickness, and in three of 12 volunteers, the needle touched or penetrated the fascia of the underlying muscle

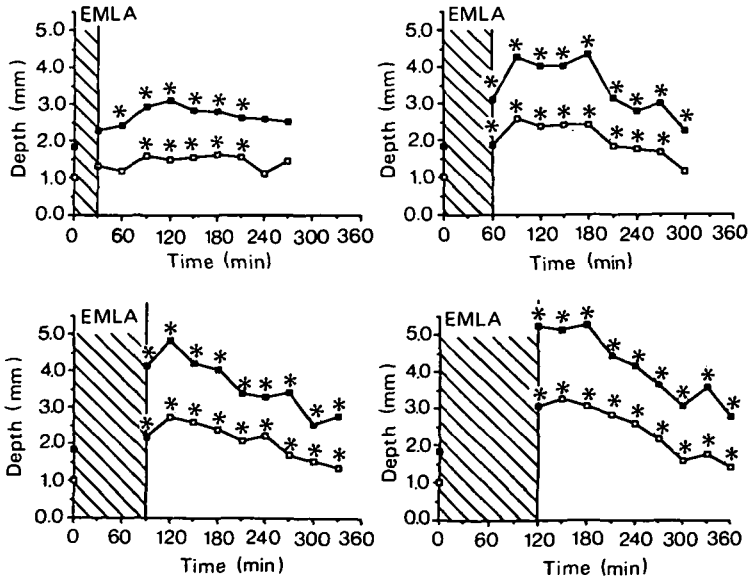

FIG. 2. Sensory (□) and pain (■) threshold depths to needle insertion before and after 30, 60, 90 and 120 min of application of EMLA cream (hatched area) (mean of 12 volunteers). *Statistically different from the initial values.

before pain was evoked. All depths measured after EMLA for 120 min were significantly increased.

Changes in sensory and pain threshold depths in relation to thresholds immediately after removal of EMLA cream

After removal of EMLA cream, analgesia progressed further down into the deeper layers of the skin and caused delayed maximal depth of analgesia (fig. 2). Sixty minutes after removal of the cream applied for 30 min, the sensory threshold depth increased significantly (53%) compared with threshold depth immediately after removal of the cream. The corresponding increase in pain threshold depth was 27% (ns). Thirty minutes after removal of the cream applied for 60 min, the sensory threshold depth increased significantly (37%) compared with the values obtained immediately after removal of the cream. The corresponding significant increase in pain threshold depth was 38%. Thirty minutes after the cream was removed after a 90-min application, the sensory and pain threshold depths were increased by 25% (ns) and 16% (ns), respectively. Only the sensory threshold depth increased slightly (7%, ns) 30 min after a 120-min application.

DISCUSSION

Dynamics of EMLA cream analgesia

The increase in depth of analgesia for increasing application times found in this study may be influenced by several factors:

(1) Cutaneous blood flow, where increased values tend to decrease anaesthetic depth by a washout effect.

(2) Epidermal and dermal thickness which affect the diffusion distance.

(3) History of atopic dermatitis. Patients with atopic dermatitis showed a shorter onset of analgesia even on non-eczematous skin after application of EMLA cream [9]. In atopics, the skin is more permeable to the cream, and subsequently needs shorter application times [9].

(4) When applied to the skin, EMLA cream presumably forms a depot of analgesics in the skin. The delayed increase of analgesia depth after EMLA application may indicate that a reservoir of analgesics is deposited and stored in the upper skin layers. After the cream has been removed, diffusion to the deeper skin layers may continue and the analgesics may accumulate in different components of the lower skin layers. Also, a possible uptake or even transport of analgesics in the nervous tissues may be important in the delayed increase of effect.

Recently, it has been shown that sensory and pain thresholds to argon laser stimulation increased for a period of 30–60 min after EMLA was removed [7]. This supports the present findings of a maximal depth of analgesia 30–60 min after EMLA cream was removed from the skin surface.

Evers and colleagues [8] evaluated the pain score to superficial minor pinprick (27-gauge needle) after 30 and 60 min of application of EMLA cream. Pain alleviation improved significantly 30–60 min after removal of the occlusive bandages and cream.

The delayed anaesthetic effect may be used clinically by outpatients before laser treatment of haemangiomas. In our department, patients apply EMLA cream for 1–1.5 h at home and remove the cream before leaving for the clinic. During transportation to the hospital, the analgesic efficiency increases [7]. The delayed effect is not only a superficial phenomenon [7] but has been shown in this study to occur in the deeper skin layers and subcutaneous tissue.

Duration of EMLA cream analgesia

The anaesthetic effect was studied 4 h after EMLA was removed. This study confirms previous observations [7] that application for 1 h, followed by immediate venous cannulation or minor surgery, might not be the optimal EMLA regimen for alleviation of pain. In contrast with the present findings, Ehrenstrom-Reiz, Reiz and Stockman [4] demonstrated a minimal effective EMLA application time of 45 min in adults. For the application times investigated, we found that the optimal conditions (maximal depth of analgesia) were obtained 30 min after a 90-min application or during the 60-min period after a 120-min application. In three cases the depth of needle insertion exceeded the measured skin thickness and reached the underlying muscle fascia. This caused a sharp radiating pain perception such as occurs with insertion of an acupuncture needle into a muscle [10].

Penetration of EMLA cream and effect on nerve fibres in the skin

Insertion of needles through intact skin can elicit neural activity in four ways:

(1) Activation of pressure sensitive (Ruffini) endings [11].

(2) Activation of movement-sensitive hair follicle receptors (Pacinian corpuscles) located in dermis or in the subcutaneous layers [11].
(3) Direct activation of the single nerve twigs innervating the mechanoreceptors may occur also by direct pressure from the needle during insertion.
(4) The perception of pain of needle insertion may arise from direct activation of the polymodal nociceptors, because they are activated by heat or intense mechanical pressure [12]. This is, however, not assumed to be the primary reason for pain in the present study, because the polymodal nociceptors are located mainly superficially, close to the dermal–epidermal border. The epidermal thickness on the flexor forearm is reported to be 0.06 mm [13], but we found a pain threshold depth of 1.85 mm on normal non-treated control skin.

Pain is assumed therefore to arise from direct pressure activation of the single nociceptive fibres. Another factor responsible for pain might be the release of prostaglandins or algesic peptides following the needle-induced cellular damage.

In the period following a 30-min application of EMLA, we observed a significant increase in pain threshold depth 30 min before the sensory threshold depth increased. It is well established that lignocaine blocks the formation and transmission of action potentials in small fibres before large ones. Our observation also indicates that, although pain is elicited directly from nerve fibres situated deeper in dermis than the mechanoreceptors (the pain threshold is reached deeper than the sensory threshold), these fibres are blocked before the more superficially located mechanoreceptors. The concentration of analgesics 1.85 mm below the skin surface is therefore sufficient to affect the small nociceptive fibres, and the higher concentration only 0.99 mm below the surface is sufficient to affect the larger fibres supplying the mechanoreceptors.

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REFERENCES

1. Hallen B, Olsson GL, Uppfeldt A. Pain-free venepuncture. *Anaesthesia* 1984; **39**: 969–972.
2. Juhlin L, Evers H, Broberg F. A lidocaine–prilocaine cream for superficial skin surgery and painful lesions. *Acta Dermatologica Scandinavica* 1980; **60**: 544–546.
3. Ohlsen L, Englesson S, Evers H. An anaesthetic lidocaine/prilocaine cream (EMLA) for epicutaneous application tested for cutting split skin grafts. *Scandinavian Journal of Plastic and Reconstructive Surgery* 1985; **19**: 201–209.
4. Ehrenstrom-Reiz G, Reiz S, Stockman O. Topical anaesthesia with EMLA, a new lidocaine–prilocaine cream and the cusum technique for detection of minimal application time. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 510–512.
5. Hallen B, Carlsson P, Uppfeldt A. Clinical study of a lignocaine–prilocaine cream to relieve the pain of venepuncture. *British Journal of Anaesthesia* 1985; **57**: 326–328.
6. Hallen B, Uppfeldt A. Does lidocaine–prilocaine cream permit pain free insertion of IV catheters in children? *Anesthesiology* 1982; **57**: 340–342.
7. Arendt-Nielsen L, Bjerring P. Laser-induced pain for evaluation of local analgesia: A comparison of topical application (EMLA) and local injection (Lidocaine). *Anesthesia and Analgesia* 1988; **67**: 115–123.
8. Evers H, von Dardel O, Juhlin L, Ohlsen L, Vinnars E. Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA). *British Journal of Anaesthesia* 1985; **57**: 997–1005.
9. Juhlin L, Rollman O. Vascular effects of a local anesthetic mixture in atopic dermatitis. *Acta Dermatologica Scandinavica* 1984; **64**: 439–440.
10. Cheng-wei, L. The Manual of China's Current Acupuncture Therapy. Medicine & Health Publishing Co., Hong Kong, 1981.
11. Mountcastle VB. Sensory receptors and neural encoding: Introduction to sensory processes. In: Mountcastle VB, ed. *Medical Physiology, Vol. 1*. Philadelphia: The C.V. Mosby Company, 1980; 327–347.
12. Adriaensen H, Gybels J, Handwerker HO, Van Hess J. Response properties of thin myelinated (A-δ) fibres in human skin nerves. *Journal of Neurophysiology* 1983; **49**: 111–122.
13. Henning JPH, Beerens EGJ, van der Leun JC. A non-invasive microscopic method for measuring epidermal thickness *in vivo*. *Archives of Dermatological Research* 1977; **258**: 25–32.