

## Comparison of the Analgesic Effect of EMLA<sup>®</sup> Cream and EMLA<sup>®</sup> Patch on Normal Skin Evaluated with Laser-induced Pain Stimuli

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**In the present study the onset, duration and efficacy of the analgesic effect of EMLA<sup>®</sup> patch compared to EMLA<sup>®</sup> cream were investigated on the skin of the forearms of 12 healthy adults. EMLA<sup>®</sup> patch and cream were applied for 30, 60 and 120 min. The pain threshold was determined 5 min after removal of the test substance, using high-energy argon laser stimuli, and thereafter every 30 min for 4 h. After 120 min of application, both EMLA<sup>®</sup> cream and EMLA<sup>®</sup> patch ensured total analgesia. The clinical analgesic efficacy of EMLA<sup>®</sup> patch was found equal to that of EMLA<sup>®</sup> cream. Key words: onset; duration; pain threshold; argon laser.**

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EMLA cream 5%, containing a eutectic mixture of lidocaine and prilocaine, is used to provide analgesia prior to venepuncture, superficial surgery and various dermatological procedures associated with superficial pain (1).

The use of EMLA cream involves application directly to the skin in the appropriate amount, after which the cream is covered with an occlusive adherent dressing. To simplify this procedure and to ensure correct administration of the drug, a patch combining EMLA cream and dressing – EMLA patch – has been developed. EMLA patch has recently been found to be equal to EMLA cream in relieving pain associated with venepuncture in children (2–4) and associated with excisional biopsy and curettage (5).

The onset and duration of the analgesic effect of EMLA cream on human skin have been investigated in previous studies (6–10).

The objective of this study was to evaluate the onset, efficacy and duration of the analgesic effect of EMLA patch compared to EMLA cream. The evaluation was made on the basis of various application times, followed by determination of the pain thresholds to painful, high-energy argon laser stimulations of the skin.

### MATERIAL AND METHODS

#### Volunteers

Twelve healthy volunteers of Caucasian origin (9 males, 3 females, mean age 28 years, range 18–40 years) participated in this study. The study was approved by the authorities and the Regional Scientific Ethics Committee.

#### Test substances

EMLA patch consists of a single-unit dose package of 1 g of EMLA emulsion 5%, eutectic mixture of lidocaine and prilocaine each in a concentration of 25 mg/ml (Astra, Sweden). Medical foam tape (3M, U.S.A.) was used as adhesive. EMLA cream 5% was used in a dose

of 2 g with Tegaderm 5 × 7 cm (3M, U.S.A.) as occlusive dressing. The EMLA placebo patch and EMLA placebo cream are similar to EMLA patch and EMLA cream, respectively, in composition and appearance, apart from the fact that they contain no anaesthetics. All the test substances were supplied by Astra, Sweden.

#### Application of test substances

In total, four patches, three EMLA and one EMLA placebo patch, and four applications of cream, three EMLA cream and one EMLA placebo cream, were applied to different test sites on both forearms of each subject at each test session. The test sites were 3 cm apart and were shaved before treatment. The study took place on two different occasions and a 1-week washout period between the two parts of the study was used. In both parts of the study, the drugs used were applied according to a prior randomization schedule.

In the first open part of the study, active EMLA cream and active EMLA patches were each applied for 30 and 60 min, respectively.

In the second, partly double-blind, part of the study, the active cream and active patch and placebo cream and placebo patch were all applied for 120 min.

#### Laser stimuli

The threshold of pain is defined as the lowest laser energy (W) which is just perceptible as a distinct, immediate pinprick (11). Baseline threshold determinations were performed immediately outside the test areas on both forearms at skin sites not previously treated and were calculated as the mean of 5 individual measurements within the same area. The laser stimuli were delivered by an argon laser (Model 168, Spectra Physics, U.S.A.) with a spot size of 3 mm and pulse time of 0.2 s. The wavelengths were 488 nm (blue) and 515 nm (green).

Five minutes after removal of the test substances the pain threshold at the site of application was determined, and this process was repeated every 30 min for the following 4 h. Determinations of the threshold of pain were obtained by finding the mean of 2–3 individual measurements within the same test area.

All the pain thresholds measured were adjusted by subtracting the individual baseline threshold and are hereafter referred to as the pain threshold. A difference in the change in pain threshold of 0.15 W was considered to be clinically relevant (11). The highest intensity of argon laser stimulation in this investigation was 3 W. Intensities higher than this can cause minor burn lesions of the stimulated skin area. When the pain threshold of the subject was not reached at a stimulation of 3 W, the pain threshold was defined as 3 W and equivalent to total analgesia (7).

#### Statistical analysis

Statistical analysis was performed using Wilcoxon's signed-rank test, and  $p < 0.05$  was regarded as the level of significance.

### RESULTS

When compared to placebo, both EMLA cream and EMLA patch induced a statistically significant increase in the pain threshold of the skin immediately after removal of the test substance after 30, 60 and 120 min of application.

*A: After 30 min of application* the pain threshold of the areas treated with EMLA patch was statistically significantly higher ( $p < 0.005$ ), compared to EMLA cream measured

90 min after removal of the test substances. The maximal analgesic effect induced by EMLA cream was reached after 1 h and with EMLA patch after 1.5 h.

*B:* After 60 min of application the pain threshold of the areas treated with EMLA patch was statistically significantly higher ( $p=0.01$ ), compared to EMLA cream measured 30 min after removal of the test substances (Fig. 1). The maximal analgesic effect induced by both cream and patch was reached after 1 h.

*C:* After 120 min of application the pain threshold of the areas treated with EMLA patch was statistically significantly higher ( $p=0.04$ ) with EMLA patch than with EMLA cream measured 120 min after removal of the test substances (Fig. 1). The maximal analgesic effect induced by both EMLA cream and patch was reached immediately after removal.

The maximal pain threshold induced by EMLA cream and patch applied for 30 and 60 min was more than 0.15 W higher than the pain threshold measured immediately after removal of the local analgesics.

The duration of the maximal analgesic effect was defined as the time after the maximal pain threshold where the pain threshold had not decreased to a value less than 0.15 W. This duration was 1.5 h after removal of all the active test substances except EMLA patch applied for 120 min, where the duration was 2 h.

In general, the level of pain threshold increased with increasing application times for both EMLA cream and patch. Consistently throughout the first hour after removal of the test substances, a statistically significantly higher pain threshold after application of EMLA cream and patch for 60 min compared to 30 min was found. A similar statistically significantly higher pain threshold was found after application of either EMLA cream or patch for 120 min compared with 30 and 60 min, respectively (Fig. 2).

DISCUSSION

In this study a statistically significantly higher level of analgesic effect was found after EMLA patch application. The differ-

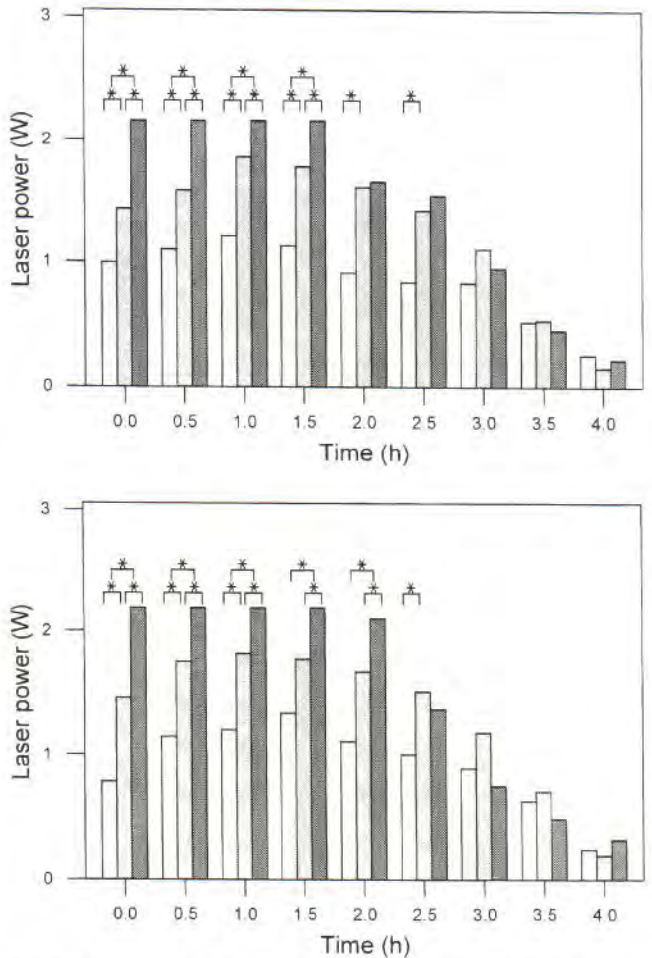
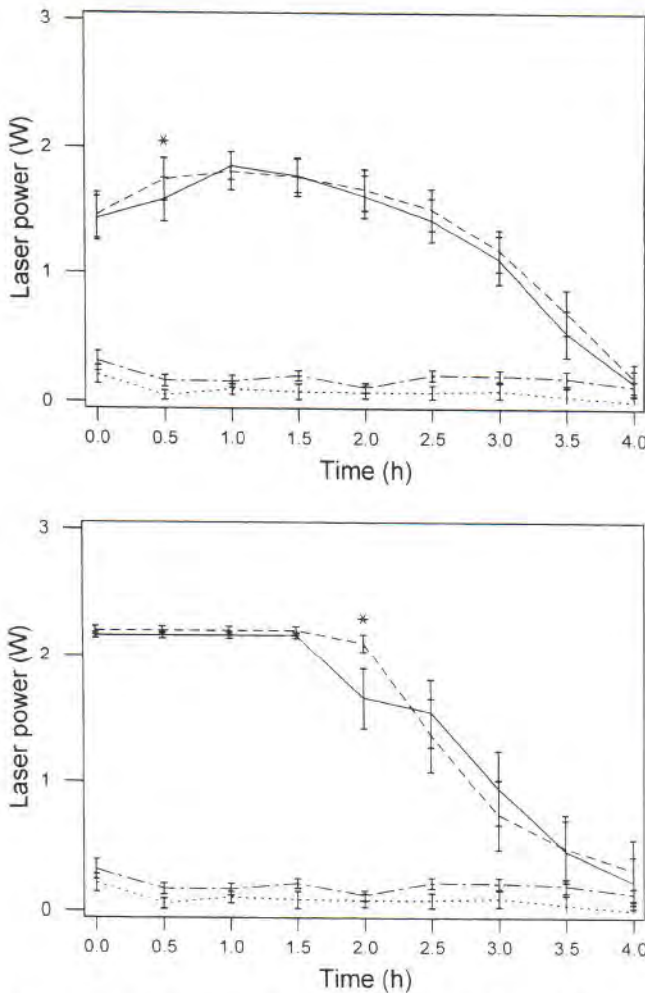


Fig. 1. Mean pain thresholds adjusted after removal of EMLA cream (—) and EMLA patch (---) applied on the forearms for 60 min (upper) and 120 min (lower). The graph also contains mean pain thresholds after removal of EMLA placebo cream (···) and placebo patch (-·-). The pain thresholds were measured 5 min after removal and every 30 min for the following 4 h. Asterisks (\*) indicate significant ( $p<0.05$ ) differences between EMLA cream and EMLA patch. The vertical bars indicate the SEM.

Fig. 2. Mean pain thresholds adjusted after removal of EMLA cream (upper) comparing 30 min □, 60 min ◐ and 120 min ◑ of application, and mean pain thresholds after removal of EMLA patch (lower) comparing 30 min, 60 min and 120 min of application. The pain thresholds were measured 5 min after removal and every 30 min for the following 4 h. Significant differences ( $p<0.05$ ) between the different times of application – between 30 and 60 min, between 60 and 120 min and between 30 and 120 min – are indicated with asterisks (\*).

ences in pain thresholds, however, were all below the pre-defined level of a clinically significant difference of 0.15 W, and the levels of the clinical analgesic effect of EMLA patch compared to EMLA cream were therefore found to be equal. This is in accordance with previous clinical studies comparing EMLA cream and patch in the relief of pain during venepuncture in children (2–4).

After removal of the local analgesics applied for 30 and 60 min, the time until the maximal analgesic effect was reached was 1 h to 1.5 h. This increasing analgesic effect induced by EMLA cream has previously been described (7–10), and a similar dynamic function seems to be involved after the application of EMLA patch.

After 120 min of application, EMLA patch and cream induced a level of absolute relief of pain from laser stimuli with an intensity of 3 W for 2 h and 1.5 h, respectively. This corresponds to total analgesia and was reached immediately after removal of the test substance in accordance with previous investigations (7–9).

Increasing duration of application of EMLA cream has previously been found to induce a higher analgesic effect (6–10), and we have found a similar effect for EMLA patch. As shown in the present study, and also in previous studies with EMLA cream, the duration of application is extremely important for a successful analgesic effect.

In the present study a small difference in the pain threshold with EMLA placebo patch and EMLA placebo cream was found. The higher pain threshold induced by the patch administration of local analgesics compared to cream and occlusive dressing could be explained by more effective occlusion of the skin by the patch due to the aluminum foil occlusive dressing. This may induce a higher degree of hydration, with swelling and whitening of the stratum corneum, thereby causing a slightly higher reflection of the laser light and a higher measured pain threshold.

The more simple application procedure involved with EMLA patch will, in our opinion, enhance both patient and staff compliance and will also ensure a correct dose of the local anaesthetics. However, the physiological variations of onset, duration and level of analgesia discussed above indicate that in order to provide an efficient analgesic effect with both EMLA patch and EMLA cream, the duration of application should be adjusted according to the site of application and the timing of the subsequent surgical procedure.

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