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Equipment

A multicentre randomized study of single-unit dose package of EMLA patch vs EMLA 5% cream for venepuncture in children

Eutectic mixture of local anaesthetics (EMLA) cream with Tegaderm was compared with pre-packaged EMLA patch with regard to analgesic effect, adhesiveness and local reactions during venepuncture in 178 children from three to ten years. One EMLA patch, or half the contents of a 5 g tube of EMLA cream plus Tegaderm was applied to the dorsum of one hand or antecubital fossa for a minimum of 60 min before venepuncture. The subject and observer assessed the degree of pain on a three-point verbal rating scale. The adhesion of the patch vs Tegaderm to the skin and local reactions were recorded. There was no difference between the two groups in pain associated with venepuncture; 95% of the EMLA patch group and 94% of the EMLA cream group reported no or slight pain. There was no difference between the two treatment groups in terms of overall local reactions. The patch was less adhesive ($P < 0.001$), but this had no apparent influence on its effectiveness. In conclusion, EMLA patch is equivalent to 5%

EMLA cream (2.5 g) in cutaneous pain relief when used for venepuncture in children.

Cette étude compare l'efficacité, l'adhésivité et les réactions locales du mélange eutectique de crème d'anesthésiques locaux (EMLA) appliqué sous une pellicule de Tegaderm avec un timbre pré-enduit d'EMLA au regard de l'effet analgésique, l'adhésivité, et des réactions locales lors d'une ponction veineuse réalisée chez 178 enfants âgés de trois à dix ans. Un timbre ou la moitié d'un tube de 5 g de crème EMLA avec Tegaderm est appliqué au dos de la main ou au pli du coude pendant au moins 60 min avant la ponction. Le sujet et l'observateur évaluent la douleur sur une échelle verbale à trois degrés. L'adhérence cutanée du timbre et celle du Tegaderm et les réactions locales sont enregistrées. On ne trouve pas de différence entre les deux groupes au regard de la douleur: 95% du groupe EMLA-timbre et 94% du groupe EMLA-crème ne rapportent que peu ou pas de douleur. Il n'y a pas de différence entre les groupes au regard des réactions locales. Le timbre adhère moins bien ($P < 0,001$), mais ceci n'a aucune influence apparente sur l'efficacité. En conclusion, le timbre EMLA équivaut à la crème (2,5 g) pour le soulagement de la douleur cutanée lorsqu'on les utilise pour la ponction veineuse chez l'enfant.

Key words

ANAESTHESIA: paediatrics;
ANAESTHETICS, LOCAL: lidocaine/prilocaine, EMLA;
VEINS: cannulation, venepuncture.

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Eutectic mixture of local anaesthetics (EMLA®, ASTRA pharmaceuticals, Sodertalje, Sweden) cream is a typical anaesthetic cream developed by Broberg and Evers for use on intact skin.¹ It has been reported to alleviate pain associated with painful skin procedures in both children and adults.² One gram of EMLA cream contains lidocaine (25 mg), prilocaine (25 mg), Arlatone® 289 (emulgent), carbomer 934-P (thickener), and distilled water. It

is an emulsion, and thereby is able to achieve adequate penetration and concentration in the superficial tissues. Each of the emulsion droplets of EMLA cream contain a high concentration of the local anaesthetics, even though the total concentration in the emulsion is relatively low (5%).

Because incorrect application of EMLA cream may result in lack of effect, a small dressing has been developed to enhance ease of application of the active product (EMLA patch). The EMLA patch is a pre-packaged dressing containing 1 g of 5% EMLA emulsion surrounded by an adhesive ring.

This multicentre randomized study was conducted to compare the analgesic effect and local skin reactions associated with EMLA patch dressing and with EMLA cream 5% applied with a Tegaderm (the standard occlusive dressing) in children who require venepuncture. A secondary objective of this study was to assess the adhesiveness of EMLA patch dressing compared with that of the Tegaderm dressing.

Methods

This study was designed as an open, randomized, comparative multicentre trial that involved five paediatric centres (three departments of anaesthesia and two departments of oncology) across Canada. Following institutional ethics committee approval from each centre, informed consent was obtained from each parent, and, where appropriate; each of the subjects. One hundred and ninety-six subjects aged three to ten years scheduled for surgical or oncological procedures necessitating venepuncture either on the dorsum of the hand or in the antecubital fossa were entered into the study. Excluded were any patients with a history of allergy, sensitivity or any other form of reaction to amide-type local anaesthetics, or any subject requiring premedication prior to the procedure.

Two parallel groups, one EMLA patch group and one EMLA cream group, were used. The randomization was stratified for centre and site of venepuncture.

The EMLA patch is a 1 mm thick, square-shaped plaster with an area of approximately 40 cm² (Figure). In its centre it contains a circle-shaped matrix measuring 10 cm² saturated with 1 g of EMLA in a 5% emulsion. The patch is surrounded by an adhesive ring. The EMLA 5% cream is a eutectic mixture of lidocaine and prilocaine, each in a concentration of 25 mg · g⁻¹ of cream. Tegaderm® (3M, USA) 5 × 7 cm was used as an occlusive dressing.

Subjects were randomized to receive either one EMLA patch of 2.5 g EMLA cream plus Tegaderm; these were applied either on the dorsum of the hand or on the antecubital fossa. The application time was specified to be

FIGURE Schematic representation of EMLA patch.

at least 60 min but no more than 180 min before venepuncture. Venepuncture was carried out uniformly using a #23-gauge Travenol butterfly intravenous cannula.

Pain during venepuncture was assessed by both the child and an observer as follows: the child was asked whether the venepuncture caused no pain, slight pain or severe pain. The observer also independently assessed the child's reaction by using a three-point rating scale graded as none (no reaction), slight (facial grimace, withdrawal of hand) or severe (cries, screams, vigorous withdrawal of hand). Identical pain assessments were also used to assess the discomfort associated with removal of either the EMLA patch or the Tegaderm.

For each subject, the degree of adhesion of the EMLA patch of Tegaderm to the skin was also assessed using a five-point scale, graded as follows: 100% (totally affixed), 75–99%, 50–74%, 1–49% and 0% (not affixed at all).

Each child was asked to identify any local sensation, i.e., itching or burning associated with the local anaesthetic site or the dressing during the application period. Local skin reactions were rated by the investigator using a four-point rating scale graded as none, mild, moderate, or severe. Local reactions such as erythema, pallor or oedema were noted if present.

Student's *t* test and Chi-square with Yates' correction for continuity were used to analyze the demographic data.

TABLE I Demographic data for EMLA patch and EMLA cream group. There is no statistical significant difference between groups. Results shown are mean $\pm$ SD (range)

	<i>EMLA patch</i>	<i>EMLA cream</i>
Patients	96	100
Age yr	6.1 $\pm$ 2.2 (3–10)	6.2 $\pm$ 2.3 (3–14)
Male:Female	39:57	61:39
Weight kg	24.6 $\pm$ 10.3 (12–64)	22.8 $\pm$ 8.2 (12–57)

The pain score during venepuncture was analyzed by means of a one-sided Chi-square test. The remaining variables were analyzed using a two-sided Wilcoxon rank sum test and Fischer's exact test. The results were considered to be statistically significant for values of $P < 0.05$.

Results

There were no differences between the two treatment groups in terms of age, sex and weight (Table I). When comparing the distribution of patients between centres and site of venepuncture between the two groups, no differences were found (Table II). One hundred and seventy-eight patients were evaluable and were therefore included in the analysis. Eighteen patients, eight from the EMLA patch group and ten from the EMLA cream group were excluded from the statistical analysis as a result of deviation from the study design.

Pain associated with venepuncture assessed by subject and observer is shown in Table III. Ninety-five percent (84/88) of the subjects from the EMLA patch group reported no or slight pain compared to 94% (85/90) from the EMLA cream group. The observers' assessments were 95% (84/88) and 97% (87/90) for the EMLA patch and EMLA cream groups respectively.

Measures of discomfort associated with removal of the patch and Tegaderm are shown in Table IV. Subject rating revealed no difference between the two groups ($P = \text{NS}$). Observer rating showed that removal of the patch was more painful ($P < 0.05$). There was a difference in adhesion between the two treatment groups (Table V), with the EMLA patch being less adhesive ($P < 0.001$). This did not, however, have any apparent influence on the effectiveness of the patch.

Overall, there was no difference between the two groups with regard to local reaction. A mild pallor under the adhesive was observed in five patients in the EMLA patch group and in no patients in the EMLA cream group ($P = \text{NS}$). One patient in the EMLA cream group complained of severe itching, which occurred approximately 15 min after application. A rash was noted four hours after removal of the cream and the rash resolved

TABLE II Distribution of patients between centres for site of venepuncture

<i>Centre</i>	<i>Site of venepuncture</i>	<i>EMLA patch</i>	<i>EMLA cream</i>
1	Hand	20	21
2	Antecubital fossa	19	19
3	Hand	22	23
4	Hand	10	9
	Antecubital fossa	8	9
5	Hand	9	9
	Antecubital fossa	8	10
Total		96	100

TABLE III Pain from venepuncture, assessed by subject and observer. There is no difference ($P < 0.05$) between the two groups with either assessment

	<i>Subject's assessment</i>			<i>Observer's assessment</i>		
	<i>No</i>	<i>Slight</i>	<i>Severe</i>	<i>No</i>	<i>Slight</i>	<i>Severe</i>
EMLA patch <i>n</i> = 88	61	23	4	69	15	4
EMLA cream <i>n</i> = 90	69	16	5	76	11	3

TABLE IV Discomfort from removal of patch and Tegaderm assessed by subject and observer

	<i>Subject's assessment</i>			<i>Observer's assessment</i>		
	<i>No</i>	<i>Slight</i>	<i>Severe</i>	<i>No</i>	<i>Slight</i>	<i>Severe</i>
EMLA patch <i>n</i> = 88	66	21	1	67	20	1
EMLA cream <i>n</i> = 90	76	14	0	78	12	0

TABLE V Adhesiveness of EMLA patch and Tegaderm

<i>Degree of adhesiveness</i>	<i>EMLA patch n</i> = 88	<i>EMLA cream n</i> = 90
100%	44	72
$\geq 75\%$	26	11
$\geq 50\%$	8	4
$\leq 50\%$	10	2
0%	0	1

within 12 hr. It was later discovered that the child was sensitive to adhesive tapes, suggesting previous exposure to similar adhesive component found in the Tegaderm.

Discussion

The use of EMLA cream as a topical anaesthetic in the paediatric population has been described for relief of pain associated with treatment of molluscum contagiosum,³⁻⁵ venepuncture⁶⁻¹¹ and intravenous catheter insertion,^{2,12-15} lumbar puncture,^{16,17} separation of preputial adhesions,¹⁸ heel lancing¹⁹ and superficial surgery.^{20,21}

On intact skin, EMLA cream should be applied under occlusion for a minimum of 60–90 min before the procedure.^{6-10,12-15} On diseased skin and mucous membranes, a shorter time of 5 to 30 min should be used.²² However, it is important to note that the product has not been approved or recommended for use on broken skin. One to two grams of cream should be applied to 10 cm², with a maximum of 10 g recommended for use at any one application. The maximum application dose is 2 g for children below the age of one year.

In the past 30 yr, numerous attempts have been made to obtain a suitable formulation for topical analgesia.²³⁻²⁷ The relative ineffectiveness of transdermal preparations has been attributed either to insufficient concentrations of the uncharged base or active form of the anaesthetic product or to poor skin absorption as a result of the lipophilic characteristics of amide derivatives.² In an attempt to increase the anaesthetic base concentration, organic solvents have been used as a solvent. Unfortunately, the solvent has resulted in unacceptable local irritation.¹ Furthermore, because the resulting compounds have poor penetration through intact skin, their only application has been for anaesthesia of mucous membranes.²⁷

An oil in water emulsion of a single anaesthetic agent permits the achievement of high concentration of the anaesthetic base with better skin penetration due to the presence of water, yet the concentration of anaesthetic base in such an emulsion is insufficient to provide effective skin analgesia.

A mixture of lidocaine and prilocaine base in a weight ratio of 1:1, results in a eutectic mixture, which melts at a lower temperature than either agent separately. This eutectic mixture is liquid at room temperature,²⁸ obviating the need for dissolving the anaesthetic base in oil before the addition of an emulsifier. This increases the concentration of the anaesthetics in the emulsion droplets from approximately 20% for lidocaine alone to 80% for the combination of lidocaine and prilocaine.¹

The uptake of lidocaine and prilocaine in EMLA cream (and patch) by skin is due to two factors: the high base concentration of the active agents and the presence of water in the formulation. Due to the water content, the hydrophilic stratum corneum absorbs water under the occlusive dressing and decreases the barrier characteristic of the skin. Another important effect, obtained by the special properties of the pharmaceutical formulation of

EMLA cream, is the high release of the active agents. In "conventional cream" some of the active substance does not leave the oil-phase, and consequently, cannot be utilized for the absorption into the skin.

The effectiveness of EMLA cream for venepuncture and intravenous cannulation has been demonstrated in numerous studies,^{2,6-15} with few reported complications associated with its use.²⁹⁻³² The mild skin changes observed with EMLA were transient and did not constitute a source of discomfort for the patient.

To enhance the ease of application of the eutectic mixture of prilocaine and lidocaine EMLA patch has been developed. This might eliminate the possibility of incorrect application of the EMLA cream that leads to lack of analgesic effect. This study compared the analgesic efficacy and local skin reactions associated with EMLA patch and with EMLA cream 5% combined with Tegaderm during venepuncture in children. We also assessed the adhesiveness of the EMLA patch compared to that of the Tegaderm dressings.

In relation to our objective, we have demonstrated that there is no difference between EMLA cream and EMLA patch in terms of either analgesic effectiveness or local reaction. Pain associated with removal is no different for either product. The decreased adhesiveness of the patch had no influence on the effectiveness of the patch.

As a single-dose, easy to apply product, EMLA patch may have a role as a convenient form of topical analgesic prior to venepuncture. With its ease of application, very limited patient or parental instruction is required.

References

- 1 Evers H, von Dardel O, Juhlin L, Ohlén L, Vinnars E. Dermal effects of compositions based on the eutectic mixtures of lignocaine and prilocaine (EMLA). *Br J Anaesth* 1985; 57: 997–1005.
- 2 Hallén B, Carlsson P, Uppfeldt A. Clinical study of a lignocaine-prilocaine cream to relieve the pain of venepuncture. *Br J Anaesth* 1985; 57: 326–8.
- 3 Rosdahl I, Edmar B, Gisslén H, Nordin P, Lillieborg S. Curettage of molluscum contagiosum in children: analgesia by topical application of a lidocaine/prilocaine cream (EMLA). *Acta Derm Venereol (Stockh)* 1988; 68: 149–53.
- 4 Wagner G, Mensing H. Perkutane anaesthetie durch anwendung einer lidocain-prilocain-creme (EMLA creme 5%) – Erfahrungen bei der therapie multipeler mollusca contagiosa im kindesalter. *Acta Dermatol* 1989; 15: 44–6.
- 5 de Waard-van der Spek FB, Oranje AP, Lillieborg S, Hop WCJ, Stolz E. Treatment of molluscum contagiosum using a lidocaine/prilocaine cream (EMLA) for analgesia. *J Am Acad Dermatol* 1990; 23: 685–8.
- 6 Juhlin L, Evers H, Broberg F. A lidocaine-prilocaine

- cream for superficial skin surgery and painful lesions. *Acta Derm Venereol* (Stockh) 1980; 60: 544–6.
- 7 Ehrenström Reiz GME, Reiz SLA. EMLA – a eutectic mixture of local anaesthetics for topical anaesthesia. *Acta Anaesthesiol Scand* 1982; 26: 596–8.
 - 8 Hellgren U, Kihamia CM, Premji Z, Danielson K. Local anaesthetic cream for the alleviation of pain during venepuncture in Tanzanian schoolchildren. *Br J Clin Pharmacol* 1989; 28: 205–6.
 - 9 Hallén B, Olsson GL, Uppfeldt A. Pain-free venepuncture. Effect of timing of application of local anaesthetic cream. *Anaesthesia* 1984; 39: 969–72.
 - 10 Cooper CM, Gerrish SP, Hardwick M, Kay R. EMLA cream reduces the pain of venepuncture in children. *Eur J Anaesthesiol* 1987; 4: 441–8.
 - 11 Hopkins CS, Buckley CJ, Bush GH. Pain-free injection in infants. Use of lignocaine-prilocaine cream to prevent pain at intravenous induction of general anaesthesia in 1–5-year-old children. *Anaesthesia* 1988; 43: 198–201.
 - 12 Hallén B, Uppfeldt A. Does lidocaine-prilocaine cream permit painfree insertion of IV catheters in children? *Anesthesiology* 1982; 57: 340–2.
 - 13 Manner T, Kanto J, Lisalo R, Lindberg R, Viinamäki O, Scheinin M. Reduction of pain at venous cannulation in children with eutectic mixture of lidocaine and prilocaine (EMLA cream): comparison with placebo cream and no local premedication. *Acta Anaesthesiol Scand* 1987; 31: 735–9.
 - 14 Maunuksela EL, Korpela R. Double-blind evaluation of lignocaine-prilocaine cream (EMLA) in children. Effect on the pain associated with venous cannulation. *Br J Anaesth* 1986; 58: 1242–5.
 - 15 Clarke S, Radford M. Topical anaesthesia for venepuncture. *Arch Dis Child* 1986; 61: 1132–4.
 - 16 Kapelushnik J, Koren G, Solh H, Greenberg M, DeVeber L. Evaluating the efficacy of EMLA in alleviating pain associated with lumbar puncture; comparison of open and double-blinded protocols in children. *Pain* 1990; 42: 31–4.
 - 17 Halperin DL, Koren G, Attias D, Pellegrini E, Greenberg ML, Wyss M. Topical skin anesthesia for venous, subcutaneous drug reservoir and lumbar punctures in children. *Pediatrics* 1989; 84: 282–4.
 - 18 MacKinlay GA. Save the prepuce. Painless separation of preputial adhesions in the outpatient clinic. *BMJ* 1988; 297: 590–1.
 - 19 Fitzgerald M, Millard C, McIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. *Pain* 1989; 39: 31–6.
 - 20 Bjerring P, Arendt-Nielsen L. Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream. *Br J Anaesth* 1990; 64: 173–7.
 - 21 Jones SK, Handfield-Jones S, Kennedy CTC. Does EMLA reduce the discomfort associated with local-anaesthetic infiltration? *Clin Exp Dermatol* 1990; 15: 177–9.
 - 22 Nykanen D, Kisson N, Rieder M, Armstrong R. Comparison of a topical mixture of lidocaine and prilocaine (EMLA) versus 1% lidocaine infiltration on wound healing. *Pediatr Emerg Care* 1991; 7: 15–7.
 - 23 Klingman AM. Topical pharmacology and toxicology of dimethyl sulphonate – Part I. *JAMA* 1956; 193: 140–3.
 - 24 Monash S. Topical anesthesia of the unbroken skin. *Arch Dermatol* 1957; 76: 752–?
 - 25 Brechner VL, Cohen DD, Pretsky I. Dermal anesthesia by the topical application of tetracaine base dissolved in dimethyl sulphoxide. *Ann N Y Acad Sci* 1967; 141: 524–31.
 - 26 Dalili H, Adriani J. The efficacy of local anesthetics in blocking the sensation of itch, burning, and pain in normal and “sunburned” skin. *Clin Pharmacol Ther* 1971; 12: 913–9.
 - 27 Russo J Jr, Lipman AG, Comstock TJ, Page BC, Stephen RL. Lidocaine anesthesia: comparison of iontophoresis, injection, and swabbing. *Am J Hosp Pharm* 1980; 37: 843–7.
 - 28 Brodin A, Nyqvist-Mayer A, Wadsten T, Forslund B, Broberg F. Phase diagram and aqueous solubility of the lidocaine-prilocaine binary system. *J Pharm Sci* 1984; 73: 481–4.
 - 29 Jakobson B, Nilsson S. Methemoglobinemia associated with a prilocaine-lidocaine cream and trimetoprim-sulphamethoxazole: a case report. *Acta Anaesthesiol Scand* 1985; 29: 453–5.
 - 30 Engberg G, Danielson K, Henneberg S, Nilsson A. Plasma concentrations of prilocaine and lidocaine and methaemoglobin formation in infants after epicutaneous application of a 5% lidocaine-prilocaine cream (EMLA). *Acta Anaesthesiol Scand* 1987; 31: 624–8.
 - 31 Norman J, Jones PL. Complications of the use of EMLA (Letter). *Br J Anaesth* 1990; 64: 403.
 - 32 James IG. EMLA: Complications (Letter). *Br J Anaesth* 1990; 65: 295.